Mediterranean Cardiology Meeting 2007

Current News in Cardiology

edited by Michele M. Gulizia

Springer

To my beloved wife Luisa

Someone said "*Love, pleasant folly…*",
I say "*Love, lunatic happiness...*"

True love doesn't know how to speak!

Michele M. Gulizia (Editor)

Current News in Cardiology

Proceedings of the
Mediterranean Cardiology Meeting
(Taormina, May 20-22, 2007)

Springer

Michele M. Gulizia, MD
Chief of Cardiology Division
"Garibaldi-Nesima" Hospital
Catania, Italy

Library of Congress Control Number: 2007927712

ISBN 13: 978-88-470-0635-5 Springer Milan Berlin Heidelberg New York
e-ISBN 13: 978-88-470-0636-2

Springer is a part of Springer Science+Business Media

Springer.com

Cover design: Simona Colombo, Milan, Italy
Typesetting: Graphostudio, Milan, Italy
Printing: Grafiche Porpora, Segrate, Italy

Printed in Italy
Springer-Verlag Italia S.r.l. – Via Decembrio 28 – I-20137 Milan

Preface

It is said that the true essence of the progress is the constant verification of that which is certain.

Clinical practice is evolving at a rapid pace, nowhere more so than in the field of cardiology.

Acute Coronary Syndromes, Sudden Cardiac Death, Heart Failure, Atrial Fibrillation, Syncope, and Prevention of Global Cardiovascular Risk are the main emerging pathologies, on which many investigators are focusing their research. Less than 10 years ago, some of them were considered of relevance only to internists, and some others as common benign arrhythmias or ineluctable illnesses. Today, their prevalence amongst the population represents a major public health problem at the beginning of the third millennium.

The need for a state-of-the-art overview of the epidemiology, physiopathological and electrogenetic mechanisms, diagnosis, pharmacological or electrical treatment, prognosis, patient management in and out of hospital, organisational and economical implications of these emerging pathologies, and the great success of the previous editions, inspired us to organise the third edition of this biannual International Meeting, to give you the "***Current News in Cardiology***".

This book contains the Proceedings of the Mediterranean Cardiology Meeting held in Taormina, Italy, 20-22 May 2007. Like the previous volumes, it boasts the participation of many nationally and internationally renowned speakers in the field of clinical and interventional cardiology who will interact actively with delegates.

The exceptional novelty of this edition is that all participants to the Meeting will receive a password for a free pdf download of all chapters of the book, which can, be found on the website of the Mediterranean Cardiology Meeting (www.mcmweb.it) via SpringerLink.

The book is divided into 8 sections, 11 sub-sections, and a total of 54 chapters, each devoted to a different topic: Atrial Fibrillation and Atrial Flutter; Heart Failure; Syncope; Sudden Cardiac Death; Cardiac Pacing; Electrocardiography; Acute Coronary Syndromes; Global Cardiovascular Risk Prevention.

It aims to provide the latest information on the most recent and modern aspects of the above mentioned pathologies. It is intended not only for cardiologists, but also for those who are actively interested in the evidence-based approach to clinical care, such as internists, emergency and critical care clinicians, physicians of general medicine, fellows, students, nurses, and technicians. It may also be helpful for individuals engaged in the development and coordination of research strategies in biological engineering, industry, and regulatory affairs, who have a strong interest in the overall management of these cardiac pathologies.

A Faculty selected from leading Italian and International experts ensures the highest quality of this volume: the publications of many of them have contributed to the scientific progress in cardiology and influenced many of our professional considerations and decisions. I am most indebted to all these authors, who have devoted the invaluable time and effort without which this book would not have been completed.

I also wish to thank the staff of Springer, and in particular Donatella Rizza, Executive Editor, who has facilitated the publication of this book since the first edition of the Mediterranean Cardiology Meeting, and who has kindly assisted me throughout this project together with her staff member Eleonora. Special and deep thanks are addressed to Rita Reggiani, professional, tireless, and wonderful Project Leader of Adria Congrex, who has helped and supported me in achieving the best possible organisation of this International Meeting, together with her staff members Silvana, Sara and Elisa.

I cannot forget to acknowledge the role of my two teachers, Antonio Circo and Salvatore Mangiameli, who encouraged my passion for cardiology and particularly for arrhythmology and clinical management.

In addition, I would like to thank my co-workers Cacia, Cardillo, Francese, Mangiameli, Portale, Raciti, Ragusa, the chief of nursing Salpietro and the entire staff of my Cardiology Division at the "Garibaldi-Nesima" Hospital of Catania for their active collaboration and support during these years of work and for the organisation of this Meeting.

Finally, a special mention goes to my dear wife Luisa, my daughters Alice and Raffaella, and my parents Raffaele and Cettina. I am especially and deeply grateful to them. Without their love and patience I could not have spent so many nights and weekends preparing the Meeting and this volume.

Michele M. Gulizia

Table of Contents

ATRIAL FIBRILLATION AND ATRIAL FLUTTER

Pharmacological Therapy

Anti-arrhythmic Drugs in Atrial Fibrillation: Historical Perspectives and New Developments 3
Berndt Lüderitz

"Pill-in-the-Pocket" Approach 11
Paolo Alboni

Lone Atrial Fibrillation: Prophylactic Anti-arrhythmic Treatment 17
Gianluca Botto, Mario Luzi, Giovanni Russo, Barbara Mariconti

Radiofrequency Ablation

Radiofrequency Ablation of Atrial Fibrillation and Atrial Flutter: Who and When? 23
Josef Kautzner, Dan Wichterle

Cryocatheter Ablation for Atrial Flutter 29
Peter Andrew, Annibale Sandro Montenero

Clinical Profile, Electrophysiological Characteristics, and Outcome after Radiofrequency Catheter Ablation of Atypical Atrial Flutter 41
Golmehr Ashrafpoor, Amir-Ali Fassa, Henri Sunthorn, Haran Burri, Pascale Gentil-Baron, Dipen Shah

The Impact of New Imaging, Mapping and Energy Delivery Technology on the Current Approach to Ablation of Atrial Fibrillation 43
Andrea Colella, Marzia Giaccardi, Luigi Padeletti, Gian Franco Gensini

Trigger vs Substrate Ablation for the Treatment of Atrial Fibrillation 49
Atul Verma

Complications of Atrial Fibrillation Ablation: How To Prevent Them 57
Giuseppe De Martino, Giovanna Rodio, Carmine Mancusi, Stefano De Vivo

Pacing in the Prevention and Therapy of Atrial Arrhythmias

Pacing in Atrial Fibrillation: Is It Still Viable? 63
Oscar Oseroff, Gustavo Iralde, Enrique Retyk

Traditional or Device Approach for the Management of Atrial Fibrillation in Patients with Heart Failure 75
Aurelio Quesada, Mónica Giménez, Victor Palanca, Javier Jiménez, José Roda

Practical Issues in Managing Atrial Fibrillation Patients

Conversion of Persistent Atrial Fibrillation to Sinus Rhythm by DC Shock: Is It Still in Use Two Years After AFFIRM? 87
Valeria Calvi, Salvatore Timineri

Lone Atrial Fibrillation and Sports Activities 93
Francesco Furlanello, Giuseppe Inama, Claudio Pedrinazzi, Luigi De Ambroggi, Riccardo Cappato

HEART FAILURE

Heart-Failure Management: Focus on Heart-Failure Practice Guidelines 101
Eugene Crystal, Rajneesh Calton

Managing Patients with Implantable CRT Devices for Heart Failure

Determination of Left Ventricular Contractile Reserve by Dobutamine Stress Echocardiography To Predict the Response to CRT 117
Carmine Muto, Bernardino Tuccillo

Focus on Optimization of Cardiac Resynchronization Therapy Techniques 119
Maurizio Lunati, Yann Poezevara, Andrea Boncompagni

Evaluation of the Clinical State of Cardiac Resynchronization Therapy Patients by Continuous Heart-Failure Monitoring 125
Henri Benkemoun, Bertrand Colombo, Jean Sacrez, Philippe Lagrange, Philippe Cabrol, Gabriel Robert, Marc Moulichon

Predicting Heart Failure Events in CRT Patients: Future Challenges 129
Roberto Mantovan, Danilo Contardi, Vittorio Calzolari, Martino Crosato, Zoran Olivari

Use of Fluid Accumulation Monitoring in HF Patients 137
Saverio Iacopino, Rossella Alemanni, Antonella Talerico, Gennaro Fabiano, Sergio Canonaco, Francesco Borrello

SYNCOPE

Diagnostic Evaluation of Patients with Recurrent Syncopal Episodes

Performing Carotid Sinus Massage 145
Roberto Maggi, Michele Brignole

Performing Tilt Testing and Physical Countermaneuvers Training 153
Giuseppina M. Francese, Michele M. Gulizia

Implanting a Loop Recorder 159
Michele Brignole

SUDDEN DEATH

Noninvasive Sudden Death Risk Stratification

Noninvasive Sudden Death Risk Stratification: Heart Rate Variability and Turbulence, and QT Dynamicity 167
Antonio Vincenti, Stefano Pedretti

Noninvasive Risk Stratification of Sudden Death: T-Wave Alternans 179
Roberto F.E. Pedretti, Simona Sarzi Braga, Raffaella Vaninetti, Antonio Laporta, Sergio Masnaghetti, Rossella Raimondo, Mario Salerno, Francesco Santoro

Risk Stratification for Sudden Death in Hypertrophic Cardiomyopathy 191
Domenico Catanzariti, Massimiliano Maines, Giuseppe Vergara

Managing Hypertrophic Cardiomyopathy: Screening in Young Subjects 197
Maurizio Santomauro on Behalf of the AIAC Task Force of Risk Management, Gianluca Botto, Corrado Diaco, Michele M. Gulizia, Giuseppe Marceca, Francesco Melandri, Franco Naccarella, Carla Riganti, Massimo Santini

Pharmacological Therapy

The Prevention of Sudden Death: New Perspectives 205
Savina Nodari, Marco Metra, Alessandra Manerba, Silvia Frattini, Giuseppe Seresini, Livio Dei Cas

Current News in Prevention of Sudden Death by Implantable Cardiac Defibrillators

Which Patient and when Should Receive an ICD? Evolving New Indications on the Horizon 215
Roberto Verlato, Maria Stella Baccillieri, Pietro Turrini

Implantable Cardiac Defibrillators: Is Defibrillation Threshold Testing Still Necessary in all Patients? 221
Franco Naccarella, Fabio Iachetti, Angela Wang, Cristina Felicani, Giovannina Lepera, Elvira Moccia, Leilei Sun, Luca Casari, Giorgio Morselli, Patrizia Capogreco, Gerald Naccarelli

Current Practice in Italy of VF Testing at Implant: What Do We Know and Where Do We Go From Here? 231
Michele Brignole, Giovanni Raciti, Maria Grazia Bongiorni, Giuseppe De Martino, Stefano Favale, Maurizio Gasparini, Raffaele Luise, Eraldo Occhetta, Alessandro Proclemer

How To Choose Between Single-Chamber and Dual-Chamber ICD 239
Maurizio Del Greco, Lorena Gramegna, Massimiliano Marini, Marcello Disertori

Which Patients Should Receive Dual Defibrillators? Results of DATAS 245
Aurelio Quesada, Mónica Giménez, Victor Palanca, Javier Jiménez, Alfonso Valle, José Roda

Prevention of Sudden Death in Patients with Genetic Arrhythmias 255
Pietro Delise

Cost-Effectiveness of ICD Therapy in the Prevention of Sudden Death in CAD and/or HF Patients 263
Andrea Pozzolini

CARDIAC PACING

Hemodynamic Issues and Practical Applications in Cardiac Pacing

Hemodynamic Impact of Right Ventricular Pacing 279
Raúl Chirife, G. Aurora Ruiz, M. Cristina Tentori

Hemodynamics in Standard Cardiac Pacing 293
Milos Taborsky

Hemodynamic Assessment with an Implanted Pacing Device 303
Maria Grazia Bongiorni, Ezio Soldati, Giuseppe Arena, Giulio Zucchelli, Andrea Di Cori, Alberto Barbetta, Franco Di Gregorio

Hemodynamic Optimization of Pacing Configuration in Bradyarrhythmias 309
Gianfilippo Neri, Rolando Zamprogno, Diego Vaccari, Giuliano Masaro, Alberto Barbetta, Franco Di Gregorio

Applications of TVI Sensing in Cardiac Stimulation 317
Eraldo Occhetta, Miriam Bortnik, Franco Di Gregorio, Alberto Barbetta, Paolo Marino

The Ideal Pacemaker for Complete AV Block 325
I. Eli Ovsyshcher

The Ideal Pacemaker for Elderly Patients 331
Gulmira Kudaiberdieva, Bulent Gorenek

ELECTROCARDIOGRAPHY

What Is New in 12-lead Electrocardiography?

Update on ACC/ESC Criteria for Acute ST Elevation Myocardial Infarction 341
Peter W. Macfarlane

ECG-MRI based Localization of Myocardial Infarction 347
Henrik Engblom, Olle Pahlm

Electrocardiographic Predictors of Arrhythmias In CCU Patients 355
Afshin Parspour, Alparslan Birdane, Bulent Gorenek

The Routine ECG as a Marker of Sudden Cardiac Death 365
Luigi De Ambroggi

ACUTE CORONARY SYNDROMES

International Guidelines on Acute Coronary Syndrome:
Practical Application and Current News in Cardiology 375
Giacomo Chiarandà, Giuseppa Strano, Angela Lazzaro, Marta Chiarandà

Is There a Limit to PTCA in Elderly Patients? 383
**Francesco Bovenzi, Roberto Lorenzoni, Mauro Lazzari,
Andrea Boni, Cristina Gemignani**

When Should Patients with Ischemic Mitral Regurgitation
Undergo Cardiac Surgery? 391
**Scipione Carerj, Concetta Zito, Giuseppe Dattilo, Grazia Di Bella,
Carmelo Nipote, Annalisa Lamari, Rossella Garufi, Salvatore Micciulla,
Francesco Arrigo**

Minimally Invasive Techniques in Cardiac Surgery:
An Opportunity for All Patients? 395
Leonardo Patanè, Alfio Cavallaro

GLOBAL CARDIOVASCULAR RISK PREVENTION

Cardiovascular Risk Management: An Overview 407
**Andrea Boni, Roberto Lorenzoni, Mauro Lazzari,
Cristina Gemignani, Francesco Bovenzi**

Is Arterial Pressure Self-Measurement Better Than Ambulatory
24-Hour Pressure Monitoring? 417
Carlo Fernandez

Role of Angiotensin-Receptor Blockers in the Prevention
of Cardiovascular Risk: Clinical Guidelines 425
**Pasquale Perrone-Filardi, Pierluigi Costanzo, Antonio Marzano,
Paolo Cesarano, Paola Gargiulo, Enrico Vassallo, Caterina Marciano,
Teresa Losco, Massimo Chiariello**

New Evidence about the Beneficial Effects of Angiotensin-Receptor Blockers on the Heart and the Kidney 433
Claudio Borghi, Marco Manca

Lercanidipine, Enalapril, and Their Combination in the Treatment of Elderly Hypertensive Patients 441
Juan Garcia Puig, Carlos Calvo, Olavi Luurila, Harri Luurila, Sakari Sulosaari, Arto Strandberg, Cristina Ghezzi

Subject Index 445

List of Contributors

Alboni P., 11
Alemanni R., 137
Andrew P., 29
Arena G., 303
Arrigo F., 391
Ashrafpoor G., 41
Baccillieri M.S., 215
Barbetta A., 303, 309, 317
Benkemoun H., 125
Birdane A., 355
Boncompagni A., 119
Bongiorni M.G., 231, 303
Boni A., 383, 407
Borghi C., 433
Borrello F., 137
Bortnik M., 317
Botto G., 17, 197
Bovenzi F., 383, 407
Brignole M., 145, 159, 231
Burri H., 41
Cabrol P., 125
Calton R., 101
Calvi V., 87
Calvo C., 441
Calzolari V., 129
Canonaco S., 137
Capogreco P., 221
Cappato R., 93
Carerj S., 391
Casari L., 221
Catanzariti D., 191
Cavallaro A., 395
Cesarano P., 425
Chiarandà G., 375
Chiarandà M., 375
Chiariello M., 425
Chirife R., 279
Colella A., 43
Colombo B., 125
Contardi D., 129
Costanzo P., 425
Crosato M., 129
Crystal E., 101
Dattilo G., 391
De Ambroggi L., 93, 365
De Martino G., 57, 231
De Vivo S., 57
Dei Cas L., 205
Del Greco M., 239
Delise P., 255
Di Bella G., 391
Di Cori A., 303
Di Gregorio F., 303, 309, 317
Diaco C., 197
Disertori M., 239
Engblom H., 347
Fabiano G., 137
Fassa A-A., 41
Favale S., 231
Felicani C., 221
Fernandez C., 417
Francese G.M., 153
Frattini S., 205
Furlanello F., 93
Gargiulo P., 425
Garufi R., 391
Gasparini M., 231
Gemignani C., 383, 407
Gensini G.F., 43
Gentil-Baron P., 41

Ghezzi C., 441
Giaccardi M., 43
Giménez M., 75, 245
Gorenek B., 331, 355
Gramegna L., 239
Gulizia M.M., 153, 197
Iachetti F., 221
Iacopino S., 137
Inama G., 93
Iralde G., 63
Jiménez J., 75, 245
Kautzner J., 23
Kudaiberdieva G., 331
Lagrange P., 125
Lamari A., 391
Laporta A., 179
Lazzari M., 383, 407
Lazzaro A., 375
Lepera G., 221
Lorenzoni R., 383, 407
Losco T., 425
Lüderitz B., 3
Luise R., 231
Lunati M., 119
Luurila H., 441
Luurila O., 441
Luzi M., 17
Macfarlane P.W., 341
Maggi R., 145
Maines M., 191
Manca M., 433
Mancusi C., 57
Manerba A., 205
Mantovan R., 129
Marceca G., 197
Marciano C., 425
Mariconti B., 17
Marini M., 239
Marino P., 317
Marzano A., 425
Masaro G., 309
Masnaghetti S., 179
Melandri F., 197
Metra M., 205
Micciulla S., 391
Moccia E., 221
Montenero A.S., 29
Morselli G., 221
Moulichon M., 125
Muto C., 117
Naccarella F., 197, 221
Naccarelli G., 221
Neri G., 309
Nipote C., 391
Nodari S., 205
Occhetta E., 231, 317
Olivari Z., 129
Oseroff O., 63
Ovsyshcher I.E, 325
Padeletti L., 43
Pahlm O., 347
Palanca V., 75, 245
Parspour A., 355
Patanè L., 395
Pedretti R.F.E., 179
Pedretti S., 167
Pedrinazzi C., 93
Perrone-Filardi P., 425
Poezevara Y., 119
Pozzolini A., 263
Proclemer A., 231
Puig J.G., 441
Quesada A., 75, 245
Raciti G., 231
Raimondo R., 179
Retyk E., 63
Riganti C., 197
Robert G., 125
Roda J., 75, 245
Rodio G., 57
Ruiz G.A., 279
Russo G., 17
Sacrez J., 125
Salerno M., 179
Santini M., 197
Santomauro M., 197
Santoro F., 179
Sarzi Braga S., 179
Seresini G., 205
Shah D., 41

Soldati E., 303
Strandberg A., 441
Strano G., 375
Sulosaari S., 441
Sun L., 221
Sunthorn H., 41
Taborsky M., 293
Talerico A., 137
Tentori M.C., 279
Timineri S., 87
Tuccillo B., 117
Turrini P., 215
Vaccari D., 309
Valle A., 245
Vaninetti R., 179
Vassallo E., 425
Vergara G., 191
Verlato R., 215
Verma A., 49
Vincenti A., 167
Wang A., 221
Wichterle D., 23
Zamprogno R., 309
Zito C., 391
Zucchelli G., 303

Anti-arrhythmic Drugs in Atrial Fibrillation: Historical Perspectives and New Developments

Berndt Lüderitz

Introduction

The treatment of atrial fibrillation (AF) remains challenging in everyday practice. Even with the introduction of catheter ablation, decision-making about the type of therapy has become more complex. The recently published guidelines of the American College of Cardiology, American Heart Association, and the European Society of Cardiology clearly show the therapeutic approaches for the different types of AF (Fig. 1).

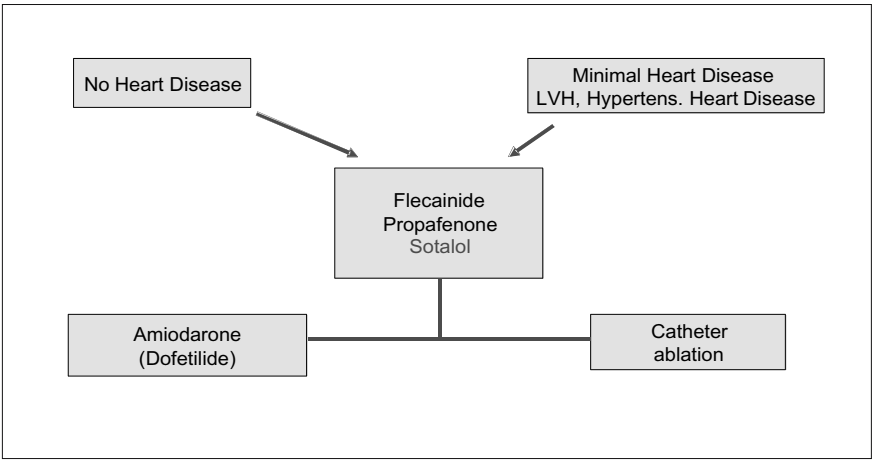


Fig. 1. From guidelines to individual treatment and maintenance of sinus rhythm. Adapted from [1]. *LVH*, Left ventricular hypertrophy

Department of Medicine - Cardiology, University of Bonn, Bonn, Germany

The fear of thromboembolism in a patient compels the physician to restore sinus rhythm and obtain perfect anticoagulation. Factors affecting the overall management strategy of AF are the type and severity of AF, the corresponding symptoms, associated cardiovascular disease, patient's age, associated medical conditions, and treatment options.

AF is the most frequently experienced cardiac arrhythmia, affecting an estimated 2.2 million people in the USA, and approximately 6 million in Europe. Approximately 1.2 million patients suffer from paroxysmal AF, and about 1 million from persistent AF. The conversion rate from paroxysmal AF to persistent AF is estimated to be 30% [2]. The prevalence of AF increases with age [3], ranging from less than 1% at 50–59 years to nearly 9% at 80–89 years [4]. In addition to palpitations, patients with AF have an increased risk of stroke and can develop decreased exercise tolerance and left ventricular dysfunction [5]. All of these problems may be reversed by the restoration and maintenance of sinus rhythm. Thus, the treatment of AF is warranted in the hope of eliminating symptoms, preventing complications, and possibly decreasing the excess mortality associated with this arrhythmia [6]. The primary intervention for maintaining sinus rhythm after restoration is use of anti-arrhythmic drugs (Tables 1, 2).

However, many of the existing drugs have only limited efficacy and are associated with considerable undesirable adverse effects. Current treatment is therefore still suboptimal [7].

The features of an ideal anti-arrhythmic drug for the treatment of AF are: namely effective suppression of symptoms, low incidence of pro-arrhythmia, low incidence of side effects and drug interactions, good cardiac safety, effective rhythm control, ease to use, simple dosing regimen, ability to initiate in an outpatient setting, and cost-effectiveness.

Table 1. Introduction of antiarrhythmic drugs: chronological overview

1918	Quinidine	1964	Propafenone
1936	Procainamide	1982	Flecainide
1948	Lidocaine	1982	Amiodarone
1950	Phenytoin	1994	Adenosine
1954	Disopyramide	1995	Ibutilide
1958	Ajmaline	1999	Dofetilide
1962	Beta receptor blocking agents		

Table 2. New class III antiarrhythmic drugs

Drug	Effect	β-Blockade	Application	Indication
Ibutilide	Blocks I_{Kr}	-	i.v.	Atrial fibrillation, atrial flutter
Azimilide	Blocks I_{Kr} and I_{Ks}	-	i.v. and p.o.	Atrial fibrillation, atrial flutter, SVT, VT/VF, SCD-prophylaxis
Tedisamil	Blocks I and I_{To}	(+)	i.v. and p.o.	Atrial fibrillation
Ersentilide	Blocks I_{Kr} and β_1	+	i.v. and p.o.	Atrial fibrillation atrial flutter, SVT, VT/VF, SCD-prophylaxis
Dofetilide	Blocks I_{Kr}	-	i.v. and p.o.	Atrial fibrillation, atrial flutter, SVT
Trecetilide	Similar to Ibutilide	-	i.v. and p.o.	Atrial fibrillation, atrial flutter
Dronedarone	Multiple effects like amiodarone	-	i.v. and p.o.	Atrial fibrillation, atrial flutter, VT, VT/VF, SCD-prophylaxis

SVT, Supraventricular tachycardia; *VT*, ventricular tachycardia; *VF*, ventricular fibrillation; *SCD*, sudden cardiac death

Concerning pharmacological rate control, we recommend digitalis as the first choice in patients with congestive heart failure; amiodarone can also be considered. Beta-receptor blocking agents, e.g., Sotalol, provide first-line treatment in ischemic heart disease. Class 1c drugs (propafenone, flecainide) are very effective for rate control; however, they are contraindicated in patients with structural heart disease. Calcium channel antagonists (verapamil, diltiazem) are first-line drugs in active patients and also in those with congestive heart disease or lung disease. Amiodarone is the drug of choice in patients with compromised left ventricular function. The pharmaceutical management strategy or decision tree in paroxysmal AF (PAF) is shown in Fig 2. If there is a first episode, observation is appropriate. If frequent episodes of PAF are observed, asymptomatic PAF requires rate control. In symptomatic PAF and structural heart disease, amiodarone is drug of first choice. In those patients without structural heart disease, 1c anti-arrhythmic drugs, such as propafenone or flecainide, are particularly suitable.

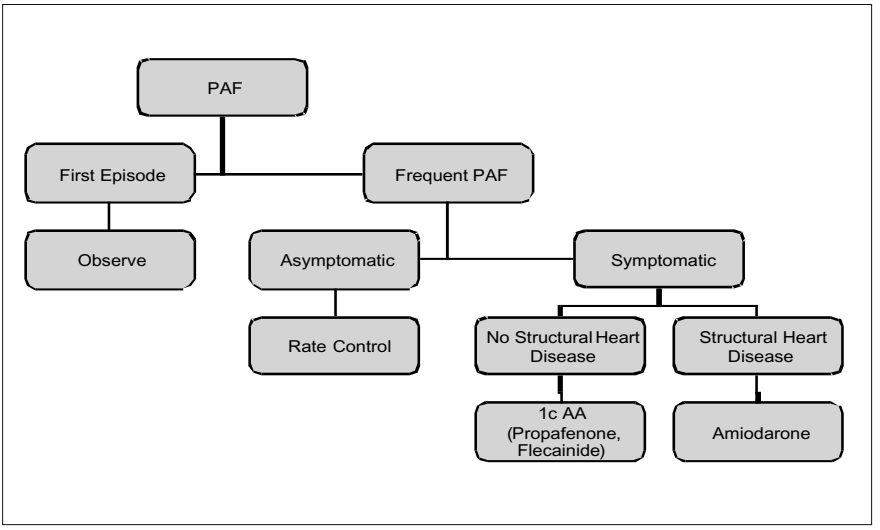


Fig. 2. Paroxysmal atrial fibrillation (*PAF*): pharmacological management

Rhythm Control or Rate Control and Anticoagulation

Clinical categorization relating to the quality of life of patients who present with AF is a major determinant of the most appropriate strategy for rhythm management. For patients with recurrent AF that has not become permanent, the two available strategies are: (1) rhythm control and anticoagulation, and (2) rate control and anticoagulation. Our knowledge about the efficacy and safety of various therapeutic strategies is insufficient, especially with respect to the direct comparison of re-establishment of sinus rhythm by drugs with rate control [8].

Which patients with AF will benefit from rhythm control? Patients with intolerable symptoms due to AF; those with AF lasting longer than 1 year; young, physically active individuals; patients suffering from paroxysmal AF; those with good response to therapy; patients with significant left ventricular (LV) hypertrophy and LV dysfunction; those with left atrial diameter > 50 mm; and patients with contraindications to anticoagulation. In concise terms, in a given patient, normal sinus rhythm is an appropriate goal if the advantages of treatment (pharmacologically or electrically) outweigh the disadvantages.

In AF patients, restoration and maintenance of sinus rhythm are the primary therapeutic goals. Once sinus rhythm is maintained, physiological rate control is restored and LV ejection fractions, cardiac output, and exercise

capacity are increased. This improved cardiovascular performance enhances the patient's ability to perform the functions of normal daily life. Effective treatment of AF is based on these objective criteria, but subjective criteria such as quality of life are also important. Rigorous yet practical approaches are needed to enable a comprehensive understanding of quality of life in patients with AF [9]. For example, it has been shown that pharmaceutical treatment can enhance quality of life in patients with AF [1]. The data are shown in Table 3, in which the components of a health-related quality of life (SF-36 categories) were assigned scores. Higher score indicates higher quality of life.

Table 3. Medical Therapy Estimates by scoring points of health-related quality of life (SF-36 categories)

SF-36 category	Medical therapy		
	Baseline	Follow-up	*p*
Physical function	71 ± 26	81 ± 24	< 0.05
Physical role	54 ± 41	65 ± 38	< 0.05
Bodily pain	67 ± 17	63 ± 245	ns
General health	68 ± 19	69 ± 21	ns
Vitality	50 ± 16	55 ± 21	ns
Social function	68 ± 24	78 ± 26	< 0.01
Emotional role	74 ± 40	78 ± 36	ns
Mental health	69 ± 15	73 ± 19	< 0.05

ns, Not significant

Discussion

The pharmacological treatment of AF continues to challenge physicians in everyday practice. Despite the introduction of catheter ablation, the choice of the most appropriate therapy has become increasingly complex. Recently published guidelines delineate the therapeutic approaches for different types of AF. The need to avoid thromboembolism in an AF patient underlines the physician's need to restore sinus rhythm and perform a perfect anticoagulation.

The history of anti-arrhythmic therapy of AF is long and fascinating. Initially, not only the anatomy and physiology of the heart but also an analysis of the pulse, which indicates the electric and hemodynamic activity of the

heart, were important considerations. The analysis of the (peripheral) pulse as a mechanical expression of heart activity goes back several millennia. Digitalis, probably the oldest "anti-arrhythmic" agent, was discovered as a cardiac active substance in the 16th century, by Leonhart Fuchs, and clinically introduced by William Withering, in Birmingham, England. Modern-day anti-arrhythmic drugs came into use at a much later stage than the cardiac glycosides. Quinidine, an optical isomer of quinine, became available as anti-arrhythmic agent in 1918. Today, the most widely used anti-arrhythmic drugs were developed in the 1960s and 1970s (e.g., disopyramide, beta-receptor blocking agents, propafenone, flecainide, amiodarone, adenosine, and ibutilide). Candidate drugs for the treatment of AF include azimilide, dofetilide, dronedarone, tedisamil, trecetilide, and ambasilide. Further non-pharmaceutical developments consist of radiofrequency ablation, atrioventricular defibrillators, and advanced anti-arrhythmic surgery. Advances in the development of pharmacological and electrical tools as well as alternative strategies, including gene and cell therapy, will continue as rapidly as before, thus equipping clinicians with a broad palette of possibilities with which to care for their patients.

References

1. Fuster V, Ryden LE, Cannom DS et al (2006) 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 114:700–752
2. Feinberg WM, Blackshear JL, Laupacis A et al (1995) Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. Arch Intern Med 155:469–473
3. Benjamin EJ, Levy D, Vaziri SM et al (1994) Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart Study. JAMA 271:840–844
4. Kannel WB, Wolf PA, Benjamin EJ et al (1998) Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 82:2N-9N
5. Krahn AD, Manfreda J, Tate RB et al (1995) The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study. Am J Cardiol 98:476–484
6. Benjamin EJ, Wolf PA, D'Agostino RB et al (1998) Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation 98:946–952
7. Lüderitz B, Jung W (2000) Quality of life in patients with atrial fibrillation. Arch Intern Med 160:1749–1757

8. Wyse DG (2000) The AFFIRM trial: main trial and substudies – what can we expect? J Interv Card Electrophysiol 4:171–176
9. Jung W, Lüderitz B (1998) Quality of life in patients with atrial fibrillation. J Cardiovasc Electrophysiol 9(Suppl 8):S177-S186

Lone Atrial Fibrillation: Prophylactic Anti-arrhythmic Treatment

Gianluca Botto, Mario Luzi, Giovanni Russo, Barbara Mariconti

Introduction

Atrial fibrillation is a common arrhythmia and the cause of substantial morbidity [1, 2]. Management strategies for its control are far from satisfactory [3]. Most importantly, whether by restoring sinus rhythm or by controlling ventricular rate, arrhythmic strategies bring with them a proarrhythmic or arrhythmogenic risk [4]. In such cases, the basic arrhythmia may be aggravated or new and more devastating arrhythmia may be produced.

The question of long-term anti-arrhythmic medication for the treatment of lone atrial fibrillation often arises. In individuals with frequent recurrences of rapid and symptomatic atrial fibrillation, prophylactic therapy is clearly indicated. In those with less frequent or asymptomatic recurrences with controlled heart rate, the major concern becomes the risk of proarrhythmic events [2]. The risk of therapy must be balanced by the known adverse effect of anti-arrhythmic medication and the benefit from its utilization.

Where to initiate anti-arrhythmic therapy is another important issue. There are two major reasons to initiate drug therapy in-hospital: to observe the effects of anti-arrhythmic agents on the arrhythmia being treated, and to permit surveillance for adverse reaction to the drugs. However, the actual risk of proarrhythmia in patients undergoing treatment for atrial fibrillation is not yet well-defined [2].

Department of Cardiology, Sant'Anna Hospital, Como, Italy

Defining the Risk of Proarrhythmic Events

Most studies of ventricular proarrhythmia include patients undergoing treatment for ventricular tachyarrhythmias [5], not supraventricular tachycardia. While most patients with ventricular arrhythmias have underlying structural heart disease, this is not the case for many patients with supraventricular tachycardia. In a review of the literature of ventricular proarrhythmia in patients treated with anti-arrhythmic drugs for supraventricular tachycardia, almost all cases occurred in patients with heart disease [6].

Thus, it is important to define more precisely which patients with supraventricular tachycardia, undergoing treatment for maintaining sinus rhythm, are at risk for proarrhythmia (particularly, ventricular proarrhythmia), and possibly sudden death.

Many of the studies assessing the proarrhythmic risk of anti-arrhythmic drugs are related to the prophylactic indication of a specific drug [7]. The assumption that proarrhythmia will occur during the initial day of therapy, when it can be detected while the patient is still under surveillance, has not been well-documented for different types of anti-arrhythmic agents. Nonetheless, in-hospital initiation of drug therapy would be unwarranted if the time from initiation of treatment to proarrhythmic event took several weeks or longer.

Types of Proarrhythmia

Proarrhythmia occurs with anti-arrhythmic drug therapy when the drug has an adverse interaction with one or more types of cardiac tissue. The various forms of proarrhythmia are reported in Table 1.

Ventricular proarrhythmia is far from being a rare event. Drugs that prolong repolarization can cause torsade de pointes, and drug-associated ven-

Table 1. Various forms of proarrhythmic events

Sinus node dysfunction with marked bradycardia
Increase in the frequency or duration of atrial arrhythmias
Slowing atrial tachycardia rate during drug therapy, facilitating rapid atrioventricular conduction
Atrioventricular nodal or His-Purkinje block
Ventricular proarrhythmia

tricular fibrillation has been reported with most anti-arrhythmic agents, regardless of their anti-arrhythmic action [8].

However, the type of ventricular proarrhythmia depends to some degree on the anti-arrhythmic drug used. In a review of 51 papers in the literature, quinidine was most commonly implicated, but this may be due in part to the sole use of quinidine for many years [7].

Torsade de pointes is the most frequently reported proarrhythmic event, probably for the above-mentioned reason. However, it has also been observed during chronic treatment with drugs that block potassium channels, such as sotalol [9], or the relatively new class III anti-arrhythmic drugs [10]. Ventricular hypertrophy appears to predispose to torsade de pointes, favoring the development of early after-depolarization. For this reason, the risk for ventricular arrhythmias is increased in patients with left ventricular hypertrophy [11].

Torsade de pointes may occur as an idiosyncratic reaction at low, even subtherapeutic plasma concentrations of drugs like quinidine [12]. For other drugs, such as sotalol, the condition is related to drug dose, with an increased incidence at doses > 320 mg per day [9].

There is little information regarding ventricular arrhythmia with class IC drugs. Heart disease is present in most patients with ventricular proarrhythmia who are on flecainide treatment, and the proarrhythmic effect was reported to occur most often during exercise [6].

The most common proarrhythmic effect during treatment with class IC drugs is atrial flutter due to regularization of atrial waves together with a slowing of tachycardia atrial rate. This facilitates atrioventricular nodal conduction, leading to a more rapid ventricular rate. An example is conversion of atrial fibrillation to a relatively slow atrial flutter with the possibility of 1:1 atrioventricular conduction, particularly during adrenergic drive (e.g., during effort). This phenomenon is more frequent with flecainide than with propafenone [13].

More than half of the proarrhythmic events that occur with drugs such as quinidine, procainamide, or dysopiramide happen within the first 3 days of therapy [6]. However, when the time from onset of therapy to the proarrhythmic event was documented for quinidine, the duration was within a few weeks of treatment [6]. Torsade de pointes was observed to occur during the first 3 days of treatment with sotalol, dofetilide, or ibutilide [10]. Atrial proarrhythmic events occurring during acute administration of class IC drugs to convert recent-onset atrial fibrillation were observed within 6 h from the onset of therapy [13]. Proarrhythmia with amiodarone often occurs during the first week of drug therapy, during the loading phase [14].

What Is the True Incidence of Proarrhythmia in Atrial Fibrillation?

Recently, a large prospective study comparing treatment strategies (AFFIRM) designed to achieve either rate or rhythm control in patients with atrial fibrillation demonstrated that patients randomized to the rhythm-control arm did not have lower all-cause mortality than those randomized to the rate-control approach. There was a trend toward a higher death rate in the rhythm-control arm [3]. In this study, the percentage of patients with lone atrial fibrillation was fairly low (16%). A few years later, the AFFIRM investigators published a further study describing the cause-specific modes of death in the main study with respect to treatment approach [15]. It was concluded that the excess mortality in the rhythm-control arm may have been associated with an increased non-cardiovascular (pulmonary and cancer) death rate instead of the more-expected increase in proarrhythmia-related deaths. In the AFFIRM study, there were 3,030 exposures to anti-arrhythmic drugs in 2,023 patients; in a 6-year follow-up 96 (3.16%) arrhythmic adverse events were detected, with an annual incidence of 0.53% per year. Furthermore, 12 episodes of torsade de pointes occurred, all of them related to the use of class III drugs and/or to coexistent favorable factors (hypokalemia, interaction with other drugs). The authors thus concluded that the overall risk of adverse arrhythmic events upon exposure to anti-arrhythmic drugs was reasonably low in the AFFIRM study [16].

Which Drugs Maintain Sinus Rhythm in Lone Atrial Fibrillation?

Very recently, the Italian Association of Arrhythmia and Cardiac Pacing (AIAC) published its national guidelines on the treatment of patients with atrial fibrillation, with particular attention given to patients with lone atrial fibrillation [17].

In patients without structural heart disease there is a trend to prescribe class 1C anti-arrhythmic drugs (propafenone or flecainide) or sotalol. These agents appear to have similar efficacies with good long-term tolerance [18]. Amiodarone and quinidine are second-choice drugs in the treatment of this subset of patients.

Unfortunately, restoration and maintenance of sinus rhythm are sometimes not possible or only attainable with high-dose medications. In these circumstances radiofrequency ablation is becoming increasingly popular. The use of radiofrequency energy is particularly safe and well-tolerated in patients without structural heart disease and could become an alternative to anti-arrhythmic drug administration [19].

Out-of-Hospital Administration of Anti-arrhythmic Drugs

Patients are hospitalized to receive anti-arrhythmic drug therapy for safety reasons, typically to prevent proarrhythmic events. Thus, whenever in doubt, in-patient initiation of therapy is acceptable. However, the low frequency of proarrhythmia suggests that in-hospital initiation of therapy may not be cost-effective [20]. Instead, there are data to support out-patient anti-arrhythmic drug treatment in patients who have no or minimal ventricular dysfunction.

In conclusion, the following strategies are recommended:

1. The first episode of atrial fibrillation or supraventricular tachycardia must be treated in-hospital to observe the effects of any anti-arrhythmic agents on the arrhythmia being treated, and to permit surveillance for adverse reactions to the drug.
2. Patients must be treated in-hospital, when quinidine, dysopiramide, procainamide, sotalol, or new class III agents are prescribed. Observation should be extended for at least 48–72 h after initiation of the drug.
3. Amiodarone loading can be initiated out-of-hospital, even in patients with structural heart disease; monitoring of multiple possible adverse events related to drug administration is mandatory in the first 2 weeks of drug loading.
4. Initiation of therapy with flecainide or propafenone should be discouraged in patients with structural heart disease, particularly when ischemic heart disease or ventricular dysfunction is present.
5. Patients without structural heart disease, sinus node dysfunction, or atrioventricular conduction abnormalities who have a normal basal QTc interval do not usually need to be hospitalized when treated with class IC drugs.

References

1. Feinberg WM, Blackshear JL, Laupacis A et al (1995) Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications. Arch Intern Med 155:469–574
2. Fuster V, Ryden LE, Cannom DS et al (2006) ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation. Circulation 114: e257-e354
3. Wyse DG, Waldo AL, DiMarco JP et al (2002) A comparison of rate control and rhythm control in patients with atrial fibrillation. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. N Engl J Med 347:1825–1833
4. Falk RH (1992) Proarrhythmia in patients treated for atrial fibrillation. Ann Int Med 117:141–150

5. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators (1989) Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. N Engl J Med 321:406–412
6. Prystowsky EN (1996) Proarrhythmia during treatment for supraventricular tachycardia: paradoxical risk of sinus rhythm for sudden death. Am J Cardiol 78:35–41
7. Coplen SE, Antman EM, Berlin JA et al (1990) Efficacy and safety of quinidine therapy for maintenance of sinus rhythm after cardioversion: a meta analysis of randomized, controlled trial. Circulation 82:1106–1116
8. Minardo JD, Heger JJ, Miles WE et al (1988) Clinical characteristics of patients with ventricular fibrillation during antiarrhythmic drug therapy. N Engl J Med 319:257–262
9. Capucci A, Villani GQ, Aschieri D et al (1998) Effects of class III drugs on atrial fibrillation. J Cardiovasc Electrophysiol 9:109–120
10. Camm AJ, Yap YG (1999) What should we expect from the next generation of antiarrhythmic drugs ? J Cardiovasc Electrophysiol 10:307–317
11. Levy D, Anderson KM, Savage DD et al (1987) Risk of ventricular arrhyhtmia in left ventricular hypertrophy: the Framingham Heart Study. Am J Cardiol 60:560–565
12. Roden DM (1994) Risk and benefit of antiarrhyhtmic therapy. N Engl J Med 331:785–791
13. Botto GL, Bonini W, Broffoni T et al (1994) Regular ventricular rhythms before conversion of recent onset atrial fibrillation to sinus rhythm. Pacing Clin Electrophysiol 11:2114–2117
14. Capucci A, Villani GQ, Aschieri D et al (2000) Oral amiodarone increase the efficacy of DC-cardioversion in restoration of sinus rhythm in patients with chronic atrial fibrillation. Eur Heart J 21:66–73
15. Steinberg JS, Sadaniantz A, Kron J et al (2004) Analysis of cause specific mortality in the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) study. Circulation 109:1973–1980
16. Kaufman ES, Zimmermann PA, Wang T et al (2004) Risk of proarrhythmic events in the atrial fibrillation follow-up investigation of rhythm management (AFFIRM) study. J Am Coll Cardiol 44:1276–1282
17. Disertori M, Alboni P, Botto GL et al (2006) Linee guida AIAC 2006 sul trattamento della fibrillazione atriale. Giornale Italiano di Aritmologia e Cardiostimolazione 9:1–71
18. Reimold SC, Cantrillon CO, Friedman PL et al (1993) Propafenone versus sotalol in suppression of recurrent symptomatic atrial fibrillation. Am J Cardiol 71:558–563
19. Cappato R, Calkins H, Chen SA et al (2005) Worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation 111:1100–1105
20. Naccarelli GV, Dell'Orfano JT, Wolbrette DL et al (2000) Cost-effective management of acute atrial fibrillation: role of rate control, spontaneous conversion, medical and direct current cardioversion, transesophageal echocardiography, and anti embolic therapy. Am J Cardiol 85:36D-45D

"Pill-in-the-Pocket" Approach

Paolo Alboni

In the clinical setting, some patients with recurrent atrial fibrillation (AF) present with episodes that are not frequent (< 1 per month) and are hemodynamically well-tolerated, but which are long enough to require emergency room (ER) intervention or hospitalization. These patients need treatment, but long-term oral prophylaxis or catheter ablation may not be the most appropriate first-line therapy. Rather, in this group of patients the "pill-in-the-pocket" approach, consisting of a single-dose oral ingestion of an anti-arrhythmic agent at the time and place of palpitation onset, may offer a more appropriate treatment strategy. The pill-in-the-pocket has already been investigated in studies carried out *in hospital*, in patients with recent-onset AF. The oral drugs that have been used to convert recent-onset AF to sinus rhythm are class IA, class IC, and class III anti-arrhythmic agents [1–7]. The class IC agents flecainide and propafenone have the advantage of being conveniently administered in a single oral dose that acts rapidly and causes minimal side effects [1, 6, 8–16]. The efficacy of a single oral loading dose of flecainide and propafenone in converting recent-onset AF to sinus rhythm has been documented by several placebo-controlled trials [1, 6, 8, 9, 11, 13, 16]. The two drugs showed similar efficacy, and their success rate varied from 58 to 95% [1, 6, 8–13], depending on the duration of AF and the observation period after drug administration. In all controlled studies, a low incidence of adverse effects has been reported [1–6, 8–13, 15, 16], the most of which is the appearance of a transient atrial flutter with high ventricular rate owing to 1:1 atrioventricular (AV) conduction (in about 1% of patients).

Division of Cardiology and Arrhythmologic Center, Ospedale Civile, Cento (FE), Italy

Very recently, out-of-hospital treatment with the "pill-in-the-pocket" approach was investigated in an Italian multicenter study [17]. Inclusion criteria were as follows: (1) patients between the ages of 18 and 75 years requiring ER intervention for recent onset (< 48 h) AF; (2) a history of palpitation with abrupt onset but hemodynamically well-tolerated (absence of symptoms such as dyspnea, presyncope, or syncope); (3) number of episodes in the last year < 1 per month; (4) absence of cardiologic symptoms apart from the arrhythmic episodes. Patients with contraindications to class IC agents were excluded. The patients could be treated either in the ER or in the cardiology ward. For AF conversion, oral propafenone and flecainide were administered in a single dose according to the weight of the patient: flecainide 300 mg for patients weighing ≥ 70 kg, or 200 mg otherwise; propafenone, 600 mg for patients weighing ≥ 70 kg, or 450 mg otherwise. Treatment was considered "successful" if the conversion time to sinus rhythm was < 6 h after drug administration, without severe side effects.

An in-hospital oral loading dose of flecainide and propafenone was administered to 268 patients with recent-onset AF. Of these, 58 were excluded from the out-of-hospital treatment: in three (1%), findings included in the exclusion criteria emerged during echocardiographic recording, in 41 (14%) the drug was not effective in restoring sinus rhythm within 6 h, and in 14 (6%) the drug induced side effects (transient hypotension in four, atrial flutter in seven, including one with 1:1 AV conduction, and slightly symptomatic bradycardia in three). The remaining 210 patients (age 59 ± 11 years) were discharged on flecainide or propafenone for "pill-in-the-pocket" treatment of recurrent AF. Of these, 118 had no signs of heart disease and the remaining 92 (43%) had mild heart disease. The mean follow-up was 15 ± 5 months; four patients were lost just after enrollment. Of the remaining 206 patients, 41 (20%) did not experience any arrhythmic recurrences during the follow-up period and 165 reported 618 episodes of palpitation with abrupt onset, 569 of which were treated with flecainide (64 patients) or propafenone (101 patients). The drug was effective in 534 out of 569 arrhythmic episodes (94%). Similar results on the efficacy of class IC drugs were recently reported by Capucci et al. [16], who investigated in hospital the reproducibility of efficacy of an oral loading dose of propafenone in restoring sinus rhythm in patients with recurrent AF. Efficacy was evaluated by electrocardiographic monitoring and was reproducible in 93% of the patients. In the Italian multicenter study, time to symptom resolution after drug ingestion was 113 ± 84 min (median 98). Sixteen arrhythmic episodes were interrupted in a time > 6 h without the patients contacting the ER. Twenty-six episodes (5%) required ER intervention, ten of which (2%) resulted in hospitalization. Out of the 618

episodes, 49 were not treated, mainly because of drug unavailability and five (10%) of these required ER intervention. Therefore, during the follow-up period, there were 31 (5%) ER contacts among the treated and untreated arrhythmic episodes, ten of which led to hospitalization. Out of the 31 calls for ER intervention, 19 were due to AF lasting > 6 h, one to acceleration of heart rate after drug ingestion (atrial flutter with 1:1 AV conduction), and 11 to anxiety (request for ER intervention although palpitation had ceased).

During follow-up, the number of calls for ER intervention per month was significantly lower than in the year before the target episode (4.9 vs. 45.6, $p < 0.001$). Even the number of hospitalizations per month during the follow-up period was significantly lower (1.6 vs. 15, $p < 0.001$). Adverse effects during one or more arrhythmic episodes were reported in 12 out of the 165 patients (7%) who used the drug during follow-up. One (0.7%) felt a marked acceleration of heart rate after drug ingestion and contacted the ER; electrocardiogram showed atrial flutter with 1:1 AV conduction. This implies that successful in-hospital treatment does not completely prevent the appearance of atrial flutter at a high rate during follow-up. The remaining 11 patients reported non-cardiac side effects, such as nausea, asthenia, or vertigo.

These results show that out-of-hospital treatment of recurrent AF with the "pill-in-the-pocket" approach is feasible and safe, in view of the high rate of patient compliance and the very low incidence of adverse effects. Data from the Italian study show that the "pill-in-the-pocket" strategy with flecainide or propafenone is effective in treating over 90% of arrhythmic episodes, after patient selection on clinical grounds and on the basis of the results of in-hospital treatment. Episodic treatment minimizes the need for ER and hospital admission during the acute event. It is noteworthy that about one-third of ER contacts were due to anxiety. Therefore, psychological management of these patients (particularly reassurance) may further reduce calls for ER intervention. The marked reduction in ER and hospital admissions, in addition to the avoidance of prophylactic treatment, will help to reduce the economic impact of AF, although in a rather small group of patients with this tachyarrhythmia. The safety of this approach without previous evaluation of in-hospital treatment remains to be investigated; therefore, at present, oral flecainide or propafenone must be tested once in hospital before it can be prescribed for the out-of-hospital treatment.

Contraindications to class IC drugs must always be considered. If the patient is treated over the long-term with anti-arrhythmic drugs, the loading dose of flecainide or propafenone cannot be used, but if the patient appears suitable for "pill-in-the-pocket treatment", long-term therapy can be suspended and the loading dose administered during the next AF relapse.

Atrioventricular nodal blockers (beta-blockers, verapamil, diltiazem) for the treatment of hypertension or other diseases can be chronically administered.

Before discharge, patients should receive the following recommendations: They must take the drug 5–10 min after any subsequent onset of typical palpitation; after ingestion of the drug, the patient should rest (supine or sitting position) until the palpitation has stopped or for at least 4 h have passed; the patient must contact the ER if palpitation has not ceased 8 h after ingestion of the drug, if he/she has symptoms that have not occurred during previous arrhythmic episodes (e.g., dyspnea, presyncope, or syncope) or if he/she senses a marked increase in heart rate after ingestion of the drug; the patient must not take more than one oral dose during a 24-h period; the patient must not self-reduce the prescribed dosage of the drug. The practical management of patients suitable for out-of-hospital treatment with the "pill-in-the-pocket" approach is summarized in Fig. 1. In the recent ACC/AHA/ESC guidelines for the management of patients with AF, this form of treatment is a class IIA recommendation [18].

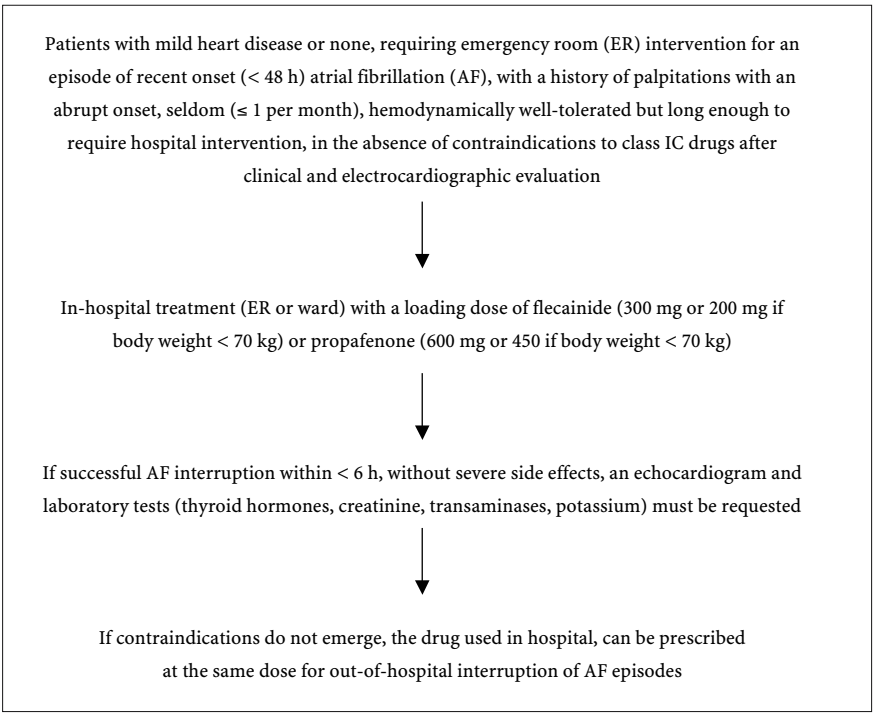


Fig. 1. Practical management of patients suitable for the "pill-in-the-pocket" approach to treating atrial fibrillation

References

1. Villani GQ, Rosi A, Piepoli M et al (1990) The efficacy of oral treatment with flecainide for paroxysmal atrial fibrillation: correlation with plasma concentration. G Ital Cardiol 20:564–568
2. Capucci A, Lenzi T, Boriani G et al (1992) Effectiveness of loading oral flecainide for converting recent-onset atrial fibrillation to sinus rhythm in patients without organic heart disease or with only systemic hypertension. Am J Cardiol 70:69–72
3. Botto GL, Bonini W, Broffoni T et al (1994) Regular ventricular rhythms before conversion of recent onset atrial fibrillation to sinus rhythm. Pacing Clin Electrophysiol 17:2114–2117
4. Capucci A, Boriani G, Botto GL et al (1994) Conversion of recent onset atrial fibrillation by a single oral loading dose of propafenone or flecainide. Am J Cardiol 74:503–505
5. Capucci A, Boriani G, Rubino I et al (1994) A controlled study on oral propafenone versus digoxin plus quinidine in converting recent-onset atrial fibrillation to sinus rhythm. Int J Cardiol 43:305–313
6. Boriani G, Capucci A, Lenzi T et al (1995) Propafenone for conversion of recent-onset atrial fibrillation; a controlled comparison between oral loading dose and intravenous administration. Chest 108:355–358
7. Halinen MO, Huttunen M, Paakkinen S et al (1995) Comparison of sotalol with digoxin-quinidine for conversion of acute atrial fibrillation to sinus rhythm (the sotalol-digoxin-quinidine trial). Am J Cardiol 76:495–498
8. Botto GL, Bonini W, Broffoni T et al (1996) Conversion of recent onset atrial fibrillation with single oral dose of propafenone: is in-hospital admission absolutely necessary? Pacing Clin Electrophysiol 19:1939–1943
9. Azpitarte J, Alvarez M, Baun O et al (1997) Value of single oral loading dose of propafenone in converting recent onset atrial fibrillation: results of a randomized, double-blind, controlled study. Eur Heart J 18:1649–1654
10. Boriani G, Biffi M, Capucci A et al (1997) Oral propafenone to convert recent-onset atrial fibrillation in patients with and without underlying heart disease: a randomized, controlled trial. Ann Intern Med 126:621–625
11. Botto GL, Capucci A, Bonini W et al (1997) Conversion of recent onset atrial fibrillation to sinus rhythm using a single loading oral dose of propafenone: comparison of two regimens. Int J Cardiol 58:55–61
12. Botto GL, Bonini W, Broffoni T et al (1998) A randomized, crossover, controlled comparison of oral loading versus intravenous infusion of propafenone in recent-onset atrial fibrillation. Pacing Clin Electrophysiol 21:240–244
13. Blanc JJ, Voinov C, Maarek M for the PARSIFAL Study Group (1999) Comparison of oral loading dose of propafenone and amiodarone for converting recent-onset atrial fibrillation. Am J Cardiol 84:1029–1032
14. Kishikawa T, Maruyoma T, Kaji Y et al (1999) Effects of oral disopyramide on acute-onset atrial fibrillation with concurrent monitoring of serum drug concentration. Int J Cardiol 68:57–62
15. Khan IA (2001) Single oral loading dose of propafenone for pharmacological cardioversion of recent onset atrial fibrillation. J Am Coll Cardiol 37:542–547
16. Capucci A, Villani GQ, Piepoli MF (2003) Reproducible efficacy of loading oral propafenone in restoring sinus rhythm in patients with paroxysmal atrial fibrillation. Am J Cardiol 92:1345–1347

17. Alboni P, Botto GL, Baldi N et al (2004) Outpatient treatment of recent-onset atrial fibrillation with the "pill-in-the-pocket" approach. N Engl J Med 351:2384–2391
18. ACC/AHA/ESC (2006) Guidelines for the management of patients with atrial fibrillation – Executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). J Am Coll Cardiol 48:854–906

Clinical Profile, Electrophysiological Characteristics, and Outcome after Radiofrequency Catheter Ablation of Atypical Atrial Flutter

Golmehr Ashrafpoor, Amir-Ali Fassa, Henri Sunthorn, Haran Burri, Pascale Gentil-Baron, Dipen Shah

Although radiofrequency (RF) catheter ablation is well accepted as the treatment of choice for typical atrial flutter, there is limited experience with its use in the treatment of atypical atrial flutter (AAF).

A study at our institution consisted of patients who underwent RF catheter ablation for an AAF pattern on the electrocardiogram between 2002 and 2006. Conventional and electroanatomic mapping were performed in most cases (90%). The ablation strategy involved delineation of the individual circuit, followed by ablation of the narrowest isthmus(es). Procedural success was defined as arrhythmia termination during RF delivery.

The 58 patients (67% males, mean age 57 ± 14 years) included in the study underwent 70 RF catheter ablation procedures (12 patients underwent a single repeat intervention) for 109 AAF types. A high proportion of patients had a history of atrial fibrillation (57%), stroke (16%), cardiac surgery (47%), previous RF catheter ablation (57%), and pulmonary-vein isolation (41%). Mean cycle length was 282 ± 58 ms. The reentrant circuit was located in the left atrium in 43 patients (74%) and in the right atrium in 13 patients (22%). In two patients (3%), a circuit dependent on both atria was identified. A pseudo-AAF (cavotricuspid isthmus dependent) was found in four patients (7%). The mean number of RF lesions was 28 ± 25. Fluoroscopic and procedure duration times were, respectively, 45 ± 19 and 185 ± 67 min. Success was achieved in 80% of the procedures, and in 79% of the patients after 1.2 procedures. Complications occurred during four procedures (6%): regressive stroke (1%), heart block requiring pacemaker implantation (1%), and local bleeding requiring intervention (1%). There were no fatalities.

Geneva University Hospitals, Geneva, Switzerland

The results indicated that patients with AAF usually have a complex substrate, characterized by significant heart disease, previous cardiac surgery, or catheter ablation. This results in a wide and variable range of reentrant circuits. Despite this complexity, an individualized strategy of catheter ablation for AAF is a safe and effective treatment in a majority of patients.

Suggested Reading

1. Shah DC, Jais P, Haissaguerre M et al (2000) Dual loop intra-atrial reentry in man. Circulation 101 (6):631–639
2. Jais P, Shah DC, Haissaguerre M et al (2000) Mapping and ablation of left atrial flutters. Circulation 101(25):2928–2934
3. Shah DC, Sunthorn H, Burri H et al (2006) Narrow, slow-conducting isthmus dependent reentry developing after ablation for atrial fibrillation: ECG characterisation and elimination by focal ablation. J Cardiovasc Electrophysiol 17:508–515

Complications of Atrial Fibrillation Ablation: How To Prevent Them

Giuseppe De Martino[1], Giovanna Rodio[2], Carmine Mancusi[1], Stefano De Vivo[3]

Introduction

In recent years, increasing surgical experience in high-volume centers, greater consistency in surgical technique, and the support of sophisticated electromedical navigation tools have increased the success treatment of atrial fibrillation ablation to 80% after the first procedure and to > 90% after the second procedure. Moreover, these results are associated with a progressive decrease in the incidence of complications. According to the data in Table 1, taken from a study published in 2003–2004 [1], major complications associated with the ablation of all pulmonary veins outside the tubular segment occurred in 2.9% of cases, as reported by the six leading centers that have adopted this approach. This compares favorably with the 5.9% reported in a worldwide survey of such procedures performed between 1995 and 2002 [2].

Table 1. Complication rates compiled from 1,033 patients

	Events (n)	Rate (%)	Range in studies (%)
Transient ischemic attack	4	0.4	0–3
Permanent stroke	1	0.1	0–1
Severe PV stenosis (> 70%, symptomatic)	3	0.3	0–3
Moderate PV stenosis (40–70%, asymptomatic)	13	1.3	0–5
Tamponade/perforation	5	0.5	0–3
Severe vascular access complication	3	0.3	0–4

[1]Arrhythmology and Decompensation Division, Santa Maria Hospital, Bari; [2]Cardiology Division, Altamura Hospital, Altamura (BA); [3]Cardiology Division, Monaldi Hospital, Naples, Italy

Cerebrovascular Events

The prevalence of permanent stroke and of transient ischemic attack is, respectively, 0.1 and 0.4%. The main cause is embolism from thrombus mobilization. Common sites of thrombus formation are the left atrial appendage, adjacent to the catheter tip and, in most cases, at the transseptal sheath. Prevention includes: (1) pre-ablation visualization of a thrombus in the left atrial appendage by transesophageal electrocardiography (TEE); (2) avoidance of thrombus formation on the ablation catheter by using irrigated-tip catheters and intracardiac echocardiography imaging (ICE) of the amount of micro-bubble formation, which allows titration of the radiofrequency (RF) energy output; (3) avoidance of thrombus formation at the transseptal sheath by high-flow perfusion (180 ml/h) and by pulling back the sheath in the right atrium; (4) aggressive anticoagulation to obtain an ACT > 300 s.

Pulmonary Vein Stenosis

The prevalence of this complication, which manifests within the first 6 months after ablation, is rapidly decreasing and was estimated at around 1.6 ± 0.3% in a recent survey [1]. Severe (> 70%) and symptomatic stenosis occurs in 0.3% of patients, and mild to moderate and asymptomatic stenosis in 1.3% of patients. The significant reduction in the incidence was obtained by adopting the technique of ablation outside the pulmonary veins, reducing the radiofrequency energy output, and by using ICE and electromedical navigation tools.

Stenosis of one pulmonary vein is frequently asymptomatic. Severe stenosis of more than one pulmonary vein may manifest as exertional dyspnea or, less frequently, dyspnea at rest, pleuritic-type chest pain, cough, and hemophthisis. Chest X-ray may reveal parenchymal consolidation and pleural effusion, which are not diagnostic. An increased pulmonary flow velocity, detected by TEE, reinforces the diagnostic suspicion. Direct diagnosis may be obtained by spiral computed tomography (CT) scanning, magnetic resonance imaging (MRI), ICE, or pulmonary-vein angiography. Percutaneous angioplasty is a proven and effective treatment of this currently very rare complication.

Cardiac Tamponade

The latest data from high-volume laboratories report the occurrence of this serious complication in < 0.5–1% of patients [1, 3]. Cardiac tamponade must

be immediately diagnosed when arterial hypotension (< 90 mmHg) occurs, as visualized by motionless cardiac borders on fluoroscopy or by the presence of pericardial fluid on echocardiography. Percutaneous drainage is successful in most patients; rarely, surgical drainage is needed.

Tamponade occurs mostly because of tissue boiling and subsequent endocardial rupture (associated with a typical popping noise), due to excessive RF power and a high catheter-tip temperature during linear ablation of the atrial wall, especially if the tip is positioned perpendicular to the wall. In a minority of patients, mechanical perforation is responsible for this complication.

Prevention is mainly based on the use of externally irrigated tip catheters and by reducing the delivered power to ≤ 30 W or, certainly, to ≤ 40 W, which minimizes the risk of "popping." The power reduction often implies an increased duration of RF delivery especially during mitral isthmus ablation. The risk of mechanical perforation has been addressed by the use of non-fluoroscopic three-dimensional mapping systems, which enable better visualization of the atrial chambers and thus facilitate catheter manipulation. ICE is another option for obtaining the same information to appropriately guide the catheter.

Severe Vascular-Access Complications

These are mainly femoral pseudoaneurysm and arteriovenous fistula. The prevalence is 0.3% in patients treated in high-volume centers and it correlates inversely with surgical skill level.

Two complications not listed in Table 1 are atrioesophageal fistula and diaphragmatic paralysis from phrenic nerve injury (PNI). While both are currently very rare, they are clinically relevant because the first is almost always fatal and in the second there is a possibility of permanent impairment of respiratory function.

Atrioesophageal Fistula

Although very infrequent, atrioesophageal fistula is the more devastating complication and is almost always fatal. This was confirmed in a recent series obtained from leading high-volume centers (0.05%) [4].

The occurrence of atrioesophageal fistula depends on the variable and sometimes minimal distance (< 5 mm) between the esophagus and the posterior wall of the left atrium. Surgical intervention is the only effective treat-

ment; early diagnosis is mandatory and the condition must be suspected as soon as a clinical picture of endocarditis following ablation develops. Others symptoms include dysphagia, gastrointestinal bleeding, and neurological or cardiac symptoms related to ischemia from embolism. The final picture is that of cardiogenic shock. Among the diagnostic procedures, TEE and esophagoscopy must be avoided because of the danger of aggravating the lesion. Noninvasive imaging, such as MRI, transthoracic echocardiography (TTE), and thoracic CT scan with water-soluble contrast, are the most useful diagnostic tools.

Prevention is based on the following techniques: (1) ICE [5] allows detection of both the amount of echogenicity changes and accelerated bubble formation at the ablated site, indicating rapid development of a lesion and possible wall necrosis. These changes indicate the necessity to reduce the power (≤ 50 W) and RF duration (≤ 20 s). (2) CT-based and electroanatomic CARTO-derived imaging [6] give a more-defined visualization of the anatomical relationships between the esophagus and posterior wall of the left atrium. When used in association with imaging fusion software, they allow navigation with the ablation catheter according to a map in which both structures are simultaneously displayed. However, since the esophagus is a mobile structure that can readily migrate in the time interval between CT acquisition and the ablation time or during the ablation procedure, these static images may be of limited value. (3) Electroanatomic reconstruction obtained with the NavX system [7, 8] is an easy and accurate approach for visualizing the left atrium and esophagus, and it overcomes some of the limitations of the previously described method. The course and relationship of the two structures are recorded and displayed in real time, so that even modest movements of the esophagus due to the mechanical pressure of the ablation catheter may be detected.

Phrenic Nerve Injury

The currently reported prevalence of PNI is 0.11–0.48% [9]; however, it may be asymptomatic in around one-third of patients. The main symptom is dyspnea; other symptoms include cough or hiccup. The diagnosis is made on chest X-ray, which shows hemidiaphragmatic paresis or paralysis with paradoxical movement. The outcome is often favorable, with complete or partial recovery after 7 ± 7 months, but some patients fail to recover. Pulmonary rehabilitation may play a role in improving recovery. In rare cases, surgical diaphragmatic plication has been performed.

PNI is related to the close proximity of the right phrenic nerve to the postero-septal part of the superior vena cava and to the antero-inferior part of the right superior pulmonary vein and of the left phrenic nerve to the left atrial appendage roof. The risk at these critical areas is independent of the type of ablation catheter or energy source employed.

To reduce the risk at these critical areas, high-output pacing should be done before the ablation procedure is started and, in the case of diaphragmatic stimulation, energy application should be avoided. Early diagnosis of PNI during RF application, suggested by cough, hiccup, or a reduction of the diaphragmatic excursion, necessitates immediate interruption of energy delivery.

Case reports describe the possible complications as including transient paralysis of the vocal cords from recurrent laryngeal nerve injury, pyloric spasm and gastric hypomotility, and vasospastic angina.

References

1. Verma A, Natale A (2005) Should atrial fibrillation ablation be considered first-line therapy for some patients? Why atrial fibrillation ablation would be considered first-line therapy for some patients. Circulation 112:1214–1231
2. Cappato R, Calkins H, Chen SA et al (2005) Worldwide survey on the methods, efficacy and safety of catheter ablation for human atrial fibrillation. Circulation 111:1100–1105
3. Hsu LF, Jais P, Hocini M et al (2005) Incidence and prevention of cardiac tamponade complicating ablation for atrial fibrillation. Pacing Clin Electrophysiol 28(Suppl 1):S106-S109
4. Pappone C, Oral H, Santinelli V et al (2004) Atrio esophageal fistula as a complication of percutaneous transcatheter ablation of atrial fibrillation. Circulation 109:2724–2726
5. Ren JF, Lin D, Marchlinski FE et al (2006) Esophageal imaging and strategies for avoiding injury during left atrial ablation for atrial fibrillation. Heart Rhythm 3:1156–1161
6. Good E, Oral H, Lemola K et al (2005) Movement of the esophagus during left atrial ablation for atrial fibrillation. J Am Coll Cardiol 46:2107–2110
7. Packer DL (2005) Three dimensional mapping in interventional electrophysiology: techniques and technology. J Cardiovasc Electrophysiol 16:1110–1116
8. De Martino G, Capuano N, Mennella S et al (2006) Real-time electroanatomical visualization of the esophagus during pulmonary vein ablation. Europace 8(Suppl 1):131
9. Sacher F, Jais P, Stephenson K et al (2007) Phrenic nerve injury after catheter ablation of atrial fibrillation. Indian Pacing Electrophysiol J 7:1–6

Cryocatheter Ablation for Atrial Flutter

Peter Andrew[1], Annibale Sandro Montenero[2]

Overview of Atrial Flutter

Atrial flutter (AFl), a common supraventricular tachyarrhythmia (SVT), results in the atria beating up to five times faster than normal, i.e., 240 to 400 beats per minute [1]. A 2:1 relation between atrial and ventricular contractions is typically observed by electrocardiogram (ECG) [2], and under these conditions of accelerated and mismatched contractile activity of the heart chambers there is ineffective pumping of blood to the systemic circulation. While AFl is usually a non life-threatening arrhythmia, it can be a chronic, life-long condition that is episodic and transient. It can cause hypotension, impair cardiac output, exacerbate pulmonary congestion, initiate myocardial ischemia, and in rare cases may lead to a tachycardia-mediated cardiomyopathy [2]. Symptoms commonly experienced by individuals with AFl include palpitations, dizziness, chest tightness, shortness of breath, and fatigue. However, some individuals are asymptomatic.

Management of Patients with AFl

Essentially, the treatment of AFl involves treating the fast heart rate, converting to or maintaining normal sinus rhythm, and reducing the risk of thromboembolic events that predispose to stroke. Nonetheless, there are many factors to be considered when selecting the appropriate treatment approach for any given patient. Presenting symptoms, symptom history (e.g., frequency, duration, and severity), risk assessment, previous response to alternative

[1]ATLAS Medical Research Inc, Miami (FL), USA; [2]Cardiology Department and Arrhythmia Center of Cardiovascular Research Institute, IRCCS Policlinico MultiMedica, Sesto S. Giovanni (MI), Italy

treatment options, convenience and patient preference for a specific treatment option, and cost-effectiveness of a treatment option are among the many factors that should be considered.

Correct diagnosis, termination of any episode in the presenting patient if they are hemodynamically unstable, and identification of the cause of the arrhythmia are typical immediate actions to be taken. Treatment of predisposing factors (e.g., hyperthyroidism, alchoholism, and obesity) can yield significant clinical benefit, and oral coagulation is recommended for patients with recurrent or chronic AFl. The goal of controlling the ventricular rate while attempting to restore sinus rhythm and prevent recurrences may be achieved by various treatment strategies that are available in clinical practice (Table 1).

Table 1. Treatment options for atrial flutter commonly available in clinical practice

Electrical cardioversion
External electrical cardioversion
Internal (implantable) electrical cardioversion 1. Pharmacological therapy 2. Catheter ablation
Radiofrequency catheter ablation
Cryocatheter ablation

Catheter Ablation

Catheter ablation is a minimally invasive, non-surgical procedure that has moved from being an experimental technique to an accepted treatment option for AFl. The procedure involves insertion of a catheter into the femoral vein, where it is subsequently advanced to within the heart. Once placed endocardially, the ablation catheter is directed to cardiac tissue conducting the signals that cause the heart to beat abnormally [3–6]. The *traditional* ablation method involves destroying the reentry circuit, which is commonly (but not always) within the region of the cavotricuspid isthmus (CTI), so as to create a bi-directional conduction block (BCB) across the isthmus (Fig. 1). Although the traditional ablation method is the standard approach that is used in clinical practice, preliminary evidence from a recent study documented the successful use of a non-traditional ablation method to treat AFl [7]. This latter method relies on the specific electrogram characteristics

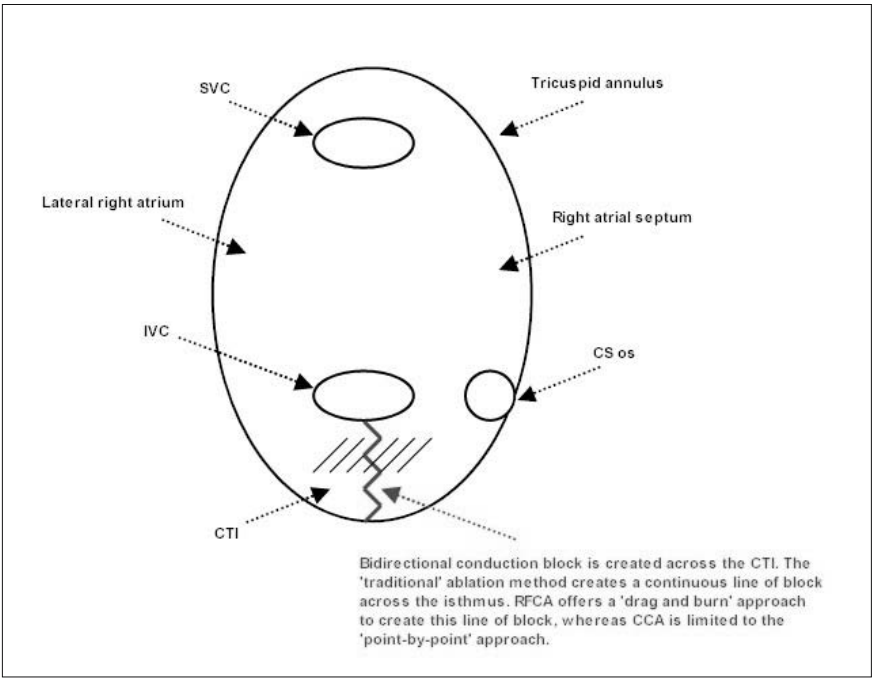


Fig. 1. The right atrium, in a 45° left anterior oblique projection, with presentation of the anatomical boundaries that demarcate the cavotricuspid isthmus (*CTI*), which is the target area for creation of a line of conduction block. *CCA*, Cryocatheter ablation; *CS os*, coronary sinus os; *IVC*, inferior vena cava; *RFCA*, radiofrequency catheter ablation; *SVC*, superior vena cava

of the targeted cardiac tissue to identify the site for ablation, rather than creating a continuous line of block across the CTI.

The catheter ablation procedure involves several key steps. First, the arrhythmia is mapped in order to determine whether the AFl is isthmus-dependent, non-isthmus-dependent, or atypical. This is necessary to define the conduction boundaries within the reentrant circuit. Second, the macroreentrant circuit is interrupted by creating either focal or linear lesions within the critical zone of slow conduction that extends to anatomical borders. Finally, termination of the arrhythmia is verified by demonstrating BCB within the AFl circuit post-ablation by electrophysiological study (EPS). A number of endpoints used to assess the safety, efficacy, and procedure characteristics of catheter ablation have been reported in clinical studies of AFl (Table 2).

Table 2. Endpoints commonly reported in studies concerning catheter ablation of atrial flutter (AFl)

1. Safety outcomes
Procedure-related adverse events and complications
Device-related adverse events and complications
Discomfort on energy delivery to cardiac tissue
2. Efficacy outcomes
Bi-directional conduction block across the isthmus
Non-inducibility of AFl post-ablation
Double potentials
Symptom recurrence[a]
Conduction recurrence[b]
3. Procedure characteristics
Procedure time
Fluoroscopy time

[a]Symptom recurrence may be documented by subjective methods (e.g., patient diary records) or objective methods (e.g., ECG, Holter monitoring, etc.). The general experience is that most cases of symptom recurrence occur within the first 6 months post ablation

[b]Only a few studies have measured persistency of bi-directional conduction block by performing a repeat electrophysiological study at 1 to 3 months post ablation

When Should Catheter Ablation Be the First-Line Treatment for AFl?

The high efficacy and outstanding safety record reported by many studies are strong evidence to support catheter ablation as the first-line treatment for many patients with AFl [8–16]. Catheter ablation should *not* be reserved as a last resort treatment for patients with AFl, but should be considered, in some patients, as first-line therapy [17]. These are likely to include patients with AFl who have heart disease and/or who have had cardiac surgery. AFl also arises in some patients due to the presence of initiating factor(s), such as metabolic imbalance and overexposure to cardiac stimulants. However, addressing the underlying initiating factor(s) is the most prudent approach to managing these patients prior to any consideration of catheter ablation. In general, suitable candidates for catheter ablation includes those patients who experience an unacceptably high frequency of recurrences, patients administered pharmacological therapy that is neither particularly effective nor well-tolerated, and patients who have contraindications for other therapeutic options for managing AFl. Natale and colleagues also suggested that catheter ablation should be the first-line treatment for patients with AFl who have a

normal or mildly enlarged left atrium [8]. Catheter ablation should *not* be considered as first-line treatment in all episodes of AFl. For example, this procedure is not suitable for patients with rhythm disturbances that are likely to spontaneously resolve or unlikely to recur [18].

Some questions concerning catheter ablation treatment of AFl remain. First, ablation and interruption of isthmus conduction do nothing to the disease mechanisms that cause the arrhythmia in the first place [19]. Hence, catheter ablation across the CTI is considered by some to not be a curative procedure, because it does not address the cause of flutter, and is only a necessary link in the circuit, i.e., the electrophysiologic and/or anatomic abnormalities within the atria persist after catheter ablation [18]. Second, there is evidence of an increase in the occurrence of atrial fibrillation following ablation treatment for AFl [20], although evidence to the contrary also exists [21, 22]. Despite a high proportion of patients developing atrial fibrillation after catheter ablation for AFl, a majority of treated patients consider the intervention beneficial due to improved quality of life [23]. But this benefit may be restricted to those patients without predominant AFl prior to ablation for AFl [23]. Third, there has been a narrow range of patient characteristics (e.g., cardiac function, associated comorbidities, prior ablation status, previous failure on AA drugs, etc.) associated with individuals enrolled in clinical studies investigating catheter ablation treatment for AFl. Consequently, it is difficult to clearly identify those patients who are likely to achieve the best results with catheter ablation over the long term. However, variation in the success rate of catheter ablation for patients with different types of AFl has been reported [14, 24].

The costs associated with catheter ablation, although not trivial, are less over time than the cost of alternatives [25, 26]. Catheter ablation requires an experienced electrophysiologist and comprehensive catheterization facilities, both of which may be resource impediments to the widespread use of this treatment option.

Cryocatheter Ablation

Cryocatheter ablation (CCA) has been reported to offer a number of potential advantages compared to radiofrequency catheter ablation (RFCA) (Table 3). Despite these many advantages, the lengthier procedure time, limitation to point-by-point focal ablation, and lack of investigator familiarity with the technology have dampened the canabalization of the AFl ablation market by cryocatheters. There are a number of recent clinical studies involving CCA for treatment of AFl (Table 4) [11, 14, 15, 27–30]. Acute success rates reported

Table 3. Advantages and disadvantages of cryocatheter ablation (CCA) versus radiofrequency catheter ablation (RFCA) for the treatment of AFl (data from [11, 14, 15, 27–40])

Advantages
1. Safety benefits
Ability to create reversible (transient) conduction block at a target site prior to creation of permanent irreversible conduction block
Greater catheter stability (cryoadhesion) enabling shorter fluoroscopy exposure
Less patient discomfort on energy delivery during the ablation procedure[a]
Fewer complications e.g., less thrombogenic, less endothelial cell disruption, and less collagen shrinkage
2. Efficacy benefits
High long-term success e.g., symptom recurrence rates relatively low in most studies
Disadvantages
1. Longer procedure time and possibly fluoroscopy exposure
2. Cryocatheters are limited to "point-by-point" ablation across the CTI whereas RF catheters can use both "point-by-point" and the "drag-and-burn" ablation methods

CCA, Cryocatheter ablation; *CTI*, cavotricuspid isthmus; *RFCA*, radiofrequency catheter ablation

[a]A recent study demonstrated that RFCA-treated patients administered nitrous oxide had reduced anxiety and discomfort with RF energy delivery [41]

with CCA range from 87 to 100%. Greater short-term success and procedure benefits (e.g., shorter procedure time) are delivered with larger-tipped cryo catheters [15]. Most studies report a relatively low rate of symptom recurrence over a reasonably lengthy period of follow-up.

The lack of large randomized controlled trials comparing CCA to RFCA for treatment of AFl has impeded a valid determination of which ablation energy is superior in a head-to-head comparison. This issue is now being addressed by a few ongoing clinical studies. The general consensus among users of both CCA and RFCA for treatment of AFl appears to be recognition of a superior safety profile for CCA, an equivalent effectiveness, but a longer procedure time.

Conclusions

Since its availability in clinical practice in the 1990s, CCA has rapidly become a curative option for AFl. This is not surprising given the excellent

Table 4. Summary of results from recent clinical studies involving CCA treatment for patients with AFl

Reference	Cryocatheter type	Ablation methods[a]	No. of patients treated with CCA	Mean age (years)	Safety outcomes for CCA[b]	Efficacy outcomes for CCA[c]	Mean follow-up (months)
[29]	CryoBlator	Traditional	15	48	No AEs reported	100% short-term success	~3
[30]	CryoBlator	Traditional	7	55	Pain score less with cryo than RF ($p < 0.05$)	100% short-term success; 0% symptom recurrence	6
[37]	CryoBlator	Traditional	73	52	No AEs reported	99% short-term success 11% symptom recurrence	15
[28]	CryoBlator	Traditional	40	56	No complications during procedure or follow-up	98% short-term success; 5% symptom recurrence	11.7
[11]	CryoBlator	Traditional	35	53	No major AEs; no thromboembolic complications	97% short-term success; 11% symptom recurrence	17.6
[32]	CryoBlator	Traditional	48	64	One serious procedure-related complication (femoral hematoma). Otherwise, CCA was well-tolerated with no discomfort on cryo energy delivery	94% short-term success; 25% symptom recurrence	6

continue →

Table 4 *continue*

Reference	Cryocatheter type	Ablation methods[a]	No. of patients treated with CCA	Mean age (years)	Safety outcomes for CCA[b]	Efficacy outcomes for CCA[c]	Mean follow-up (months)
[14]	Freezor Xtra	Non-traditional	45	62	No AEs or discomfort reported with cryo energy delivery	87% short-term success; 31% conduction recurrence at 3 month repeat EPS; 0% symptom recurrence at 9 month follow-up	9
[27]	Freezor MAX	Non-traditional	77	60	No AEs or discomfort reported with cryo energy delivery	96% short-term success; 30% conduction recurrence at 3 month repeat EPS; 0% symptom recurrence at 6 month follow-up	6
[15]	Freezor Xtra vs Freezor MAX	Non-traditional	94	60	No AEs or discomfort reported with cryo energy delivery	100% short-term success; ~32% conduction recurrence at 3 month repeat EPS; 0% symptom recurrence at 9 month follow-up	9
[31]	Freezor MAX vs RF	Traditional	9	NR	No procedural complications and pain score less with cryo than RF ($p = 0.0002$)	100% short-term success; 11% symptom recurrence	~ 3

Table 4 *continue*

[7]	Freezor MAX	Non-traditional	26	60	No AEs or discomfort reported with cryo energy delivery	100% short-term success; 44% conduction recurrence at 3-month repeat EPS; 4.5% symptom recurrence	6
Montenero (unpublished)	FreezorMAX vs RF	Non-traditional	20	63	No AEs or discomfort reported with cryo energy delivery	100% short-term success	~ 3

AE, Adverse event; *CCA*, cryocatheter ablation; *EPS*, electrophysiological study; *NR*, data not reported in abstract

[a] Traditional ablation method with a cryocatheter refers to the point-by-point ablation technique with creation of a continuous line of block across the isthmus. The CryoBlator cryocatheter (CryoCor)comes in three tip lengths: 6.5,10, and 15 mm. CryoCor's CryoBlator cryocatheters are currently under investigational use for the treatment of AFl and AF within the USA. The CryoBlator cryocatheters are CE-Mark approved and commercially available for use in the EU. The Freezor Xtra cryocatheter (CryoCath Technologies) is a 7Fr unidirectional catheter with a 6-mm ablation segment, 108-cm working length, with 4 mapping electrodes with 2-5-2 spacing, and is available in three reach lengths (short, medium, and long). The Freezor MAX cryocatheter (CryoCath Technologies)is a 9Fr unidirectional catheter with an 8-mm ablation segment, 90-cm working length, with four mapping electrodes with 3-5-2 spacing, and is available in two reach lengths (medium, and long). Both Freezor Xtra and Freezor MAX cryocatheters are CE-Mark approved and commercially available for use in the EU, and are also commercially available for use in the USA

[b] To date, there have been no reports of permanent AV conduction block in the many hundreds of patients that have been treated by CCA for various cardiac arrhythmias, including AFl

[c] Symptom recurrence rate was calculated over the mean length of follow-up

safety and effectiveness profile associated with regulatory-approved CCA technologies. A possible ceiling on its use is that it requires an experienced cardiac electrophysiologist plus comprehensive catheterization facilities. However, the long-term cost-effectiveness of CCA versus alternative treatment options will likely support the wider use of this curative option.

Acknowledgements
All data were analyzed by an independent organization (ATLAS Medical Research, Miami, FL, USA). For disclosure purposes, this organization has previously analyzed data and compiled biomedical and regulatory documentation for medical device, pharmaceutical, and biotech companies, as well as university groups involved in various areas of medical research.

References

1. Lee KW, Yang Y, Scheinman MM (2005) Atrial flutter: a review of its history, mechanisms, clinical features, and current therapy. Curr Probl Cardiol 30(3):121–167
2. Wellens HJ (2002) Contemporary management of atrial flutter. Circulation 106(6):649–652
3. Foldesi C, Pandozi C, Peichl P et al (2003) Atrial flutter: arrhythmia circuit and basis for radiofrequency catheter ablation. Ital Heart J 4(6):395–403
4. Yee R, Connolly S, Noorani H (2003) Clinical review of radiofrequency catheter ablation for cardiac arrhythmias. Can J Cardiol 19(11):1273–1284
5. Feld GK (2004) Radiofrequency ablation of atrial flutter using large-tip electrode catheters. J Cardiovasc Electrophysiol 15(10 Suppl):S18-S23
6. Feld G, Wharton M, Plumb V et al (2004) Radiofrequency catheter ablation of type 1 atrial flutter using large-tip 8- or 10-mm electrode catheters and a high-output radiofrequency energy generator: results of a multicenter safety and efficacy study. J Am Coll Cardiol 43(8):1466–1472
7. Montenero AS, Bruno N, Antonelli A et al (2006) Low clinical recurrence and procedure benefits following treatment of common atrial flutter by electrogram-guided hot spot focal cryo ablation. J Interv Card Electrophysiol 15(2):83–92
8. Natale A, Newby KH, Pisano E et al (2000) Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in patients with atrial flutter. J Am Coll Cardiol 35(7):1898–1904
9. Marrouche NF, Schweikert R, Saliba W et al (2003) Use of different catheter ablation technologies for treatment of typical atrial flutter: acute results and long-term follow-up. Pacing Clin Electrophysiol 26(3):743–746
10. Montenero AS, Bruno N, Antonelli A et al (2004) Safety and efficacy of catheter cryoablation for the treatment of atrial flutter: acute and long term results. Ital Heart J 5(Suppl 1):131S-137S
11. Manusama R, Timmermans C, Limon F et al (2004) Catheter-based cryoablation permanently cures patients with common atrial flutter. Circulation 109(13):1636–1639
12. Nakagawa H, McClelland J, Beckman K et al (1993) Radiofrequency catheter ablation of common type atrial flutter. Pacing Clin Electrophysiol 16:850

13. Fischer B, Jais P, Shah D et al (1996) Radiofrequency catheter ablation of common atrial flutter in 200 patients. J Cardiovasc Electrophysiol 7(12):1225–1233
14. Montenero A, Bruno N, Antonelli A et al (2005) Long-term efficacy of cryo catheter ablation for the treatment of atrial flutter – results from a repeat electrophysiologic study. J Am Coll Cardiol 45:573–580
15. Montenero AS, Bruno N, Antonelli A et al (2005) Comparison between a 7 French 6 mm tip cryothermal catheter and a 9 French 8 mm tip cryothermal catheter for cryoablation treatment of common atrial flutter. J Interv Card Electrophysiol 13(1):59–69
16. Calkins H, Canby R, Weiss R et al (2004) Results of catheter ablation of typical atrial flutter. Am J Cardiol 94(4):437–442
17. Tracy CM, Akhtar M, DiMarco JP et al (2000) American College of Cardiology/American Heart Association Clinical Competence Statement on invasive electrophysiology studies, catheter ablation, and cardioversion: a report of the American College of Cardiology/American Heart Association/American College of Physicians-American Society of Internal Medicine Task Force on Clinical Competence. Circulation 102(18):2309–2320
18. Garcia-Cosio F, Pastor A, Nunez A (1999) [Radiofrequency ablation as the first line of treatment in patients with common atrial flutter. The arguments con]. Rev Esp Cardiol 52(4):233–236
19. Cosio FG (2005) Should ablation be the first line treatment for supraventricular arrhythmias? Heart 91(1):5–6
20. Bertaglia E, Zoppo F, Bonso A et al (2004) Long term follow up of radiofrequency catheter ablation of atrial flutter: clinical course and predictors of atrial fibrillation occurrence. Heart 90(1):59–63
21. De Sisti A, Leclercq JF, Fiorello P et al (1998) [The effects of the ablation of atrial flutter in patients with and without a clinical history of paroxysmal atrial fibrillation]. G Ital Cardiol 28(11):1253–1260
22. Schmieder S, Ndrepepa G, Dong J et al (2003) Acute and long-term results of radiofrequency ablation of common atrial flutter and the influence of the right atrial isthmus ablation on the occurrence of atrial fibrillation. Eur Heart J 24(10):956–962
23. Anne W, Willems R, Adriaenssens B et al (2006) Long-term symptomatic benefit after radiofrequency catheter ablation for atrial flutter despite a high incidence of post-procedural atrial fibrillation. Acta Cardiol 61(1):75–82
24. Della BP, Fraticelli A, Tondo C et al (2002) Atypical atrial flutter: clinical features, electrophysiological characteristics and response to radiofrequency catheter ablation. Europace 4(3):241–253
25. Cheng CH, Sanders GD, Hlatky MA et al (2000) Cost-effectiveness of radiofrequency ablation for supraventricular tachycardia. Ann Intern Med 133(11):864–876
26. Bathina MN, Mickelsen S, Brooks C et al (1998) Radiofrequency catheter ablation versus medical therapy for initial treatment of supraventricular tachycardia and its impact on quality of life and healthcare costs. Am J Cardiol 82(5):589–593
27. Montenero AS, Bruno N, Zumbo F et al (2005) Cryothermal ablation treatment of atrial flutter-experience with a new 9 French 8 mm tip catheter. J Interv Card Electrophysiol 12(1):45–54
28. Manusama R, Timmermans C, Philippens S et al (2004) Single cryothermia applications of less than five minutes produce permanent cavotricuspid isthmus block in humans. Heart Rhythm 1(5):594–599
29. Rodriguez LM, Geller JC, Tse HF et al (2002) Acute results of transvenous cryoabla-

tion of supraventricular tachycardia (atrial fibrillation, atrial flutter, Wolff-Parkinson-White syndrome, atrioventricular nodal reentry tachycardia). J Cardiovasc Electrophysiol 13(11):1082–1089
30. Timmermans C, Ayers GM, Crijns HJ, Rodriguez LM (2003) Randomized study comparing radiofrequency ablation with cryoablation for the treatment of atrial flutter with emphasis on pain perception. Circulation 107(9):1250–1252
31. Collins N, Barlow M, Leitch JW et al (2005) Cryoablation Versus Radiofrequency Ablation in the Treatment of Atrial Flutter Trial (CRAAFT). Heart Rhythm 2005 Scientific Sessions, New Orleans, LA, USA, May 4–7, 2005
32. Daubert JP, Hoyt RH, John R et al (2005) Performance of a new cardiac cryoablation system in the treatment of cavotricuspid valve isthmus-dependent atrial flutter. Pacing Clin Electrophysiol 28(Suppl 1):S142-S145
33. Friedman PL (2005) Catheter cryoablation of cardiac arrhythmias. Curr Opin Cardiol 20(1):48–54
34. Khairy P, Chauvet P, Lehmann J et al (2003) Lower incidence of thrombus formation with cryoenergy versus radiofrequency catheter ablation. Circulation 107(15):2045–2050
35. Kuniss M, Kurzidim K, Greiss H et al (2005) Persistency of bi-directional conduction block in the cavotricuspid isthmus one month after cryocatheter ablation (8mm-tip) of common atrial flutter. Heart Rhythm 2005 Scientific Sessions, New Orleans, LA, USA, May 4–7, 2005
36. Lowe MD, Meara M, Mason J et al (2003) Catheter cryoablation of supraventricular arrhythmias: a painless alternative to radiofrequency energy. Pacing Clin Electrophysiol 26(1 Pt 2):500–503
37. Rodriguez LM, Timmermans C (2004) Transvenous cryoablation of cardiac arrhythmias. Technol Cancer Res Treat 3(5):515–524
38. Skanes AC, Yee R, Krahn AD, Klein GJ (2002) Cryoablation of atrial arrhythmias. Card Electrophysiol Rev 6(4):383–388
39. Skanes AC, Klein G, Krahn A, Yee R (2004) Cryoablation: potentials and pitfalls. J Cardiovasc Electrophysiol 15(10 Suppl):S28-S34
40. van Oeveren W, Crijns HJ, Korteling BJ et al (1999) Blood damage, platelet and clotting activation during application of radiofrequency or cryoablation catheters: a comparative in vitro study. J Med Eng Technol 23(1):20–25
41. Laurent G, Bertaux G, Martel A et al (2006) A randomized clinical trial of continuous flow nitrous oxide and nalbuphine infusion for sedation of patients during radiofrequency atrial flutter ablation. Pacing Clin Electrophysiol 29(4):351–357

Radiofrequency Ablation of Atrial Fibrillation and Atrial Flutter: Who and When?

Josef Kautzner, Dan Wichterle

Introduction

While typical atrial flutter (AFL) is a characteristic macroreentrant atrial tachycardia originating in the right atrium, atrial fibrillation (AF) is triggered in most subjects by arrhythmogenic foci localized in the myocardium around pulmonary veins and maintained by functional reentrant circuits in the left atrial myocardium. However, there is a close relationship between the two arrhythmias. They often coexist in the same patient and may degenerate into each other [1]. The reasons for this coexistence are not clear. It is possible that pulmonary venous triggers also initiate AFL or convert AFL into AF [2].

Catheter Ablation of Atrial Flutter

High procedural success rates (close to 100%) have been reported after cavotricuspid isthmus ablation for typical AFL [3]. Two prospective, randomized studies [4, 5] compared oral anti-arrhythmic therapy to radiofrequency ablation as a first-line therapy in patients with AFL. Both studies, irrespective of certain methodological limitations, demonstrated a significantly higher efficacy of non-pharmacological approaches; however, a substantial incidence of AF episodes was observed during follow-up [5]. Therefore, cavotricuspid isthmus ablation appears to be less successful in those with more frequent episodes of AF. Some evidence suggests that, in patients with AFL as the predominant clinical arrhythmia, cavotricuspid isthmus ablation reduces recurrences of AF over a long period of time. Patients with AF who develop AFL while receiving class IC or III anti-

Department of Cardiology, Institute for Clinical and Experimental Medicine, Prague, Czech Republic

arrhythmic drugs also seem to profit from cavotricuspid isthmus ablation, displaying a reduced incidence of AF after AFL ablation. In these patients, the drug that caused conversion should be continued [6]. This notion is supported by our data from a series of 126 subjects who underwent catheter ablation for AFL and were followed for 10 ± 8 months. While subjects with isolated AFL presented with subsequent AF in 22% of cases and those with IC or III AFL in only 28%, patients with documented AF and AFL developed recurrences of AF in 71% of cases.

The above indications were summarized in the joint ACC/AHA/ESC 2003 guidelines for the management of patients with supraventricular arrhythmias [7]. According to the guidelines, catheter ablation of cavotricuspid isthmus might be the option for long-term AFL management when the first episode of tolerated arrhythmia is documented (recommendation class I, level of evidence B). In the case of a single episode of poorly tolerated (in exceptional circumstances 1:1 AV conduction associated with life-threatening symptoms) or recurrent well-tolerated AFL, catheter ablation is the preferential mode of therapy (recommendation class I, level of evidence B). The only alternative is administration of dofetilide (recommendation class IIa, level of evidence C), whereas the usefulness or efficacy of other anti-arrhythmic drugs is even less well-established (recommendation class IIb, level of evidence C). The same strategy applies for AFL appearing after use of class Ic agents or amiodarone for treatment of AF; catheter ablation should be preferred to facilitate further pharmacologic management (recommendation class I, level of evidence B) rather than substituting the current drug with another (recommendation class IIa, level of evidence C).

Catheter Ablation of Atrial Fibrillation

Enormous progress in catheter ablation of AF has been achieved in the last decade [8]. The goals of this therapy are elimination of symptoms, improvement in quality of life, prevention of complications and, at least theoretically, improvement in prognosis. The current criteria for patient selection for AF ablation are influenced by many factors, such as safety, efficacy, availability, the risk-to-benefit ratio, and patient preference. As the ablation strategies for elimination of AF continue to evolve, the reported efficacy varies broadly, depending on the type of AF, ablation strategy, and the methods and duration of follow up. Although the classical definition of success has been the maintenance of sinus rhythm in the absence of anti-arrhythmic therapy, a significant decrease in AF burden and/or rhythm control with previously ineffective drugs may also be clinically meaningful. In this respect, it has to

be emphasized that more extended ECG monitoring will detect a higher proportion of asymptomatic episodes and thus decreases the success rate [9].

The above advances in AF ablation have been partially incorporated in the recent (2006) update of the ACC/AHA/ESC guidelines [10], with the recognition that such vital details as patient selection, optimum ablation sites, absolute rates of treatment success, and the frequency of complications remain incompletely defined. In patients with AF likely benefiting from maintenance of sinus rhythm and in whom no precipitating or reversible causes of arrhythmia (such as hyperthyroidism) have been found, drugs are typically the first choice. Left atrial catheter ablation is a reasonable second-line alternative to pharmacological therapy to prevent recurrent AF in symptomatic patients, especially in those with little or no left atrial enlargement (recommendation class IIa, level of evidence C).

So far, the role of catheter ablation has been established in symptomatic AF patients, whereas the appropriateness of catheter ablation in asymptomatic subjects has to be further studied. At present, asymptomatic patients may be considered for catheter ablation when they are young or have evidence of possible tachycardia-mediated cardiomyopathy. Along the same lines, a trial of anti-arrhythmic drugs is usually required prior to catheter ablation. However, catheter ablation is increasingly indicated after the failure of one or two drugs. The results of a pilot study suggested that catheter ablation may be superior to drug therapy even when applied as the first-line treatment [11].

With the development of ablation strategies, clinical efficacy has improved even in subjects with chronic AF. A recent trial documented that about three fourths of patients with chronic AF may remain in sinus rhythm with improvement of left ventricular ejection fraction and a decrease in left atrial size [12]. Similarly, the feasibility and safety of catheter ablation for AF have been documented even in patients with congestive heart failure and left ventricular dysfunction [13]. Regarding patient age, catheter ablation has been performed in those as young as 16 years up to those in their eighties. Despite comparable efficacies documented in the elderly, some studies reported a higher incidence of periprocedural complications [14].

Based on data from several series, a left atrial diameter > 50–55 mm appears to predict lack of procedural success [15]. Similarly, AF of long duration may be associated with a higher probability of recurrence after ablation. Finally, in patients who require cardiac surgery for any indication, concomitant ablation for AF is appropriate. In subjects without indications for surgery, no data are available to support surgical ablation as a stand-alone procedure.

Conclusions

Catheter ablation of cavotricuspid isthmus has become the first-line therapy in patients with typical AFL. Catheter ablation of AF, aimed at electrical isolation of pulmonary veins and various forms of substrate modification, is a still-developing strategy that should be primarily restricted to symptomatic subjects who have failed or have contraindications to medical treatment. However, the indications for catheter ablation are likely to broaden in the near future.

Aknowledgements
Supported by a Research grant MZO 00023001 of the Ministry of Health of the Czech Republic.

References

1. Roithinger FX, Lesh MD (1999) What is the relationship of atrial flutter and fibrillation? Pacing Clin Electrophysiol 22:643–654
2. Wazni O, Marrouche NF, Martin DO et al (2003) Randomized study comparing combined pulmonary vein-left atrial junction disconnection and cavotricuspid isthmus ablation versus pulmonary vein-left atrial junction disconnection alone in patients presenting with typical atrial flutter and atrial fibrillation. Circulation 108:2479–2483
3. Wellens HJ (2002) Contemporary management of atrial flutter. Circulation 106:649–652
4. Natale A, Newby KH, Pisano E et al (2000) Prospective randomized comparison of antiarrhythmic therapy versus first-line radiofrequency ablation in patients with atrial flutter. J Am Coll Cardiol 35:1898–1904
5. Da Costa A, Thevenin J, Roche F et al (2006) Results from the Loire-Ardeche-Drome-Isere-Puy-de-Dome (LADIP) trial on atrial flutter, a multicentric prospective randomized study comparing amiodarone and radiofrequency ablation after the first episode of symptomatic atrial flutter. Circulation 114:1676–1681
6. Nabar A, Rodriguez LM, Timmermans C et al (1999) Effect of right atrial isthmus on the occurrence of atrial fibrillation. Circulation 99:1441–1145
7. Blomstrom-Lundqvist C, Scheinman MM, Aliot EM et al (2003) AAC/AHA/ESC guidelines for the management of patients with supraventricular arrhythmias. Circulation 108:1871–1909
8. Riley MJ, Marrouche NF (2006) Ablation of atrial fibrillation. Curr Probl Cardiol 31:361–390
9. Kottkamp H, Tanner H, Kobya R et al (2004) Time courses and quantitative analysis of atrial fibrillation episode number and duration after circular plus linear left atrial lesions; trigger elimination or substrate modification: early or delayed cure? J Am Coll Cardiol 44:869–877
10. Fuster V, Ryden LE, Cannom DS et al (2006) ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: full text. Europace 8:651–745

11. Wazni O, Marrouche NF, Martin DO et al (2005) Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of symptomatic atrial fibrillation: a randomized trial. JAMA 293:2634–2640
12. Oral H, Pappone C, Chugh A et al (2006) Circumferential pulmonary vein ablation for chronic atrial fibrillation. N Engl J Med 354:934–941
13. Hsu LF, Jais P, Sanders P et al (2004) Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 351:2373–2383
14. Oral H, Hall B, Chugh A et al (2004) Age and catheter ablation of atrial fibrillation. Circulation 110:348 (abs)
15. Oral H, Morady F (2006) How to select patients for atrial fibrillation ablation. Heart Rhythm 3:615–618

The Impact of New Imaging, Mapping and Energy Delivery Technology on the Current Approach to Ablation of Atrial Fibrillation

Andrea Colella[1], Marzia Giaccardi[2], Luigi Padeletti[1], Gian Franco Gensini[1]

Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice. It is frequently symptomatic and contributes to significant morbidity and mortality, independent of all other cardiac comorbidities [1]. Providing effective treatment of AF is one of the challenges of electrophysiology, and it is the focus of major research initiatives in the scientific community. The level of concern and interest regarding AF has increased over the years with the advent of curative ablative techniques.

Optimal treatment of AF has yet to be achieved. Drug therapy has always shown poor efficacy in restoration and maintenance of sinus rhythm (SR) and reduction of AF complications (heart failure, stroke). In addition, the potential advantage of maintaining SR with anti-arrhythmic agents is counterbalanced by their propensity to cause serious side effects, including life-threatening pro-arrhythmic ones, and to exacerbate ischemia or heart failure by their negative inotropic actions. Moreover, a recent AFFIRM sub-study showed that only warfarin use and SR maintenance affect mortality, whereas anti-arrhythmic drugs do not modify survival [2]. For this reason, the search for therapeutic approaches effective and different from pharmacological therapy has become an increasingly active one.

The past decade has witnessed extraordinary growth in all fields of knowledge regarding AF. Many clinicians now agree that AF is not a unique arrhythmia but is made up of various mechanisms in several clinical settings. These may provide optimal substrates for a "tailored therapy" approach by catheter-mediated ablation of the trigger or substrate.

[1]Heart and Vessels Department, Azienda Ospedaliera Universitaria Careggi, Florence; [2]Pediatric Cardiology, Azienda A. Meyer, Florence, and Don Gnocchi Foundation, Florence, Italy

Ablation of Atrial Fibrillation

The remarkable results of surgical Maze procedures in treating AF [3] have encouraged the introduction and development of the percutaneous ablation approach in an attempt to expand this surgical technique. The therapeutic action and target substrates of AF ablation are now understood to be more complex than previously recognized. While catheter ablation of AF initially focused on pulmonary vein isolation, more recently it has widened substantially to include alternative or supplementary approaches. Four different approaches to catheter ablation of AF are emerging [4]:

1. Isolation of the triggers and perpetuating re-entrant circuits located in the pulmonary veins (pioneered by Jais and Haissaguerre [5, 6]).
2. Disruption of the substrate for perpetuating rotors in the antra of the pulmonary veins and the posterior left atrium (pioneered by Pappone [7]).
3. Targeted ablation of ganglionated automonic plexi in the epicardial fat pad (pioneered by Platt, Jackman, and Scherlag [8, 9]).
4. Disruption of the putative dominant rotors in the left and right atria as recognized by high-frequency complex fractionated electrograms during AF mapping (pioneered by Nadamanee [10]).

Technical Developments

As our knowledge regarding AF has grown over the last decade, AF treatment by radiofrequency (RF) ablation has evolved. Historically, cardiac angiography represented the standard methodology to investigate the cardiac structures and to define their anatomy. In fact, angiography combined with the electrophysiological assessment has long been used to relate cardiac anatomy to the electrical physiology of the heart. Unfortunately, this technique is not able to provide three-dimensional (3D) information and it is inadequate for preliminary patient evaluation. Additionally, several recently proposed approaches for AF treatment involve a deeper knowledge of the anatomy of the left atrium and the pulmonary veins.

New technical developments in the field of catheter ablation of AF include greater accuracy due to reconstruction of the virtual geometry by 3D navigation and mapping systems, and integration of 3D magnetic resonance imaging (MRI) and computed tomography (CT) data sets with those systems. This advance allows manipulation of catheters in an anatomically accurate 3D environment, making the procedure easier and, presumably, safer. Approaches based on magnetic resonance or ultrasound imaging are

also expected to serve as a stepping stone to the ultimate goal of real-time anatomical guidance of catheter ablation and potential elimination of radiation exposure. Progress is expected to be facilitated by robotic remote catheter navigation, both mechanically and magnetically guided. Shorter procedural times and more extensive practice of catheter ablation techniques to cure AF will derive from the introduction of customized coil- and balloon-based catheters that make use of alternative energy sources.

Alternative Energy Sources

Nowadays, RF energy ablation remains the gold standard in clinical practice, as most types of atrial and ventricular arrhythmias can be cured using localized ablation. Despite its widespread use, this type of ablation is commonly known to have several limitations, i.e., risks of coagulum formation, carbonization, steam popping, crater formation, and myocardial rupture.

These limitations have motivated the evaluation of modified electrode systems and new RF catheter designs, among which the most important is cooling tips. Cooled RF ablation has been shown to be effective in the production of larger lesions and useful in the management of patients with recurrent VT and AF. Even if the cooling technology does not completely exclude the risk of increased impedance and popping, it allows the delivery of sufficient amounts of energy to achieve a larger lesion size and depth. The success in curing some arrhythmias using RF ablation has been, in itself, a milestone in the field of arrhythmia management. However, some common arrhythmias remain difficult to treat by simple ablation; thus, other forms of ablation energy, including cryothermy, microwave, ultrasound, and laser, have been evaluated.

Many forms of energy have been used for medical purposes. Tissue destruction in the treatment of tumors and other tissue anomalies has been attempted with different kinds of energy [11–19]. Recently, these types of energy have been implemented in arrhythmology as well. In the treatment of arrhythmia, cryoablation has been used for many years, as it was found to be effective for the ablation of any type of arrhythmia substrate, including accessory pathways as well as the ventricular tachycardia (VT) form in chronic ischemic heart disease. The safety and efficacy of cryoenergy ablation of myocardial tissue is well-recognized [20]. Its unique, reversible effect was also demonstrated in a study in which AV nodal conduction resumed after withdrawal of cooling at -45°C. Permanent block was noted at temperatures below -60°C applied for 90–120 s [21, 22]. The other potential significant benefit with cryoablation is the absence of thrombus formation [23, 24],

which is a major concern when a number of RF applications are required, as in left-sided ablation cases. The utility of cryoablation for left atrial ablation was recently reported, and its efficacy, safety, and ease of use were confirmed. In particular, there was no occurrence of pulmonary-vein stenosis or phrenic-nerve paralysis. Thus, cryoablation has indeed evolved as a potentially useful tool in the treatment of complex ablation, e.g., for treating large or deep lesions. The reversible effect of this technique may also prove to be useful for the ablation of critical areas, such as sites close to the atrioventricular node, by allowing validation of the ablation site with "cryomapping" before cryoablation. At the present time, clinical investigations of new prototypes are ongoing in several countries. If the results obtained show a decreased risk of recurrence, thus preserving the efficacy of RF ablation while maintaining the safety profile of cryoablation, this kind of energy has the potential to become a safe and preferred alternative to current RF techniques.

The use of laser, ultrasound, and microwave energies for ablation is currently under investigation, but applications are still in the development phase. Both laser and ultrasound balloon delivery systems have been proposed for pulmonary-vein isolation. The laser system is still very dependent on contact, despite the fact that the lesions created are precise with well-defined edges and excellent control of their depth is possible. Although ultrasound must be designed to specifically control the size and depth of lesions, its advantages are that it does not require intimate tissue contact and it is able to generate deeper lesions than other modalities. However, long-term results have to show minimal recurrence and complications.

Finally, microwave is relatively new for AF ablation applications and still under clinical investigation. Theoretically, this energy should provide sufficient lesions independent of contact, but distance, antenna design, and orientation are still important considerations.

Alternative forms of energy do provide some promise in terms of larger, deeper, and complex lesions but their application is still relatively in their early process. Nevertheless, preliminary data are promising. Clinicians and patients will no doubt soon benefit from safe and effective forms of ablation for treating the many other types of arrhythmias whose control remains elusive.

Stereotaxis

The advent of the Stereotaxis (Stereotaxis, St. Louis, Missouri) remote catheter-navigation system offers the opportunity to improve the success of

complex ablation procedures while maximizing the capabilities of an advanced 3D mapping system. By reducing the risk of catheter perforation, limiting fluoroscopy exposure, and improving accuracy, catheter navigation and mapping provide a unique marriage of capabilities for electrophysiological procedures. Stereotaxis technology, currently used for AF ablation, allows magnetic navigation into the heart by remote control. In contrast to stiffer traditional catheters, it allows very accurate catheter tip control, avoiding the stretching of tissue and distortion of cardiac structures, which can produce false spaces when creating chamber geometry. Beyond radiological-exposure reduction, stereotaxis technology has a shorter learning curve than conventional ablation techniques. Early clinical results have demonstrated that stereotaxis technology is safe and effective, opening up possibilities that until now were considered to be as unlikely as remote transcatheter ablation [25].

References

1. Benjamin EJ, Larson MG, Keyes MJ et al (2004) Clinical correlates and heritability of flow-mediated dilation in the community: the Framingham Heart Study. Circulation 109:613–619
2. Corley SD, Epstein AE, DiMarco JP et al (2004) Relationship between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. Circulation 109:1509–1513
3. Cox JL, Schuiessler RB, Lappas DG et al (1996) An 8?-year clinical experience with surgery for atrial fibrillation. Ann Surg 224:267–273
4. Keane D, Reddy V, Ruskin J (2005) Emerging concepts on catheter ablation of atrial fibrillation from the tenth annual Boston Atrial Fibrillation Symposium. J Cardiovasc Electrophysiol 16:1025–1028
5. Jais P, Haissaguerre M, Shah DC et al (1997) A focal source of atrial fibrillation treated by discrete radiofrequency ablation. Circulation 95:572–576
6. Haissaguerre M, Jais P, Shah DC et al (1998) Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 339:659–666
7. Pappone C, Rosanio S, Oreto G et al (2000) Circumferential radiofrequency ablation of pulmonary vein ostia: a new anatomic approach for curing atrial fibrillation. Circulation 102:2619–2628
8. Platt M, Mandapati R, Scherlag BJ et al (2004) Limiting the number and extent of radiofrequency applications to terminate atrial fibrillation and subsequently prevent its inducibility. Heart Rhythm 1:S11 (abs)
9. Scherlag BJ, Nakagawa H, Jackman WM et al (2005) Electrical stimulation to identify neural elements on the heart: their role in atrial fibrillation. J Interv Card Electrophysiol 13(Suppl 1):37–42
10. Nademanee K, McKenzie J, Kosar E et al (2004) A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Am Coll Cardiol 43:2044–2053

11. Bain C, Cooper KG, Parkin DE (2002) Microwave endometrial ablation versus endometrial resection: a randomized controlled trial. Obstet Gynecol 99:983–987
12. Anidjar M, Teillac P (1995) Non-surgical instrumental treatment of benign hypertrophy of the prostate. Presse Med 24:1477–1480
13. D'Agostino HB, Solinas A (1995) Percutaneous ablation therapy for hepatocellular carcinomas. AJR Am J Roentgenol 164:1165–1167
14. Miyake O, Itatani H, Itoh H et al (1995) Laser-TURP with a lateral firing fiber for contact irradiation. Nippon Hinyokika Gakkai Zasshi 86:273–278
15. Kigure T, Harada T, Satoh Y et al (1996) Microwave ablation of the adrenal gland: experimental study and clinical application. Br J Urol 77:215–220
16. Hodgson DA, Feldberg IB, Sharp N et al (1999) Microwave endometrial ablation: development, clinical trials and outcomes at three years. Br J Obstet Gynaecol 106:684–694
17. Korn AP (2000) Endometrial cryoablation and thermal ablation. Clin Obstet Gynecol 43:575–583
18. Johnson DB, Nakada SY (2001) Cryosurgery and needle ablation of renal lesions. J Endourol 15:361–368
19. Mitka M (2002) Tumoricidal temperature-related treatments. JAMA 287:440–441
20. Lister J, Hoffman BF (1964) Reversible cold block of the specialized conduction tissues of the anaesthesized dog. Science 145:723–725
21. Gallagher JJ, Sealy WC, Anderson RW et al (1977) Cryosurgical ablation of accessory atrioventricular connections: a method for correction of the pre-excitation syndrome. Circulation 55:471–479
22. Harrison L, Gallagher JJ, Kasell J et al (1977) Cryosurgical ablation of the A-V node-His bundle: a new method for producing A-V block. Circulation 55:463–470
23. Dubuc M, Roy D, Thibault B et al (1999) Transvenous catheter ice mapping and cryoablation of the atrioventricular node in dogs. Pacing Clin Electrophysiol 22:1488–1498
24. Rodriguez LM, Leunissen J, Hoekstra A et al (1998) Transvenous cold mapping and cryoablation of the AV node in dogs: observations of chronic lesions and comparison to those obtained using radiofrequency ablation. J Cardiovasc Electrophysiol 9:1055–1061
25. Pappone C, Vicedomini G, Manguso F et al (2006) Robotic magnetic navigation for atrial fibrillation ablation. J Am Coll Cardiol 47:1390–1400

Trigger vs Substrate Ablation for the Treatment of Atrial Fibrillation

Atul Verma

Introduction

Radiofrequency ablation of atrial fibrillation (AF) has emerged as a very effective technique for the treatment of this vexing arrhythmia. When AF ablation was first described by Haissaguerre et al., nearly 10 years ago, the technique focused on the elimination of focal triggers for AF emanating largely from the pulmonary veins (PVs) [1]. In patients with predominantly paroxysmal AF and little structural heart disease, this paradigm remained successful, with evidence confirming that elimination of all possible triggers via pulmonary vein isolation (PVI) would successfully prevent AF recurrence. However, the high success rates of PVI procedures were not replicated in populations with more persistent and permanent AF. In these patients, there is greater interest in identifying the critical elements of the atrial "substrate" required for maintaining AF. By targeting this "substrate," it is hoped that AF ablation will result in better cure rates in a wider spectrum of AF patients. While markers of AF substrate have been proposed as potential targets of ablation, the efficacy of using such targets is not well known. Furthermore, whether such targets should be eliminated alone, or in conjunction with known triggers is also not well understood.

Trigger-Based Ablation

The goal of most present-day AF ablation techniques is to electrically "disconnect" the PVs from the rest of the atrium by ablating around the origin of

Southlake Regional Health Centre, Newmarket, Ontario, Canada

the veins. In their original article, Haissaguerre et al. showed that in the majority of patients with paroxysmal, lone AF (94%), focal triggers for AF were found in one or more of the PVs [1]. Although non-PV sites may also trigger AF, this is less common, occurring in no more than 6–10% of paroxysmal AF patients [2]. Thus, most present-day techniques are focused on ablating around the PVs. This typically involves applying lesions circumferentially around and outside of all four PVs, with the goal of achieving complete electrical disconnection between PVs and left atrium (LA) [3]. Although this technique has many names and variations, including "pulmonary vein antrum isolation," "circumferential PV ablation," and "extraostial isolation," the lesion sets produced by the procedures are all very similar. The success rates are also similar, with recent pooled analyses showing success in the 80% range [4].

Evidence has also suggested that the success of such ablation procedures is directly related to eliminating conduction between the PVs and the LA. Verma et al. studied patients post-PV antrum isolation and found that those with successful outcomes had significantly more PVs isolated than those who failed [5]. Furthermore, patients who were responsive to antiarrhythmic medications had more conduction delay between the LA and PVs than those who were not responsive. Ouyang et al. found that recurrent LA-PV conduction was the predominant finding in patients with recurrent arrhythmia post-PV antrum isolation [6]. In both studies, patients were successfully cured by re-isolating all of the PV antra. The majority of patients in these studies had paroxysmal, lone AF; therefore, these results are not necessarily applicable to more populations with persistent AF. Furthermore, wide PV antral isolation requires very extensive lesion sets, which presents risks including perforation and stroke. Additional or alternative lesions may be required to modify the atrial substrate for AF maintenance beyond trigger-based ablation.

Substrate-Based Ablation

There is no general consensus on what exactly constitutes the "substrate" in clinical AF, making the use of this term somewhat problematic. It seems that when most clinicians talk about targeting the AF substrate, they are referring to critical regions or components of the left atrial anatomy/eletrophysiology that are responsible for allowing AF to perpetuate. Investigators have proposed different ablation targets to try and identify these critical regions, including complex fractionated electrograms (CFEs), dominant frequencies (DFs), and autonomic ganglionated plexi (GPs).

Complex Fractionated Electrograms

From early animal and human experiments, it was found that atrial regions exhibiting very rapid activation may represent critical rotors responsible for maintaining AF [7]. Furthermore, regions demonstrating very fragmented potentials, to the point of almost continuous baseline activity, may represent pivot points or regions of very slow conduction responsible for continued fibrillatory conduction [8]. Nademanee et al. first described targeting these types of electrograms exclusively to ablate AF [9]. They defined "complex fractionated atrial electrograms" as electrograms with either: (1) two deflections or more and/or having a perturbation of the baseline with continuous deflections from a prolonged activation complex, or (2) very short cycle length (< 120 ms) with or without multiple potentials. These electrograms also typically have very low voltages of 0.06–0.25 mV. By ablating these targets, the authors described a 76% success rate after one procedure (91% after two). Other investigators have also shown that by adding complex atrial electrograms to ablation, success rates may be increased [10]. However, no other centers have yet validated the CFE-alone technique. One reason is the subjectivity in identifying CFEs. To this end, mapping algorithms have been developed to automatically identify CFEs and early results have been promising (Fig. 1) [11]. Furthermore, there is some controversy as to the relevance of

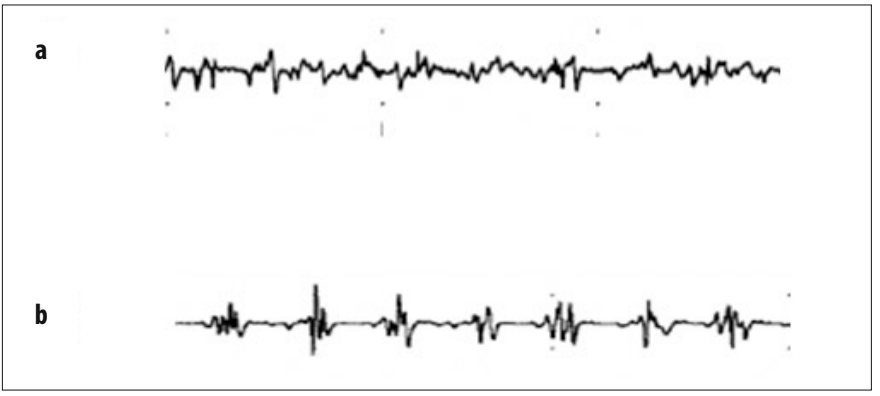


Fig. 1a, b. Examples of electrograms that have been labeled as complex fractionated electrograms (CFEs). **a** Low-amplitude electrograms with multiple components, to the point of showing almost continuous deflection of the recording baseline. **b** Electrograms with two or three components are regarded as "fractionated." However, they are not of low amplitude, nor is there continuous electrical activity (extensive lengths of flat lines between electrograms), and the cycle length is not particularly short. Thus, these electrograms would not be considered as CFEs

using CFE as a target. There is debate as to the temporal and spatial stability of CFE and whether these electrograms represent transient regions of wavefront collision as opposed to critical, stable regions of AF perpetuation [12]. Part of the problem is that the definition of CFE varies in the literature, with some studies defining any electrogram with more than two components as a "CFE," regardless of the cycle length or continuity of the signal (Fig. 2). While an EGM with two or more components may technically be "fractionated," only low-voltage electrograms with rapid or continuous activity have been described as ablation targets or "CFE." Perhaps "complex atrial electrograms" would be a better term than CFE to avoid confusion. These complex electrograms have been reported to be spatially stable and their elimination results in AF cycle-length prolongation, regularization, and possibly long-term AF reduction [9, 13]. Some investigators have reported searching for such complex activity sites during sinus rhythm by examining the Fourier transform of sinus electrograms and looking for multiple late, rightward-shifted frequencies, or "fibrillar" myocardium [14].

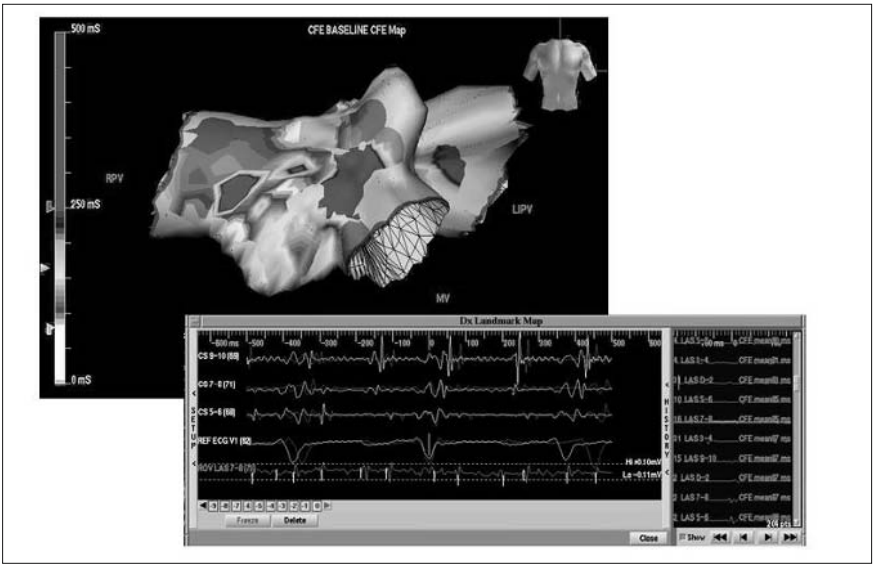


Fig. 2. Example of a three-dimensional representation of the left atrium (AP view) with different shaded regions indicating areas of complex fractionated activity, as determined using an automated mapping algorithm (Ensite NavX, St Jude Medical, St Paul, MN). By performing point-by-point recording of electrograms, the algorithm automatically detects the number of local electrogram peaks. By averaging the number of peaks over a period of several seconds, an average cycle length can be calculated. Regions of short cycle length (< 120 ms) represent regions of complex activity (either very rapid activity, or continuous deflections of the baseline). These regions may then be targeted for ablation

Dominant Frequency

Since the identification and interpretation of complex signals during AF can be very challenging, some investigators have used DF sites to identify regions of high-frequency atrial activity. Sanders et al., for example, reported that AF termination or AF cycle-length prolongation during ablation was usually seen during ablation over a DF site [15]. They also showed that the distribution of DF may vary from patients with paroxysmal AF to those with permanent disease, with DFs less likely to be associated with the PVs in non-paroxysmal patients. However, as with CFE, there is some question regarding the temporal and spatial stability of DFs. Ng et al. showed that DF values were significantly impacted by local electrogram factors, such as amplitude variation, frequency fluctuation, and electrogram ordering or phase [16]. Thus, DF sites may not necessarily correlate with atrial regions exhibiting the most rapid or complex atrial activity. There have not yet been any studies validating the approach of targeting DF sites for AF ablation.

Autonomic Ganglionated Plexi

It has been suggested that autonomic inputs from ganglionated plexi surrounding the heart may contribute to both the initiation and maintenance of AF [17]. High-frequency stimulation of epicardial autonomic plexi can induce triggered activity from the pulmonary veins and affect the atrial refractory periods so as to provide a substrate for the conversion of PV firing into sustained AF [17]. Elimination of vagal inputs prevented AF recurrence in animal and patient models of vagal AF [18, 19]. In AF patients, recent data suggested that the identification and ablation of autonomic ganglia during PV isolation may improve the long-term success of treatment [20]. However, in another report, the use of ganglionated plexus ablation alone in vagal AF patients had a success rate of less than 30% [19]. The location of these plexi has been correlated with the presence and location of CFE [20], but whether targeting plexi alone will ultimately prove effective remains unclear.

The Need for Clinical Trials

Ultimately, several targets have been proposed for AF ablation, each with their own supporting evidence and limitations. It is also quite likely that for any given approach, there will be overlap in the targets that are ablated. The creation of circumferential lesions around the PVs may not only isolate

them, but may also eliminate some sites of CFE and some autonomic inputs. However, whether we need to systematically add other targets to PVI or move beyond PVI as a whole remains a somewhat controversial issue. The only way to definitively determine the efficacy and utility of different approaches is to subject them to the rigor of randomized clinical trials. One such trial, *Substrate versus Trigger Ablation for Reduction of Atrial Fibrillation* (STAR-AF) is designed to specifically look at the utility of targeting CFE vs. PVI. In this randomized, three-arm, multicenter comparison involving AF patients with largely persistent disease, PVI will be compared to CFE alone as well as to a hybrid procedure combining PVI and CFE. The primary outcome will be freedom from AF at one year. Canadian and European centers are now actively enrolling in the pilot phase of this trial and results should be available within the next 1–2 years.

References

1. Haissaguerre M, Jais P, Shah DC et al (1998) Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 339(10):659–666
2. Finta B, Haines DE (2004) Catheter ablation therapy for atrial fibrillation. Cardiol Clin 22(1):127–145, ix
3. Verma A, Marrouche NF, Natale A (2004) Pulmonary vein antrum isolation: intracardiac echocardiography-guided technique. J Cardiovasc Electrophysiol 15(11):1335–1340
4. Verma A, Natale A (2005) Should atrial fibrillation ablation be considered first-line therapy for some patients? Why atrial fibrillation ablation should be considered first-line therapy for some patients. Circulation 112(8):1214–1222, discussion 1231
5. Verma A, Kilicaslan F, Pisano E et al (2005) Response of atrial fibrillation to pulmonary vein antrum isolation is directly related to resumption and delay of pulmonary vein conduction. Circulation 112(5):627–635
6. Ouyang F, Antz M, Ernst S et al (2005) Recovered pulmonary vein conduction as a dominant factor for recurrent atrial tachyarrhythmias after complete circular isolation of the pulmonary veins: lessons from double Lasso technique. Circulation 111(2):127–135
7. Morillo CA, Klein GJ, Jones DL, Guiraudon CM (1995) Chronic rapid atrial pacing. Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation 91(5):1588–1595
8. Konings KT, Kirchhof CJ, Smeets JR et al (1994) High-density mapping of electrically induced atrial fibrillation in humans. Circulation 89(4):1665–1680
9. Nademanee K, McKenzie J, Kosar E et al (2004) A new approach for catheter ablation of atrial fibrillation: mapping of the electrophysiologic substrate. J Amer Coll Cardiol 43(11):2044–2053
10. Verma A, Patel D, Famy T et al (2007) Efficacy of adjuvant anterior left atrial ablation during intracardiac echocardiography-guided pulmonary vein antrum isolation for atrial fibrillation. J Cardiovasc Electrophysiol (in press)

11. Verma A, Novak P, Macle L et al (2006) Effects of ablating complex fractionated electrograms identified by a novel real-time automated mapping algorithm on atrial fibrillation cycle length, termination, and inducibility. Can J Cardiol 22(Suppl D):162D (abs)
12. Rostock T, Rotter M, Sanders P et al (2006) High-density activation mapping of fractionated electrograms in the atria of patients with paroxysmal atrial fibrillation. Heart Rhythm 3(1):27–34
13. O'Neill MD, Jais P, Takahashi Y et al (2006) The stepwise ablation approach for chronic atrial fibrillation. Evidence for a cumulative effect. J Interv Card Electrophysiol 16(3):153–167
14. Pachon MJ, Pachon ME, Pachon MJ et al (2004) A new treatment for atrial fibrillation based on spectral analysis to guide the catheter RF-ablation. Europace 6(6):590–601
15. Sanders P, Berenfeld O, Hocini M et al (2005) Spectral analysis identifies sites of high-frequency activity maintaining atrial fibrillation in humans. Circulation 112(6):789–797
16. Ng J, Kadish AH, Goldberger JJ (2006) Effect of electrogram characteristics on the relationship of dominant frequency to atrial activation rate in atrial fibrillation. Heart Rhythm 3(11):1295–1305
17. Patterson E, Po SS, Scherlag BJ, Lazzara R (2005) Triggered firing in pulmonary veins initiated by in vitro autonomic nerve stimulation. Heart Rhythm 2(6):624–631
18. Schauerte P, Scherlag BJ, Pitha J et al (2000) Catheter ablation of cardiac autonomic nerves for prevention of vagal atrial fibrillation. Circulation 102(22):2774–2780
19. Scanavacca M, Pisani CF, Hachul D et al (2006) Selective atrial vagal denervation guided by evoked vagal reflex to treat patients with paroxysmal atrial fibrillation. Circulation 114(9):876–885
20. Scherlag BJ, Nakagawa H, Jackman WM et al (2005) Electrical stimulation to identify neural elements on the heart: their role in atrial fibrillation. J Interv Card Electrophysiol 13(Suppl 1):37–42

Pacing in Atrial Fibrillation: Is It Still Viable?

Oscar Oseroff, Gustavo Iralde, Enrique Retyk

Introduction

Atrial fibrillation (AF) is one of the most intensively studied topics in the cardiology community due to its growing prevalence, its high morbidity and costs, and its expanding therapeutic options following new insights into the disease. The prevalence of AF is around 1% of the general population, and increases to up to 4% in the population over 65 years old. Similarly, the number of patients that need a pacemaker is constantly growing, and these patients have much in common with the AF population (elderly, coronary artery disease, heart failure). Thus, the number of patients with a combination of AF and pacemakers is increasing [1, 2].

This article offers an analysis of the role of cardiac stimulation therapy in the prevention and treatment of AF. The different pacing modes are compared and the impact on the incidence of AF, the alternatives that pacing therapy offer in the prevention of AF, and the results of pacing and cardiac resynchronization therapy (CRT) in patients who need AV nodal ablation for heart rate control are discussed.

Physiopathologic Targets for Pacing in AF

Episodes of AF are frequently preceded by atrial premature beats (APBs), which are the trigger for reentry mechanisms in the atrium. The combination of short atrial refractory periods, dispersion of atrial repolarization, and slow conduction favor the initiation of AF as well as recurrences.

Pacing and Electrophysiology Division, Bazterrica Clinic, Buenos Aires, Argentina

Bradycardia and post-extrasystolic pauses are also associated with APBs and increase the dispersion of atrial repolarization. Also, atrial wall distension generated by left ventricular dysfunction or dyssynchrony favors AF [3–8].

AF initiation mechanisms in paced patients mostly followed a greater density of APBs and bradycardia. In 70% of the observations, a single direct trigger, such as frequent APBs or a short burst of atrial tachycardia, was identified. The recurrences mostly took place after finishing a switch mode episode (early recurrent atrial fibrillation, ERAF) [9, 10].

These observations suggest that, in a pacemaker patient with a risk of AF, intervention can be targeted to the substratum (bradycardia, dispersion of repolarization, long conduction times, post-extrasystolic pauses), to diminishing AF triggers (overdrive suppression of APBs, rate stabilization post-APBs, post-switch mode overdrive pacing), and to avoiding situations of high myocardial stress (ventricular dyssynchrony, atrioventricular dissociation).

Pacing-Mode Selection

During VVI pacing, the ventricular activation pattern begets, in many patients, atrial contraction against a closed AV valve, VA conduction, or AV dissociation, and an abnormal pattern of ventricular contraction with impaired LV function. This inadequate mechanical function of the heart leads to pressure overload of the atrium, pacemaker syndrome, and AF.

In a retrospective analysis, Santini et al. observed a higher prevalence of chronic AF in patients with VVI pacing than in patients with AAI or DDD pacing (46.4 vs 3.7 and 12.6%). This difference was followed by a higher stroke-related death in VVI paced patients [11].

In a randomized study that compared AAI vs VVI pacing in sinus node disease (SND), Andersen et al. found a 46% risk reduction in AF incidence with physiologic pacing [12].

Different studies comprising thousands of patients have shown similar results in patients with SND, i.e., AF relative risk reductions between 18 and 46% with physiologic pacing. In patients with AV block (AVB), the results were not as good, probably due to methodology limitations (Table 1) [13–16].

Thus, physiologic pacing is the preferred approach in SND patients due to the higher incidence of AF in the VVI mode.

Table 1. Studies comparing VVI vs Physiologic pacing modes

Study	Population	Modes	n	Mean follow up	AF	RR	*p*
Andersen et al. (1997)	SND	AAI vs VVI	250	5.5 y	AAI = 23.6% VVI = 34.7%	0.54	0.012
Mattioli et al. (1998)	SND and AVB	Physiologic vs VVI	210	2 y	Physiol. = 20% VVI = 32%	0.62	0.03
PAC-A-TACH (1998)	Tachy-Brady	DDD vs VVI	198	2 y	DDD = 43%VVI = 48%	-	NS
CTOPP (2000)	SND and AVB	Physiologic vs VVIR	2568	3 y	Physiol. = 5.3%/y VVIR = 6.5%/y	0.82	0.05
MOST (2001)	SND	DDDR vs VVIR	2010	2.7 y	DDDR = 15.2% VVIR = 26.7%	0.56	0.001
UKPACE (2005)	AVB	DDD vs VVI	2021	3 y	DDD = 3% VVI = 2.8%	-	NS

SND, Synus node disease; *AVB*, atrioventricular block; *NS*, not significant

Right Ventricular Pacing and Dyssynchrony: How Can It Be Avoided?

Right ventricular pacing (RVP) begets an abnormal pattern of ventricular contraction, with inter- and intraventricular dyssynchrony. It is therefore not surprising that in Andersen's trial, AAI pacing yielded the best results in terms of reduction of AF episodes [12].

In a MOST (Mode Selection Trial) substudy that compared VVI vs DDD pacing in SND, the prevalence of RVP and its effects was analyzed in a subgroup of 1339 patients with SND and normal QRS duration. The observation was that in patients paced in DDDR mode with a nominal AV interval the cumulative percentage of RVP was higher than in VVI paced patients (90 vs 58%, p =0.001), and it was linearly related with the number of heart failure (HF)-related hospitalizations and AF episodes. There was a 25% increase in AF relative risk for every 25% increase in RVP, and it was not dependent on the pacing mode [17].

More recently, Tops et al. analyzed 55 AF patients with 100% RV pacing after AV nodal ablation. They found that 49% of the patients had a septal to posterior wall motion delay > 130 ms, which is a well-known left ventricular dyssynchrony parameter. Patients with dyssynchrony showed a worsening in their New York Heart Association functional class (NYHA FC) and a decrease in left ventricular ejection fraction (LVEF) [18].

Different algorithms have been developed and employed to maintain a physiologic pattern of ventricular activation, avoiding RV pacing during DDD pacing. One option is a pacing feature to maintain AAI pacing until an atrial event is not followed by a sensed QRS, at which point pacing shifts to a DDD mode (Managed Ventricular Pacing-MVP, Medtronic, Minnesota, MN, USA). In a study of this type of pacing, Sweeney et al. showed a decrease in RV pacing from 59.1% with DDD with a long programmed AV delay to 6.5% with MVP mode. More recently, with a similar feature (AAIsafeR, Ela Medical, Montrouge, France), Pioger et al. found similar reductions in RV pacing (9 vs 95%). Other devices able to search for intrinsic AV conduction (search AV, AV hysteresis) have achieved similar results [19–25].

Thus, currently, in a patient with SND and a pacemaker with the above-described programmable possibilities, RV pacing and thereby the incidence of AF can be reduced.

Special Tools for AF Prevention and Treatment

With the objective of AF prevention, different pacing algorithms have been developed. The basic mechanism behind all of them is an increase in atrial pac-

ing, avoidance of post-extrasystolic pauses, prevention of ERAF, and the use of anti-tachycardia pacing (ATP) to terminate atrial tachycardia episodes which trigger AF. Also, and with a different focus, atrial stimulation from different sites has been analyzed with the goal of diminishing repolarization dispersion.

AF-Prevention Algorithms

In several series of patients with DDD pacing for SND, fewer AF episodes were observed in patients who had higher atrial-paced percentages (APP). Thus, a rational treatment approach is to maintain atrium pacing most of the time, with the objective of overdrive suppression of APBs [26].

Levy et al. initially tested the effect of programming the basic rate 10 beats faster than the intrinsic heart rate of the patient, in a fixed form. They observed a modest increase in the percentage of atrial pacing but without any effect on AF episodes [27]. Subsequently, different and more complex algorithms were developed to dynamically maintain the atrium paced over the rate of the patient's heart rate. With this feature (APP), (atrial overdrive pacing, atrial preference pacing, atrial pacing preference, pace conditioning or dynamic atrial overdrive, depending on the manufacturer) an APP between 90 and 95% was consistently maintained [28–37].

Another tool available in some devices is post-switch-mode overdrive pacing (PSOP), which is used to pace at a higher rate when an AF episode has ended (detected as a finished switch-mode episode) to overdrive suppress atrial arrhythmias, which frequently appear shortly after an AF episode, while avoiding ERAF episodes. These algorithms have been shown to reduce ERAF episodes, but are limited with respect to the time necessary to detect sinus rhythm and begin intervention. In many episodes, the intervention starts when the AF is already in progress [33].

A third feature is the shortening in the escape interval after an APB in order to avoid short/long sequences, which favor the initiation of arrhythmia. This feature is referred to as atrial rate stabilization or post-PAC response, depending on the manufacturer [34–37].

Finally, some devices offer overdrive pacing of certain atrial tachycardia events in order to terminate them (anti-tachycardia pacing, ATP). This feature has excellent diagnostic accuracy and results in the termination of > 50% of atrial tachycardia episodes. Of course, success with less-organized rhythms such as AF is limited [28, 32, 34, 36, 37].

Despite the rationales behind these tools, there is a lack of consistency in the results of the trials aimed at testing them and methodology limitations (number of patients, many therapies compared in the same trial, different

endpoints, etc.). It is therefore premature to draw any conclusions about these approaches. The SAFARI trial, with more than 500 patients enrolled, might overcome some of the methodology limitations, but the results are not yet available [38].

Multisite Pacing

A different strategy for AF prevention is to focus on substrate modification, that is, to diminish the intra-atrial conduction delay and dispersion of repolarization by means of alternative-site or multi-site atrial stimulation [39].

Although this strategy yielded a reduction in activation times across the atrium, manifested by a shorter duration of P waves, there was no change in AF recurrence. The only exception was post-cardiac surgery AF, the incidence of which was reduced by biatrial transient epicardial pacing. There are also technical issues that make this tool less attractive [40–49].

Ablate and Pace: Role of Cardiac Resynchronization Therapy

In patients with permanent AF, one of the most important treatment targets is rate control. Usually, it is accomplished with combinations of AV nodal blocking drugs [1].

Although in most of patients, drug therapy improves symptoms, a significant number of patients do not achieve rate control objectives ; their symptoms persist or they develop tachycardiomyopathy. In the AFFIRM study, a trial specially designed to test rate control in one of its arms, many patients needed more than one drug for rate control, and the target of rate control was achieved only in 70% of the patients [50].

This implies that 30% of patients with permanent AF need a non-pharmacological alternative for rate control. Ablation of AV node and RV pacing is a well recognized alternative and has been evaluated in many small trials with different endpoints. When analyzed together in a meta-analysis, the two approaches brought about an improvement of symptoms as well as other endpoints, e.g., HF-related admissions and LVEF [51].

Nonetheless, not all patients improve with this therapy or their symptoms may even worsen. One possible explanation is the left ventricular dyssynchrony generated by RV pacing. Tops et al. found, in 55 patients with AV nodal ablation and RV pacing, that 49% developed echocardiographic parameters of dyssynchrony, and that the presence of dyssynchrony resulted in a worst NYHA functional class and a decrease in LVEF [52].

It is difficult to define *a priori* which patient will develop symptoms due to LV dyssynchrony arising from right ventricular (RV) apex pacing. One alternative is to upgrade to a CRT device in those patients whose symptoms worsen and who experience LV dyssynchrony in the follow-up. This approach was tested by Leon et al., who found that the upgrade to a CRT improved NHYA functional class in those patients with RV pacing after AV nodal ablation who developed severe symptomatic heart failure and a decrease in LVEF [53].

If about half of the patients will develop dyssynchrony with RV pacing, then the implantation of a CRT device should lead to improvements in this group. This strategy was tested in the PAVE study, which randomized 252 patients with permanent AF and AV nodal ablation, to RV or biventricular pacing. The mean LVEF was 46%, and 70% of all patients were in NYHA functional class I–II. The primary endpoint was modification of the distance walked in the 6-min test at 6 months. In CRT patients, this distance increased more than in RV-paced patients (31 vs 24%, $p = 0.004$). The improvement with CRT was higher in the subgroup of patients with LVEF < 45% and in those with more severe symptoms (NYHA II–III). The differences were due to a worsening in RV-paced patients more than an improvement in CRT patients [54].

Thus, RV pacing after AV node ablation may be desirable for patients with preserved LV function, with upgrade to CRT if heart failure and LV dyssynchrony ensue. CRT is recommended for patients with LVEF < 45% and NYHA functional class II–III.

Conclusions

In conclusion among the different therapeutic options for AF, pacing is a useful tool in many of these patients. In SND physiologic pacing is preferred over VVI. Better algorithms are needed prevent AF. After AV node ablation in AF, CRT has demonstrated better outcomes with respect to rate control in patients with lower LVEF.

References

1. Fuster V, Rydén LE, Cannom DS et al (2006) ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With

Atrial Fibrillation). J Am Coll Cardiol 48(4):e149-e246
2. Gregoratos G, Gibbons RJ, Antman EM et al (2002) ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 106:2145–2161
3. Haissaguerre M, Jais P, Shah D et al (1998) Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med 339:659–666
4. Maurits A, Ausma J, Schotten U (2002) Electrical, contractile and structural remodeling during atrial fibrillation. Cardiovasc Res 54:230–246
5. Waldo A (2003) Mechanism of atrial fibrillation. J Cardiovasc Electrophysiol 14:S267-S274
6. Nattel S (2002) Therapeutic implications of atrial fibrillation mechanisms: can mechanistic insights be used to improve AF management? Cardiovasc Res 54:347–360
7. Bennett MA, Pentecost BL (1970) The pattern of onset and spontaneous cessation of atrial fibrillation in man. Circulation 41:981–988
8. Solti F, Vecsey T, Kekesi V et al (1989) The effect of atrial dilatation on the genesis of atrial arrhythmias. Cardiovasc Res 23:882–886
9. Capucci A, Groppi F, Ruiter J et al, on behalf of the AF Therapy Study Group (2000) Evaluation of re-initiation of atrial fibrillation through a pacemaker with focused diagnostics. Pacing Clin Electrophysiol 23:722 (abs)
10. Hoffmann E, Janko S, Hahnewald S et al (2000) The Atrial Fibrillation Therapy (AFT) trial: novel information on dominant triggers of paroxysmal atrial fibrillation.Circulation 102:II481-II482 (abs)
11. Santini M, Alexidou G, Ansalone G et al (1990) Relation of prognosis in sick sinus syndrome to age, conduction defects and modes of permanent atrial pacing. Am J Cardiol 65:729–735
12. Andersen HR, Thuesen L, Baggar JP et al (1994) Prospective randomised trial of atrial versus ventricular pacing in sick-sinus syndrome. Lancet 344:1523–1528
13. Skanes AC, Krahn AD, Yee R et al, for the CTOPP Investigators (2001) Progression to chronic atrial fibrillation after pacing: the Canadian Trial of Physiologic Pacing. J Am Coll Cardiol 38:167–172
14. Lamas G, Lee K, Weeney M et al, for the Mode Selection Trial in Sinus-Node Dysfunction (2002) Ventricular pacing or dual chamber pacing for sinus node dysfunction. N Engl J Med 346:1854–1862
15. Lamas GA, Orav EJ, Stambler BS et al, for the Pacemaker Selection in the Elderly Investigators (1998) Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. N Engl J Med 338:1097–1104
16. Toff WD, Camm AJ, Skehan JD (2005) Single-chamber versus dual chamber pacing for high-grade atrioventricular block. N Engl J Med 353:145–155
17. Sweeney MO, Hellkamp AS, Ellenbogen KA et al, for the Mode Selection Trial (MOST) Investigators (2003) Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 107:2932–2937
18. Tops LF, Schalij MJ, Holman ER (2006) Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation. J Am Coll Cardiol 48:1642– 1648

19. Sweeney M, Ellenbogen K, Casavant D et al; The Marquis MVP Download Investigators (2005) Multicenter, prospective, randomized safety and efficacy study of a new atrial-based managed ventricular pacing mode (MVP) in dual chamber ICDs. J Cardiovasc Electrophysiol 16:811–817
20. Pioger G, Leny G, Nitzsche R, Ripart A (2007) AAIsafeR Limits Ventricular Pacing in Unselected Patients. PACE 30:S66-S70
21. Milasinovic G, Sperzel J, Smith TW et al, on behalf of The Worldwide EnPulse Investigators) (2006) Reduction of RV pacing by continuous optimization of the AV interval. Pacing Clin Electrophysiol 29(4):406–412
22. Melzer C, Sowelam S, Sheldon TJ et al (2005) Induction of right ventricular pacing in patients with sinus node dysfunction using an enhanced search AV algorithm. Pacing Clin Electrophysiol 28:521–527
23. Olshansky B, Day J, McGuire M, Pratt T (2005) Inhibition of unnecessary RV pacing with AV search hysteresis in ICDs (INTRINSIC RV): design and clinical protocol. Pacing Clin Electrophysiol 28:62–66
24. Mayumi H, Kohno H, Yasui H et al (1996) Use of automatic mode change between DDD and AAI to facilitate native atrioventricular conduction in patients with sick sinus syndrome or transient atrioventricular block. Pacing Clin Electrophysiol 19:1740–1747
25. Iliev I, Yamachika S, Muta K et al (2000) Preserving normal ventricular activation versus atrioventricular delay optimization during pacing: the role of intrinsic atrioventricular conduction and pacing rate. Pacing Clin Electrophysiol 23:74–83
26. Inoue N, Ishikawa T, Sumita S et al (2006) Suppression of atrial fibrillation by atrial pacing. Circulation J 70:1398–1401
27. Levy T, Walker S, Rex S, Paul V (2000) Does atrial overdrive pacing prevent paroxysmal atrial fibrillation in paced patients? Int J Cardiol 75:91–97
28. Friedman P, Dijkman B, Warman E et al, for the Worldwide Jewel AF Investigators (2001) Atrial therapies reduce atrial arrhythmia burden in defibrillator patients. Circulation 104:1023–1028
29. Terranova P, Valli P, Terranova P et al (2006) Pacemaker Prevention therapy in drug–refractory paroxysmal atrial fibrillation: reliability of diagnostics and effectiveness of prevention pacing therapy in Vitatron™ Selection® Device. Indian Pacing Electrophysiol J 6(2):63–74
30. Puglisi A, Altamura G, Capestro F et al (2003) Impact of closed-loop stimulation, overdrive pacing, DDDR pacing mode on atrial tachyarrhythmia burden in brady-tachy syndrome. A randomized study. Eur Heart J 24:1952–1961
31. De Simona A, Senatore G, Donnici G et al (2007) Dynamic and dual-site atrial pacing in the prevention of atrial fibrillation: The STimolazione Atriale Dinamica Multisito (STADIM) Study. PACE 30:S71-S74
32. Gillis A, Unterberg-Buchwald C, Schmidinger H et al, for the GEM III AT Worldwide Investigators (2002) Safety and efficacy of advanced atrial pacing therapies for atrial tachyarrhythmias in patients with a new implantable dual chamber cardioverter-defibrillator. J Am Coll Cardiol 40:1653–1659
33. Pürerfellner H, Doza P, Ruiter P et al, for the PMOP Investigators (2006) Reduction of atrial tachyarrhythmia episodes during the overdrive pacing period using the post-mode switch overdrive pacing (PMOP) algorithm. Heart Rhythm 3:1164–1171
34. Israel C, Hu B, Unterberg C et al, on behalf of the AT500 Verification Study Investigators (2001) Pace-termination and pacing for prevention of atrial tachyarrhythmias: results from a multicenter study with an implantable device for atrial therapy. J Cardiovasc Electrophysiol 12:1121–1128

35. Carlson M, Ip J, Messenger J et al, for the ADOPT Investigators (2003) A new pacemaker algorithm for the treatment of atrial fibrillation. Results of the Atrial Dynamic Overdrive Pacing Trial (ADOPT). J Am Coll Cardiol 42:627–633
36. Lee M, Weachter R, Pollak S et al, for the ATTEST Investigators (2003) The effect of atrial pacing therapies on atrial tachyarrhythmia burden and frequency results of a randomized trial in patients with bradycardia and atrial tachyarrhythmias. J Am Coll Cardiol 41:1926–1932
37. Friedman P, Dijkman B, Warman E et al (2001) Atrial therapies reduce atrial arrhythmia burden in defibrillator patients. Circulation 104:1023–1028
38. Gold MR, Hoffmann E, for the SAFARI Investigators (2006) Rationale and design of a randomized clinical trial to assess the role of overdrive and triggered prevention pacing therapies in reducing atrial fibrillation: the Study of Atrial Fibrillation Reduction (SAFARI). Am Heart J 152:231–236
39. Misier AR, Opthof T, van Hemel NM (1992) Increased dispersion of refractoriness in patients with idiopathic atrial fibrillation. J Am Coll Cardiol 19:1531–1535
40. D'Allonnes GR, Pavin D, Leclercq C et al (2000) Long term effects of biatrial synchronous pacing to prevent drug-refractory atrial tachyarrhythmia: a 9-year experience. J Cardiovasc Electrophysiol 11:1081–1091
41. Daubert C, Leclercq C, Le Breton H et al (1997) Permanent left atrial pacing with a specifically designed coronary sinus lead. Pacing Clin Electrophysiol 20:2755–2764
42. Saksena S, Prakash A, Hill M et al (1996) Prevention of recurrent atrial fibrillation with chronic dual-site right atrial pacing. J Am Coll Cardiol 28:687–694
43. Delfault P, Saksena S, Prakash A et al (1998) Long-term outcome of patients with drug-refractory atrial flutter and fibrillation after single- and dual-site right atrial pacing for arrhythmia prevention. J Am Coll Cardiol 32:1900–1908
44. Saksena S, Prakash A, Ziegler P et al, for the DAPPAF Investigators (2002) Improved suppression of recurrent atrial fibrillation with dual-site right atrial pacing and antiarrhythmic drug therapy. J Am Coll Cardiol 40:1140–1150
45. Leclercq JF, De Sisti A, Fiorello P et al (2000) Is dual site better than single site atrial pacing in the prevention of atrial fibrillation? Pacing Clin Electrophysiol 23:2101–2107
46. Lau CP, Tse HF, Yu CM et al (2001) Dual-site atrial pacing for atrial fibrillation in patients without bradycardia. Am J Cardiol 88:371–375
47. Mirza I, James S, Holt P (2002) Biatrial pacing for paroxysmal atrial fibrillation. A randomized prospective study into the suppression of paroxysmal atrial fibrillation using biatrial pacing. J Am Coll Cardiol 40:457–463
48. Levy T, Walker S, Rex S et al (2001) No incremental benefit of multi-site atrial pacing compared with right atrial pacing in patients with drug refractory paroxysmal atrial fibrillation. Heart 85:48–52
49. Crystal E, Connolly SJ, Sleik K et al (2002) Interventions on prevention of postoperative atrial fibrillation in patients undergoing heart surgery. A meta-analysis. Circulation 106:75–80
50. Olshansky B, Rosenfeld L, Warner A et al; the AFFIRM Investigators (2004) The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Approaches to control rate in atrial fibrillation. J Am Coll Cardiol 43:1201–1208
51. Wood M, Brown-Mahoney C, Kay G, Ellenbogen K (2000) Clinical outcomes after ablation and pacing therapy for atrial fibrillation – a meta-analysis. Circulation 101:1138–1144

52. Tops L, Schalij M, Holman E et al (2006) Right ventricular pacing can induce ventricular dyssynchrony in patients with atrial fibrillation after atrioventricular node ablation. J Am Coll Cardiol 48:1642–1648
53. Leon A, Greenberg J, Kanuru N et al (2002) Cardiac resynchronization in patients with congestive heart failure and chronic atrial fibrillation. Effect of biventricular pacing after chronic right ventricular pacing. J Am Coll Cardiol 39:1258–1263
54. Doshi R, Daoud E, Fellows C et al for the PAVE Study Group (2005) Left ventricular-based cardiac stimulation post av nodal ablation evaluation (The PAVE Study). J Cardiovasc Electrophysiol 16:1160–1165

Traditional or Device Approach for the Management of Atrial Fibrillation in Patients with Heart Failure

Aurelio Quesada, Mónica Giménez, Victor Palanca, Javier Jiménez, José Roda

Introduction

Atrial fibrillation (AF), the most prevalent sustained arrhythmia, is an increasingly common risk factor in patients with severe left ventricular dysfunction. Moreover, it is associated with a poor prognosis and reduced quality of life for patients with heart failure (HF) syndrome. Trials involving HF patients have shown that the prevalence of AF in such patients is high, over 20–40% [1, 2] and increases with progressive NYHA class. AF is a relevant factor in terms of the incidence of stroke, morbidity, refractory arrhythmic episodes, and number of hospitalizations. Moreover, the results of the GUSTO-III trial confirmed that AF is an independent factor for increased mortality after myocardial infarction [3]. A retrospective analysis in the Studies of Left Ventricular Dysfunction Prevention and Treatment Trials showed that patients with AF at baseline, compared to those in sinus rhythm, had significantly greater all-cause mortality (34 vs 23%), death attributed to pump failure (16.7 vs 9.4%), and were more likely to reach the composite end point of death or hospitalization for HF (45 vs 33%). The European GEM DR Evaluation [4] also detected a higher early mortality of patients with implanted cardioverter/defibrillators – a population with a high prevalence of HF and left ventricular dysfunction, related to episodes of AF.

Anatomical factors, such as stretch secondary to increased atrial pressure and volume, are largely involved in the pathophysiology of AF in the presence of chronic heart failure (CHF). Also, the complex activation of neurohormonal pathways (bradykinin, renin-angiotensin-aldosterone system), resulting in fibroblast proliferation, collagen accumulation, hypertrophy, and

Cardiac Electrophysiology and Arrhythmias Section, Department of Cardiology, Hospital General Universitario de Valencia, Valencia, Spain

apoptosis, plays a critical role in the mechanism of AF in HF. These events lead to loss of atrial contraction and dilatation, conduction defects, and atrial remodeling, all of which likely result in AF episodes [5].

Factors inducing anatomical and electrical remodeling make the atrium and its surrounding structures difficult substrates to approach, such that the treatment of AF in the HF population is particularly challenging. Furthermore, this group of patients has the poorest response to the traditional therapeutic approach to AF, i.e., one that is based on the use of antiarrhythmic drugs, but it is also the group most urgently requiring adequate AF control. Thus, in this setting, non-pharmacological approaches seem especially appropriate, even more if left ventricular systolic dysfunction is present [6]. This article reviews the results of the use of each type of device, including a quick look at pulmonary vein ablation as an essential part of the armamentarium for treating patients with both AF and HF, and current approaches to managing these difficult patients.

Pulmonary Vein Ablation

Since its introduction, ablation techniques have evolved from early attempts to target individual and ectopic foci [7–9] with simple, fluoroscopy-guided pulmonary vein isolation in focal AF to segmentary, circumferential, and anatomical approaches. At the present time, even more complex procedures targeting not only anatomical structures but also those producing electrophysiologically fractionated electrograms, sites of dominant frequency, and local non-venous drivers have been proposed as possible targets for patients with persistent and permanent AF. Although increasing success rates (60–90% free-symptoms AF, mean follow up 4–12 months) has been demonstrated with circumferential and anatomical isolation techniques in paroxysmal AF, worse results have been obtained with persistent AF [10–12]. Even more, the risk of complications rise according to patient age and the success rate trends to decrease. These findings confirm the need for randomized trials to assess the wider application of ablation therapy in persistent AF, which is the type often implicated in the heart failure population.

To date, pulmonary vein ablation for AF has been performed primarily in patients with preserved left ventricular ejection fraction (LVEF). However as noted above, AF and HF are frequently linked and, when associated, produce additive deleterious effects. There are only a few investigations regarding ablation techniques in patients with AF and low ejection fraction [13, 14]. In a prospective study, Hsu et al. [14] showed, in 58 patients with CHF, that the restoration and maintenance of sinus rhythm by catheter ablation in drug-

refractory AF yielded significant improvement in left ventricular performance (increased ejection fraction and fractional shortening of 21 and 11%, respectively), left ventricular dimensions (decreases in the diastolic and systolic diameters of 6 and 8 mm, respectively), exercise capacity, symptoms, and quality of life. In terms of success rate after initial pulmonary vein isolation, AF recurrence in patients with an impaired LVEF was higher than in subjects with normal LVEF [15]. Gentlesk et al. [16] recently reported similar success rates regarding arrhythmia-free follow-up in 67 (18%) patients with AF and left ventricular systolic dysfunction compared to those with normal LVEF. Thus, pulmonary vein isolation is a feasible therapeutic option in AF patients with impaired LVEF, although the potential advantages and disadvantages of this technique must be carefully weighed for each patient. Randomized studies with more patients and longer follow-up are warranted.

If HF is primarily due to the arrhythmia, especially in younger patients (< 65 years) with paroxysmal AF usually due to focal mechanisms (focus or microreentry), pulmonary vein ablation probably should be the first option, particularly in patients with preserved LVEF. This is important to keep in mind since the later the treatment is performed, the more difficult it is to avoid electrical and histological remodeling. In contrast, HF in the older population is frequently the result of a combined mechanism; thus, while in selected cases pulmonary vein ablation may be considered, in the vast majority of the patients the best choice would probably involve a simpler procedure (pacemaker device with or without atrioventricular node ablation regarding LVEF damage, see below).

Atrioventricular Node Ablation and Pacemaker Implantation

Atrioventricular node (AVN) ablation is the simplest treatment alternative in patients with permanent AF and poorly controlled ventricular rate or in those with complex, refractory, and highly symptomatic episodes of arrhythmia. However, the mandatory requirements for pacemaker implant have raised concerns about the long-term performance of these devices, especially regarding the risk of worsening HF.

The MOST substudy [17] showed that, the higher the percentage of right ventricular pacing, the higher the number of HF-related hospitalizations and episodes of AF. For this reason, although it is currently the most frequently prescribed technique, doubts remain about the role of AVN ablation and the type of device that is indicated, i.e., single (or dual in paroxysmal AF) chamber or biventricular ones. Therefore, concurrently with these options, pacemaker implantation without AVN ablation should be considered.

While symptomatic benefits have been described following AVN ablation, these may be the only ones demonstrated as neither a reduction in the burden or number of AF episodes nor a consistent long-term hemodynamic benefit have been definitively proven. In the PA3 study [18], patients with paroxysmal, drug-refractory AF were randomized after AVN ablation to VVI or DDDR pacing; no significant differences in terms of episodes and time to first recurrence between the groups was found. Furthermore, Anguera et al. [19] described a detrimental hemodynamic effect in patients who underwent AVN ablation, mainly in those with left ventricular systolic dysfunction. By the time of that work, detrimental consequences on LV fuction were not suspected. So, the authors attributed the impairment to an increase in the severity of mitral regurgitation.

Direct, solid evidence about the long-term results of RV pacing plus AVN ablation is lacking, but at least theoretically the effect of subsequent dyssynchrony must be considered in this setting. The PAVE study [20] mildly supported this hypothesis in that cardiac resynchronization therapy (CRT) in AF patients after AVN ablation yielded modest results in terms of morbidity improvement (6-min walk test) at 6-month follow-up, although improvement was greater in patients with low LVEF. Until further trials have been conducted, it seems prudent to use the information derived from the MOST trial in daily practice, avoiding RV pacing in patients with HF or left ventricular systolic dysfunction, in whom a cumulated percentage of ventricular pacing > 40% is associated with a very high risk of worsening HF and increasing HF-related hospitalizations [21]. Ongoing trials such as APAF (*Ablate and Pace in Atrial Fibrillation*) will provide additional and explanatory information on this subject.

While taking into account the results of atrial pacing in AF prevention, in some patients it is nonetheless worthwhile to wait longer than usual (our practice is to perform AVN ablation 1 month after pacemaker insertion) in order to determine whether the new setting allows better control of the arrhythmia. Atrial pacing minimizing ventricular stimulation can decrease the number of AF episodes, making it less likely that the patient will develop permanent AF, especially if there is coexisting bradycardia. This was demonstrated by Andersen et al. in the Danish study [22] comparing AAI/R pacemakers with VVI/R, although obviously the results were partially linked to the detrimental effects of ventricular pacing, In the MOST study [17], there were significantly fewer AF episodes in bicameral than with ventricular stimulation. Similar results were recorded in the CTOPP trial [23].

In the Danish trial, the NYHA classification was also higher (and worsened) in the ventricular group vs the atrial group at long-term follow-up.

The mean dose of diuretics increased in the ventricular group vs the atrial group, while death due to cardiovascular causes was reduced [22]. Nielsen et al. [24] compared AAIR and DDDR with different programmed AV intervals and found impaired LVEF in DDDR mode and increased left atrial diameter. The shorter AV interval was the most harmful setting, as it resulted in decreased LVEF and an increased number of AF episodes (7.4, 17.5, 23.3% in AAIR, DDDR with larger and shorter AV interval, respectively).

Further investigations (MVP, PreFER) will reveal whether the avoidance of ventricle stimulation lessens the incidence of AF arrhythmic and HF events.

In addition, the exact value of the available, dedicated, AF-prevention algorithms remains to be determined. The efficacy of these algorithms has been shown in the setting of bradycardia pacing indication [25–28], except in the AFTherapy trial [29]. These studies evaluating prevention algorithms have reported a significant reduction in supraventricular ectopic beats and AF burden and no increase in the incidence of new episodes of AF. Whether these effects can work synergistically with ventricular pacing reduction algorithms is so far unknown.

Dual Implantable Cardioverter Defibrillator for Atrial Fibrillation

Delivery of synchronous shocks between the high right atrial wall and coronary sinus effectively terminated episodes of AF in a sheep model [30]. Based on these findings, the efficacy of an implantable atrial defibrillator was evaluated as an alternative in patients with AF [31]. Although initially atrial stand-alone implantable cardioverter defibrillators (ICDs) were used, these are no longer available and have been replaced by dual ICDs (Fig. 1). Anti-tachycardia therapies and atrial and ventricle shocks were shown to improve quality of life and decrease hospitalizations in patients with drug-refractory AF in the Jewel AF-only study [32]. However, in a small but significant number of patients a large number of atrial discharges is required. Unfortunately, the energy needed to restore normal sinus rhythm (over 10 J) is uncomfortable without sedation, making such devices difficult to recommend for wide clinical use.

Recently, the DATAS trial [33, 34] studied 354 patients with class I indication for ICD who were randomized to either dual-chamber or single-chamber defibrillator. The devices were programmed to avoid ventricular pacing. The composite endpoint (all-cause mortality, invasive intervention, hospitalization due to cardiovascular causes, inappropriate shocks, and sustained

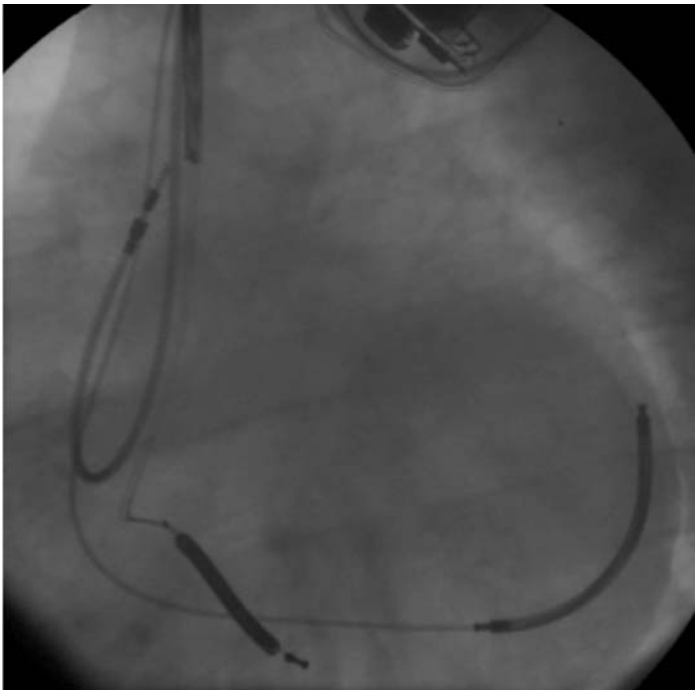


Fig. 1. Left anterior oblique projection. Use of a dual defibrillator for the treatment of drug-refractory atrial fibrillation (AF), with an additional lead in the coronary sinus. The lead has a coil allowing shock delivery affecting both atria

symptomatic atrial tachyarrhythmias) was significantly reduced in the dual-ICD group (RR 0.42, 95% CI = 0.18–0.97) compared to those with single-chamber ICDs. While further investigation is needed in this field, the DATAS trial nonetheless showed that in patients with class I indication for ICD, i.e., a population with a high incidence of atrial tachyarrhythmias and HF, the tolerance and efficacy of dual-chamber ICD can be maintained when careful technique and programming that minimizes complications are employed. Thus, dual-chamber ICDs have an important role in patients without permanent AF and who have ICD indications. In patients with AF only, further investigations are required to better delineate the most appropriate subgroup of candidates.

Cardiac Resynchronization Therapy

Up to 40% of unselected patients with HF and left ventricular systolic dysfunction who fulfill CRT inclusion criteria have AF [34]. As already stated,

AF has an important deleterious influence in the prognosis of HF [35]. However, albeit as yet unconfirmed, it is possible that if CRT reduces NYHA class, the prevalence of AF and the consequences of this condition will decrease accordingly. It is important to keep in mind that, although patients with AF were excluded from large trials that support current CRT guidelines, relevant work delineating both the efficacy of CRT in AF patients and the ability of this technique to reduce AF episodes is available.

Several studies pointed out that the results of CRT in AF patients are very similar to those obtained in sinus rhythm patients. Kies et al. [36] showed that 6 months of CRT resulted in significant clinical benefits with significant left atrial and left ventricular reverse remodeling. Despite these beneficial effects, 93% of patients did not revert to sinus rhythm.

Perhaps, one of the main challenges imposed by AF in CRT is the difficulty to adequately deliver therapy, as shown in Fig. 2. Regardless of this limitation, in one large Spanish registry, the SPARE registry, which enrolled more than 200 CRT recipients with permanent AF and compared them with sinus rhythm patients, there were no differences in terms of clinical status or

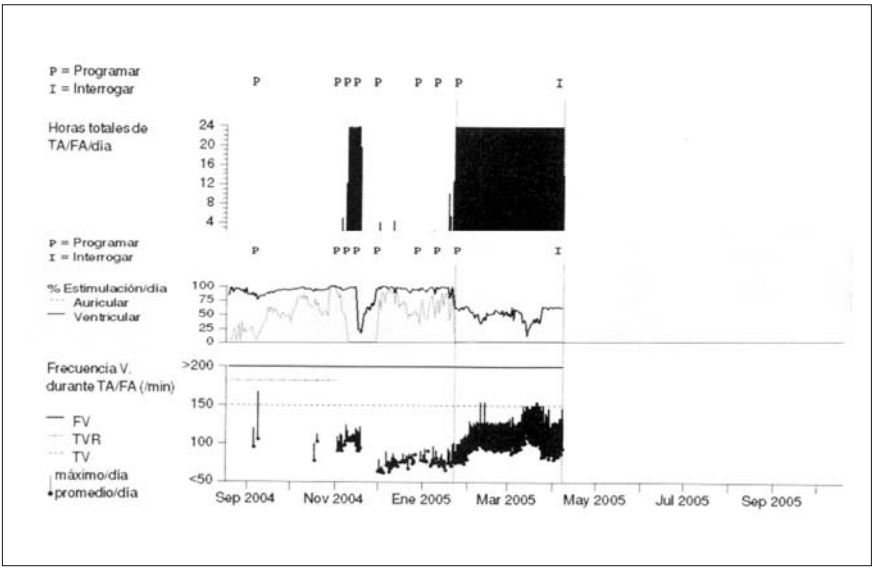


Fig. 2. Effect of AF on CRT evaluated by the Cardiac Compass storaged data (Medtronic). Coincident with persistent AF episodes (*upper panel*) spontaneously conducted at a high rate to the ventricle (*lower panel*) there is a significant loss of biventricular pacing (*middle panel*). Thus, therapy is not or incompletely delivered. Even many of the beats marked virtually as paced will be fusion beats with no resynchronization capability

anatomical remodeling between the two groups. Interestingly, mortality in AF patients remained higher than in the control group [37].

Few studies are available on the influence of CRT on the efficacy of atrial therapies. Complexes devices, such as Concerto (Medtronic) and Renewal 4 AVT (Boston Guidant), offer CRT, atrial anti-tachycardia therapy, and atrial shocks. Preliminary results have supported the idea that this combined approach is effective. Fung et al. [38] found that CRT reduced the incidence of AF in patients with poor left ventricular systolic function, although this was not the case in CARE-HF patients, probably due to the type of analysis [39]. Our group [40] described a lower rate of AF (hours of AF and AF episodes > than 12 h) was associated with CRT vs ICD (7.7 vs 31%, $p = 0.03$, 95% CI). Based on the lack of significant changes in atrial dimension observed in this study, our data support a beneficial effect on atrial electrical remodeling in patients with CRT compared to those with ICD.

Several studies are currently evaluating CRT and AF. The aim of the MASCOT study (Management of Atrial fibrillation Suppression in AF-HF Comorbidity Therapy) is to evaluate whether resynchronization therapy and AF prevention algorithms improve the prognosis of these patients [41]. RENEWAL 4 AVT has completed enrolment and is now analyzing the system performance of LV-Offset and LV-Only CRT modes in HF patients and the complication-free rate in patients with a history of atrial tachyarrhythmias.

What Is the Best Approach to Drug-Refractory Atrial Fibrillation in HF Patients?

The best approach is to define. In daily practice, age and left ventricular function used to be the two most important factors in deciding upon a therapeutic strategy. In the young population (< 65 years old) with HF, the first option might be pulmonary vein ablation. Unsuccessful results would then recommend AVN ablation subsequent to a pacing device as the next step. In patients with preserved ejection fraction without prior ischemic heart disease, a single pacemaker should suffice, with subsequent control of LVEF in the follow-up. In case of impairment (or if LVEF is already reduced at implant time), biventricular pacing should be considered. In older patients, in whom pulmonary vein ablation is riskier and less successful, this approach to treatment must be considered on a restricted, individual basis. In the majority of cases, other options are preferable: if LVEF is preserved and AF is probably permanent, our first option would be CRT pacemaker with AVN ablation. In patients with systolic dysfunction (< 40%) we recommend implantation of a biventricular ICD, but electrical cardioversion with

ACEi or ARB plus amiodarone (if tolerated or not previously used) should be attempted beforehand. If sinus rhythm is maintained during the following 1–2 months, we suggest placing an atrial lead and a device with atrial antitachycardia properties. If sinus rhythm is not restored, a biventricular ICD should be implanted. Finally, all patients should complete treatment with drugs aimed at establishing optimal ventricular rate control, but on some occasions AVN ablation will also be needed.

Conclusions

Atrial fibrillation is an increasingly frequent comorbidity in patients with severe HF, especially in the presence of left ventricular dysfunction. In several settings, the pharmacological approach is ineffective such that non-pharmacological alternatives must be considered. Pulmonary vein ablation is the option in patients with paroxysmal, focal AF without structural heart disease. If there is associated sinus node dysfunction, atrial-based pacing with dedicated preventive algorithms can improve outcome. CRT-ICD or dual ICD is the preferred strategy in patients with poor LVEF, whether or not asynchrony is present. In patients with permanent AF, AVN ablation with resynchronization therapy is the method of choice. Nonetheless, the majority of patients will need a hybrid approach with different combinations of ablation, pacing, resynchronization, atrial antitachycardia pacing, and shock. These approaches may have beneficial and synergistic effects with CRT.

References

1. Johnstone D, Limancher M, Rousseau M et al (1992) Clinical characteristics of patients in studies of left ventricular dysfunction. Am J Cardiol 70:894–900
2. CONSENSUS Investigators (1987) Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. N Engl J Med 316:1429–1435
3. Al-Khatib SM, Stebbins AL, Califf RM et al (2003) Sustained ventricular arrhythmias and mortality among patients with acute myocardial infarction: results from the GUSTO-III trial. Am Heart J 145:515–521
4. Deneke T, Lawo T, Gerritse B et al (2004) The European GEM DR Trade. Mortality of patients with implanted cardioverter/defibrillators in relation to episodes of atrial fibrillation. Europace 6:151–158
5. Savelieva I, Camm J (2004) Atrial Fibrillation and heart failure: natural history and pharmacological treatment. Europace 5:S5-S19
6. Packer DL, Asirvathan S, Munger TM (2003) Progress in nonpharmacological therapy of atrial fibrillation. J Cardiovasc Electrophysiol 14:S96-S309

7. Haissaguerre M, Jais P, Dipen C et al (2000) Electrophysiological end point for catheter ablation of atrial fibrillation initiated from multiple pulmonary venous foci. Circulation 101:1409–1417
8. Pappone C, Augello G, Santinelli V (2005) Atrial Fibrillation ablation. Ital Heart J 6:190–199
9. Huang H, Wang X, Chun J et al (2006) A single pulmonary vein as electrophysiological substrate of paroxysmal atrial fibrillation. J Cardiovasc Electrophysiol 17:1193–1201
10. Pappone C, Rosanio S, Angello G et al (2003) Mortality, morbidity and quality of life alter circumferential pulmonary vein ablation for atrial fibrillation: outcomes from a controlled nonrandomized long term study. J Am Coll Cardiol 42:185–197
11. O'Neill MD, Jais P, Takahashi Y et al (2006) The stepwise ablation approach for chronic atrial fibrillation. Evidence for a cumulative effect. J Interv Card Electrophysiol 16:153–167
12. Calo L, Lamberti F, Loricchio ML et al (2006) Left atrial ablation versus biatrial ablation for persistent and permanent atrial fibrillation; a prospective and randomized study. J Am Coll Cardiol 47:2504–2512
13. Tondo C, Mantica M, Russo G et al (2006) Pulmonary vein vestibule ablation for the control of atrial fibrillation; a prospective and randomized study. Pacing Clin Electrophysiol 29:962–970
14. Hsu LF, Jais P, Senders P et al (2004) Catheter ablation for atrial fibrillation in congestive heart failure. N Engl J Med 351:2373–2383
15. Chen MS, Marrouche NF, Khaykin Y et al (2004) Pulmonary vein isolation for the treatment of atrial fibrillation in patients with impaired systolic function. J Am Coll Cardiol 43:1004–1009
16. Gentlesk PJ, Saner WH, Gerstenfeld EP et al (2007) Reversal of left ventricular dysfunction following ablation of atrial fibrillation. J Cardiovasc Electrophysiol 18:15–17
17. Sweeny MO, Hellkamp AS, Ellenbogen KA et al (2003) Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 107:2932–2937
18. Gillis AM, Connolly SJ, Lacombe P et al (2000) Randomized crossover comparison of DDDR versus VDD pacing after atriventricular junction ablation for prevention of atrial fibrillator. The atrial pacing peri-ablation for paroxysmal atrial fibrillation (PA3 Study Investigators). Circulation 102:736–741
19. Anguera I, Brugada J, Brugada P et al (1998) Deterioro hemodinámico en pacientes sometidos a ablación del nodo auriculoventricular. Rev Esp Cardiol 51:307–313
20. Doshi RN, Daoud EG, Fellows C et al; PAVE Study Group (2005) Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol 16:1160–1165
21. Sweeney MO, Hellkamp AS (2006) Heart failure during cardiac pacing. Circulation 113:2082–2088
22. Andersen HR, Nielsen JC, Thomsen PEB et al (1997) Long-term follow up of patients from randomised trial of atrial versus ventricular pacing for sick sinus syndrome. Lancet 350:1210–1216
23. Connolly SJ, Kerr CR, Gent M et al (2000) Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. N Engl J Med 342:1385–1391
24. Nielsen JC, Kristensen L, Andersen HR et al (2003) A randomized comparison of

atrial and dual chamber in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. J Am Coll Cardiol 42:614–623
25. Ricci R, Santini M, Puglisi A et al (2001) Impact of consistent atrial pacing algorithm on premature atrial complexe number and paroxysmal atrial fibrillation recurrences in brady-tachy syndrome: a randomized prospective cross over study. J Interv Card Electrophysiol 5:33–44
26. Carlson MD, Ip J, Messenger J et al, for the Atrial Dynamic Overdrive Pacing Trial (ADOPT) investigators (2003) A new pacemaker algorithm for the treatment of atrial fibrillation. Results of the Atrial Dynamic Overdrive Trial (ADOPT). J Am coll Cardiol 42:627–633
27. Funck RC, Adamec R, Lurje L et al (2000) Atrial overdriving is beneficial in patients with atrial arrythmias: first results of the PROVE Study. Pacing Colin Electrophysiol 23:1891–1893
28. Gold M, Hoffman E (2006) The impact of atrial prevention pacing on AF burden: primary results of the Study for Atrial Fibrillation Reduction (SAFARI). Cardiostim 2006, Nice, France. Europace 8 (Suppl 1):222/3 (abs)
29. Camm J (2002) AF therapy study: preventive pacing for paroxysmal atrial fibrillation. Abstract presented at the 23rd Scientific Sessions NASPE, San Diego, May 2002. Pacing Clin Electrophysiol 24:554 (abs)
30. Ayers M, Alferness CA, Ilina M et al (1994) Ventricular proarrhythmic effects of ventricular cycle length and shock strength in a sheep model of transvenous atrial defibrillation. Circulation 89:413–422
31. Levy S, Ricard P, Lau CP et al (1997) Multicenter low energy transvenous atrial defibrillation (XAD) trial results in different subsets of Atrial fibrillation. J Am Coll Cardiol 29:750–755
32. Ricci R, Quesada A, Pignalberi C et al (2004) Dual defibrillator improves quality of life and decreases hospitalizations in patients with drug refractory atrial fibrillation. J Interv Card Electrophysiol 10:85–92
33. Quesada A, Almendral J, Arribas F et al (2004) The DATAS rationale and design: a controlled, randomized trial to assess the clinical benefit of dual chamber (DDED) defibrillator. Europace 6:142–150
33. Almendral J, Arribas F, Quesada A et al (2006) Are dual chamber ICD beneficial? The DATAS trial: a randomised trial focused on clinically significant adverse events. Cardiostim 2006, LBCT Session, Nice, France
34. Farwell D, Patel NR, Hall A et al (2000) How many people with heart failure are appropriate for biventricular resynchronization? Eur Heart J 21:1246–1250
35. Khaun AG, Cleland JG, Deedwania PC (2002) Prevention of medical therapy of atrial arrhythmias in heart failure. Heart Fail Rev 7:267–283
36. Kies P, Leclercq C, Bleeker GB et al (2006) Cardiac resynchronisation therapy in chronic atrial fibrillation: impact on left atrial size and reversal to sinus rhythm. Heart 92:490–494
37. Tolosana JM, Garcia Bolao I, Fernadez Lozano I et al (2007) Atrial fibrillation, an independent predictor of cardiovascular mortality in patients submitted to CRT. Europace 2007, Lisbon, Portugal, June 24–27. Abstract in press
38. Fung JW, Yu CM, Chan JY et al (2006) Effects of cardiac resynchronization therapy on incidence of atrial fibrillation in patients with poor left ventricular systolic function. Am J Cardiol 96:728–731
39. Hoppe UC, Casares JM, Eiskjaer H et al (2006) Effect of cardiac resynchronization on the incidence of atrial fibrillation in patients with severe heart failure. Circulation 114:18–25

40. Valle A, Quesada A, Albero V et al (2007) Incidence of atrial fibrillation in patients with cardiac resynchronization therapy, a case control study. Europace 2007 Lisbon, Portugal, June 24–27. Abstract in press
41. Padeletti L, Musilli N, Porciani MC et al (2004) Atrial fibrillation and cardiac resynchronization therapy: the MASCOT study. Europace(5 Suppl 1):S49-S54

Conversion of Persistent Atrial Fibrillation to Sinus Rhythm by DC Shock: Is It Still in Use Two Years After AFFIRM?

Valeria Calvi, Salvatore Timineri

The AFFIRM trial compared a rhythm-control option, which included cardioversion and maintenance of sinus rhythm (SR), to a rate-control option, without cardioversion and with control of ventricular rate, in patients with atrial fibrillation (AF). The 4,060 patients with AF and risk factors for stroke or death who were enrolled in the study were randomized to one of the two therapeutic options. At the conclusion of the study, no differences were found between the two groups with respect to death or composite morbidity; an increase in the number of hospitalizations was found in the rhythm control group (80.1 vs 73%) and, surprisingly, the strategy of maintaining sinus rhythm did not lead to a lower rate of ischemic stroke. It was concluded that, along with anticoagulation, controlling ventricular rate is as effective in preventing morbidity and mortality in patients with AF as traditional anti-arrhythmic strategies [1–3].

However, upon closer analysis, these conclusions are questionable.

Firstly, cross-overs between strategies and subsequent return to the original strategy were common during the trial [3]. For this reason, it is necessary to analyze the data not only on the basis of an "intention to treat principle," as done in the primary analysis of the AFFIRM study, but also and especially on the basis of an "on-treatment principle," using different types of time-dependent covariates that permit the evaluation of patients according to their actual treatment and status [4]. In this way it is possible to distinguish the true differences between the two treatment groups and to dissociate the use of anti-arrhythmic drugs (AADs) from the presence of SR, for a more careful analysis. Indeed, it is interesting to notice that in this analysis SR was

Cardiology Clinic, University of Catania, Ferrarotto Hospital, Catania, Italy

associated with a superior life expectancy and use of AADs was related to a higher death rate and to a greater number of hospitalizations. This reflects the fact that currently used AADs are not completely safe and effective.

From the results, it can be concluded that the high mortality in the rhythm-control arm of the study was due to both the secondary and pro-arrhythmic effects of AADs [4]. More importantly, it is clear that the results of the study could be altered by another intrinsic defect: the very small difference between the percentages of patients in SR in the two arms of the study [5] could have falsified and reduced the awareness of the benefits obtained by the goal of establishing SR. Moreover, after an accurate data analysis, the higher mortality in the rhythm-control group was found to be due mainly to non-cardiac deaths [6], and subjects with heart failure (HF) and those with a reduced ejection fraction (EF) were not adequately represented. However, both groups would have most likely reaped particular benefit in terms of reduced mortality from the maintenance of SR [1, 2].

These considerations help us to understand how far the AFFIRM data are from proving a real equivalence in terms of survival between rhythm and rate control. Moreover, a fundamental purpose of AF therapy is to guarantee, in addition to a longer life, a better quality of life. It is well-known that AF can cause a vast stream of symptoms, and different studies have shown that the quality of life for patients with AF is similar to that for patients with HF [7].

In this sense, the AFFIRM study revealed a substantial equivalence of the two strategies, i.e., rate and rhythm control [8]. This was probably due to the fact that 40% of patients in the rhythm-control group had AF at the end of the study [9], to the negative effects of AADs [4], and to the exclusion from the study of patients who could have benefited most from the restoration of SR, i.e., young patients with "lone AF" and strongly symptomatic patients [1–3]. Other studies have shown an increase in the quality of life and physical performance of patients whose AF was converted to SR [7, 10–12]. Finally AFFIRM did not include young patients or symptomatic patients with little underlying heart disease, in whom restoration of SR must be considered a useful therapeutic option.

Nonetheless, how can we use the findings and observations of AFFIRM in clinical practice? And did the outcomes and implications of the AFFIRM study change our views on the role of DC shock in the conversion of persistent AF to SR? The conclusions we can draw from AFFIRM are the lack of a widely effective method for maintaining SR, one that has few side effects. Also, the management of arrhythmia should be tailored to the patient's characteristics, with the most appropriate therapeutic strategy chosen according

to patient history. Rate-control should be reserved for elderly patients with minimal symptoms related to AF. The physician should assess the symptoms associated with AF, the presence of HF or other cardiovascular disease, and the patient's age, preference, and compliance with therapy.

Although AFFIRM compared two mid-/long-term pharmacological therapeutic strategies for AF, it did not change current indications for DC shock, which is the most effective method for restoring SR in patients with persistent AF and is not a mid-/long-term form of treatment. DC shock has several advantages, including a high success rate and immediate restoration of SR, as opposed to the unpredictable time required with pharmacologic cardioversion, and the avoidance of potential adverse drug reactions. It is also an elective therapy in patients with AF during acute myocardial infarction, in the presence of hemodynamic impairment, in patients with Wolff-Parkinson-White (WPW) syndrome, and in those with chronic AF resistant to pharmacologic cardioversion. Thus, DC shock remains the most effective procedure to treat AF, with a success rate close to 100% [13–15].

DC shock consists of the delivery of an electrical shock that is synchronized with the intrinsic cardiac activity by R-wave sensing on an ECG lead. Successful treatment depends on the patient's characteristics and underlying disease and on the current density delivered to the myocardium. The latter is related to defibrillator voltage, output waveform, size and position of the electrode paddles, and thoracic impedance. Regarding underlying disease, it is very important to detect clinical and echocardiographic predictors for successful electrical cardioversion and maintenance of SR.

The most important negative predictive factors for short-term success of DC shock seem to be a body mass index (BMI) > 30 and hypertension [16], whereas factors determining AF recurrence after electrical cardioversion are older age [16–18], long AF duration [18, 19], and left atrial enlargement [17, 19]. Pre-treatment with beta-blockers prior to cardioversion, if possible, has been suggested [16].

Thoracic electrical impedance is higher in women, increases with increasing BMI and hemoglobin concentration, and is lower in patients with HF [20]. It is an essential factor in defining the relation between delivered energy and transmyocardial current, which is one of the most important determinants of effectiveness [21]. Thus, the energy delivered should be adjusted according to clinical variables affecting thoracic electrical impedance in order to obtain sufficient transmyocardial current for successful cardioversion, with minimal myocardial injury.

The output waveform influences the energy delivered during DC shock. Sinusoidal monophasic shock and biphasic shock can be applied; in the for-

mer, current transits in only one direction, while in the latter current transits between the two electrodes, first in one direction and then in the other. A rectilinear biphasic waveform is safer because it requires fewer shocks and lower delivered energy. The effectiveness of this approach, which is nearly 100%, with minor energy delivery and less dermal and myocardial injury, has been shown in several studies [13–15, 22, 23]. Finally, electrode configuration is important for successful cardioversion, as an anterior-posterior position was shown to be better than an anterior-anterior one [24, 25].

In conclusion, since the AFFIRM study did not address DC shock as a therapeutic option, the indications for its use have not changed. At the same time, the results of the AFFIRM study calls attention to the need for new treatment strategies to maintain SR in patients with cardioverted AF, i.e., new atrial-specific AADs [26] or non-pharmacologic therapies, to avoid the negative effects of the currently used anti-arrhythmics.

References

1. The planning and steering committees of the AFFIRM study for the NHLBI AFFIRM Investigators (1997) Atrial fibrillation follow-up investigation of rhythm management: the AFFIRM study design. Am J Cardiol 79:1198–1202
2. The AFFIRM Investigators (2002) Baseline characteristics of patients with atrial fibrillation: the AFFIRM study. Am Heart J 143:991–1001
3. The Atrial Fibrillation follow-up investigation management (AFFIRM) Investigators (2002) A comparison of rate control and rhythm control in patients with atrial fibrillation. N Eng J Med 347:1825–1833
4. The AFFIRM Investigators (2004) Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Study. Circulation 109:1509–1513
5. Chung MK, Shemans KIL, Sherman DG et al, for the AFFIRM investigators (2005) Functional status in rate-versus rhythm-control strategies for atrial fibrillation: result of the Atrial Fibrillation Follow-Up Investigation of Rhythm Management (AFFIRM) Functional Status Sub-study. J Am Coll Cardiol 46:1891–1899
6. Steinberg JS, Sadaniantz A, Kron J et al (2004) Analysis of cause-specific mortality in the atrial fibrillation follow-up investigation of rhythm management study. Circulation 109:1973–1980
7. Dorian P, Jung W, Newman D et al (2000) The impairment of health related quality of life in patients with intermittent atrial fibrillation: implications for the assessment of investigational therapy. J Am Coll Cardiol 336:1303–1309
8. The AFFIRM investigators (2005) Quality of life in Atrial Fibrillation Follow-Up Investigations of The Rhythm Management (AFFIRM) study. Am Heart J 149:112–120
9. Singh SN, Tang XC (2006) Quality of life and exercises performance in patients in sinus rhythm versus persistent atrial fibrillation. A Veterans Affairs cooperative studies program sub-study. J Am Coll Cardiol 48:721–730
10. Singh BN, Singh SN, Reda DJ et al; Sotalol Amiodarone Atrial Fibrillation Efficacy

Trial (SAFE-T) Investigators (2005) Amiodarone versus sotalol for atrial fibrillation. Veterans Affairs cooperative study. N Engl J Med 352:1861–1872
11. Dorian P, Paquette M, Newman D et al; CTAF Investigators (2002) Quality of life improves with treatment in the Canadian Trial Fibrillation. Am Heart J 143:984–990
12. Hagens VE, Ranchor AV, Sonderen EV et al; RACE Study Group (2004) Effect of rate or rhythm control on quality of life in persistent AF. J Am Coll Cardiol 43:241–247
13. Mittal S, Ayati S, Stein KM et al (2000) Transthoracic cardioversion of atrial fibrillation: comparison of rectilinear biphasic versus damped sine wave monophasic shocks. Circulation 101:1282–1287
14. Santomauro M, Borrelli A, Ottaviano L et al (2004) Transthoracic cardioverson in patients with atrial fibrillation: comparison of three different waveforms. Ital Heart J Suppl 5:36–43
15. Lindell P, Svenarud P, Albage A et al (2001) Electrical conversion of atrial fibrillation. Superior effects of biphasic transthoracic method when compared with the conventional monophasic method. Lakartidningen 25:3319–3321
16. Miry B, Yeouda E (2006) Electrical cardioversion for persistent or chronic atrial fibrillation: outcome and clinical factors predicting short and long term success rate. Int J Cardiol 107:389–394
17. Alt E, Ammer R, Lehmann G et al (1997) Patient characteristics and underlying heart disease as predictors of recurrent atrial fibrillation after internal and external cardioversion in patients treated with sotalol. Am Heart J 134:419–425
18. Duytschaever M, Haerynck F, Tavernier R et al (1998) Factors influencing long term persistence of sinus rhytm after a first electrical cardioversion for atrial fibrillation. Pacing Clin Electrophysiol 21:284–287
19. Frick M, Frykman V, Jensen Urstad M et al (2001) Factors predicting success rate and recurrence of atrial fibrillation after first electrical cardioversion in patients with persistent atrial fibrillation. Clin Cardiol 24:238–244
20. Fumagalli S, Boni N, Padeletti M et al (2006) Determinants of thoracic electrical impedance in external electrical cardioversion of atrial fibrillation. Am J Cardiol 98:82–87
21. American Heart Association (2000) Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care; Part 6: advanced cardiovascular life support; Section 2: defibrillation. The American Heart Association in collaboration with the international Liaison Committee on resuscitation. Circulation 102:I90-I94
22. Block M, Hammel D, Bocker D et al (1994) A prospective randomized cross-over comparison on mono- and biphasic defibrillation using non thoracotomy lead configurations in humans. J Cardiovasc Electrophysiol 5:581–590
23. Krasteva V, Trendafilova E, Cansell A, Dasalov I (2001) Assessment of balanced biphasic defibrillation waveforms in transthoracic atrial cadioversion. J Med Eng Technol 25:68–73
24. Page RL, Kerber RE, Russell JK et al (2002) Biphasic versus monophasic shock waveform for conversion of atrial fibrillation: the results of an international randomized, double-blind multicenter trial. J Am Coll Cardiol 39:1956–1963
25. Botto GL, Politi A, Bonini W et al (1999) External cardioversion of atrial fibrillation: role of paddle position on technical efficacy and energy requirements. Heart 82:726 –730
26. Roy D, Rowe BH, Stiell IG et al (2004) A randomized, controlled trial of RSD1235, a novel antiarrhythmic agent, in the treatment of recent onset atrial fibrillation. J Am Coll Cardiol 44:2355–2361

Lone Atrial Fibrillation and Sports Activities

Francesco Furlanello[1,2], Giuseppe Inama[3], Claudio Pedrinazzi[3], Luigi De Ambroggi[1], Riccardo Cappato[1]

Introduction

Atrial fibrillation (AF) and atrial flutter (AFl) are two of the most frequent causes of prolonged palpitations [1–8] in young competitive athletes, even including those performing sport activities at an elite level. Specifically, these arrhythmias can occur frequently during training and competitions or in the post-exercise recovery period, but rarely at rest.

Recurrences of paroxysmal AF in young competitive athletes may interfere with competitive professional activity, mainly if they are characterized by a high ventricular rate and if their occurrence is exercise-related. In such cases, AF and AFl may be a cause of non-eligibility for competitive sport activity [9]. From the pathophysiological point of view, AF in competitive athletes (with intact heart) seems to be due to adrenergic or vagal mechanisms in "susceptible" subjects, with neurohormonal imbalance related to prolonged athletic training [1–7, 10]. An interesting animal model of AF can be found in racehorses, in which there is a combination of a large heart (including the atria), high vagal tone, and episodes of strenuous exercise leading to atrial stimulation through sudden and strong epinephrine release [11, 12]. The role of a long-term vigorous and regular sport practice in favoring AF occurrence is supported by the higher prevalence of AF/AFl in "master" than in younger (< 35 years) athletes and in the general population [13–17].

From 1974 until March 2007, we studied and monitored a population of 3,222 arrhythmic competitive athletes, with a mean age of 22.3 years [5]. In this population, 285 subjects performed sports activities at an elite level

[1]IRCCS Policlinico San Donato, University of Milan; [2]Casa di cura Villa Bianca, Trento; Department of Cardiology, Ospedale Maggiore, [3]Crema (CR), Italy

(mean age 24.2 years). Through standardized noninvasive and invasive workups during a long-term follow-up, we found a prevalence of AF/AFl of about 5% among arrhythmic symptomatic competitive athletes and of 5.2% in those performing sport at an elite level [6].

Even though the "lone" form of AF/AFl is the most frequent clinical presentation [15, 16, 18], AF/AFl can be the first sign of an underlying heart disease, i.e., myocarditis, hypertrophic cardiac myopathy (HCM), dilated cardiomyopathy (DCM), Brugada syndrome, arrhythmogenic right ventricular disease (ARVD), ischemic heart disease, and short QT syndrome [17, 19]. A well-identified initiation mechanism, such as atrioventricular nodal reentrant tachycardia (AVNRT), a concealed form of Wolff-Parkinson-White (WPW) syndrome, or focal atrial tachycardia, besides left atrial ectopic beats may sometimes be found.

The present management of athletes with AF is complicated by the problem of illicit drug consumption. The majority of illicit drugs included in the IOC WADA 2007 list that are taken to improve athletic performance or as masking agents (in particular alcohol, stimulants, cocaine, cannabinoids, anabolic androgenic steroids, or a combination of different forbidden substances, or certain dietary supplements) may induce AF through a direct or indirect arrhythmogenic effect, in healthy subjects and in those with a latent underlying arrhythmogenic heart disease, including some forms related to the consumption of illicit drugs [17, 20–24].

Discussion

The prevalence of AF/AFl among young competitive athletes actively practicing sport activities and who complain of palpitations is about 5%. This condition predominantly affects males and it is frequently associated with a sinus bradyarrhythmia mimicking sick sinus syndrome. Moreover, in these patients AFl is almost always present. If the prescribed medication is taken correctly by patients, in some cases detraining may be useful in order to avoid arrhythmia recurrences without the need for catheter ablation. However, the interventional approach is the most effective way to treat this type of arrhythmias.

Furthermore, it is very important to point out that among athletes > 35 years of age who continue to perform sports activities there is a relative risk of developing AF/AFl of about 3 when compared to young competitive athletes. However, in some cases the arrhythmia may be resolved by a period of detraining. In consideration of the high prevalence of AFl, interventional

treatment of this arrhythmia is very important in patients undergoing radiofrequency catheter ablation for lone AF. In fact, AFl rarely occurs in the isolated typical or atypical form (originating from the left atrium); instead, during the clinical course of patients with AF who are on anti-arrhythmic therapy, episodes of I–IIIC, drug-induced AFl are relatively frequent. These are easily prevented through radiofrequency ablation. Moreover, AFl should be considered as an additional risk factor for the development of AF over time in endurance athletes who continue to practice their sport [25].

Radiofrequency catheter ablation is also effective in treating some cases of sinus bradyarrhythmia resembling sick sinus syndrome in competitive athletes affected by AF/AFl. In such cases, successful ablation of the AF substrate can effectively resolve this associated condition. This approach avoids the necessity of cardiac pacing, which has been frequently proposed as a treatment option in middle-aged athletes with particularly evident bradyarrhythmic episodes, especially during the recovery period [26, 27].

There is a growing interest in studying the pathophysiological mechanisms of AF not only in populations of young athletes performing sports activities at a highly competitive level [1, 3, 4, 6, 7, 28] but even more so in subjects who continue intense-endurance sports activities after age 35 [15, 18, 29, 30]. Both types of subjects are more highly predisposed than sedentary people to develop AF [31]. It would be very interesting to determine whether there is a link between excessively strenuous sports activities and the development of AF with respect to the pathophysiological mechanisms of the "overtraining syndrome." The latter may be the cause of inflammatory processes and immunological modifications, including the presence of increased levels of C-reactive protein. It may be that the morphofunctional modifications occurring beyond the paraphysiological adaptations to sports activities can be adequately addressed by the prescription of glucocorticoids, statins, ACE inhibitors, and angiotensin-receptor blockers, in addition to detraining.

Aknowledgements
The authors thank secretary Anna Stenghel for her help in preparing the manuscript.

References

1. Furlanello F, Bertoldi A, Dallago M et al (1998) Atrial fibrillation in elite athletes. J Cardiovasc Electrophysiol 9(Suppl):S63-S68
2. Zehender M, Meinertz T, Keul J et al (1990) ECG variants and cardiac arrhythmias in athletes: clinical relevance and prognostic importance. Am Heart J 119:1378–1394

3. Biffi A, Piovano G, Verdile L et al (1997) Prognostic evaluation on supraventricular arrhythmias in athletes. In: Pelliccia A, Caselli G, Bellotti P (eds) Advances in sport cardiology. Springer, Berlin-New York-Milan, pp 40–44
4. Delise P, Bonso A, Corò L et al (1992) Electrophysiologic substrates of idiopathic atrial fibrillation in the general population and in athletes. New Trends Arrhyth 8:719–724
5. Furlanello F, Bertoldi A, Fernando F, Biffi A (2000) Competitive athletes with arrhythmias. Classification, evaluation and treatment. In: Bayes de Luna A, Furlanello F, Maron BJ, Zipes DP (eds) Arrhythmias and sudden death in athletes. Kluwer Academic, Dordrecht, pp 89–105
6. Naccarella F, Furlanello F, Bertoldi A et al (2003) "Lone" atrial fibrillation in athletes: a consequence of long-term intensive sport practice. In: Raviele A (ed) Cardiac Arrhythmias 2003, Proceedings of the 8th International Workshop on Cardiac Arrhythmias. Springer Verlag Italia, Milan, pp 11–21
7. Furlanello F, Bertoldi A, Dallago M et al (1994) Atrial fibrillation in top-level athletes. In: Olsson SB, Allessie MA, Campbell RWF (eds) Atrial fibrillation: mechanisms therapeutic strategies. Futura, Armonk, NY, pp 203–204
8. Durin O (2005) La fibrillazione atriale nello sportivo: quale significato e quali provvedimenti. In: Inama G (ed) Corso di Aggiornamento ANMCO. Problemi aperti in Cardiologia dello Sport. Crema, Aprile 2005, pp 15–26
9. Heidbuchel H, Panhuyzen-Goedkoop N, Corrado D et al (2006) Recommendations for participation in leisure-time physical activity and competitive sports in patients with arrhythmias and potentially arrhythmogenic conditions. Part I: Supraventricular arrhythmias and pacemakers. Eur J Cardiovasc Prev Rehab 13:475–484
10. Link MS, Hamud MK, Wang PJ et al (2001) Cardiac arrhythmias in the athlete. Cardiol Rev 9:21–30
11. Williams RB, Harkins LS, Hammond CJ, Wood JL (2001) Racehorse injuries, clinical problems and fatalities recorder on British race courses from flat racing and National Hunt racing during 1996, 1997 and 1998. Equine Vet J 33:478–486
12. Bove AA (2004) Arrhythmias in professional athletes: focus and atrial fibrillation. ACC Curr J Rev 2004:47–48
13. Hood S, Northcoic BJ (1999) Cardiac assessment of veteran endurance athletes: a 12-year follow up study. Br J Sports Med 33:239–243
14. Karjalaine U, Kujala U, Kaprio J et al (1998) Lone atrial fibrillation in vigorously exercising middle aged men: case-control. BMJ 316:1784–1785
15. Elosua R, Arquer A, Mont L et al (2006) Lone atrial fibrillation and sport practice. The no gain without pain history revisited again? Int J Cardiol (epub ahead of print)
16. Elosua R, Arquer A, Mont L et al (2006) Sport practice and the risk of lone atrial fibrillation: a case-control study. Int J Cardiol 108:332–337
17. Saoudi N, Yaici K, Zarkane N et al (2005) Arythmies du sportif. Arch Mal Coeur 98:48–53
18. Turhan H, Aksoy Y, Yetkin E et al (2006) An undesirable cardiac impact of vigorous sport practice: Lone atrial fibrillation. Int J Cardiol (epub ahead of print)
19. Liuk MS, Hamoud MK, Wang PJ (2002) Cardiac arrhythmias in the athlete: the evolving role of electrophysiology. Curr Sci Sports Med Report 1:75–85
20. Furlanello F, Bentivegna S, Cappato R, De Ambroggi L (2003) Arrhythmogenic effect of illicit drugs in athletes. Ital Heart J 4:829–837

21. Kloner AR (1998) Illicit drug use in the athlete as a contributor to cardiac events. In: Estes NA, Salem DN, Wang Pj (eds) Sudden cardiac death in the athlete. Futura, Armonk, NY, pp 441–451
22. Rich EC, Siebold C, Campion B (1985) Alcohol-related acute atrial fibrillation. A case-control study and review of 40 patients. Arch Intern Med 145:830–833
23. Bove AA (2002) Dietary supplements in athletes. ACC Curr J Rev 11:18–20
24. Sullivan ML, Martinez CM, Gallagher EJ (1999) Atrial fibrillation and anabolic steroids. J Emerg Med 17:851–857
25. Heidbuchel H, Anne W, Willems R et al (2006) Endurance sports is a risk factor for atrial fibrillation after ablation for atrial flutter. Int J Cardiol 107:67–72
26. Khaykin Y, Marrouche N, Martin D et al (2004) Pulmonary vein isolation for atrial fibrillation in patients with symptomatic sinus bradycardia or pauses. J Cardiovasc Electrophysiol 15:784–789
27. Furlanello F, Esposito C, Lupo P et al (2005) Fibrillazione atriale parossistica nel bradicardico. In: Prati PL (ed) Conoscere e curare il cuore 2005. Essebiemme Editore, Firenze, pp 261–270
28. Pelliccia A, Maron BJ, Di Paolo FM et al (2005) Prevalence and clinical significance of left atrial remodeling in competitive athletes. J Am Coll Card 46:690–696
29. Karjalainen J, Kujala UM, Kaprio J et al (1998) Lone atrial fibrillation in vigorously exercising middle aged men: case-control study. BMJ 316:1784–1785
30. Mont L, Sambola A, Brugada J et al (2002) Long-lasting sport practice and lone atrial fibrillation. Eur Heart J 23:477–482
31. Swanson DR (2006) Atrial fibrillation in athletes: implicit literature-based connections suggest that overtraining and subsequent inflammation may be a contributory mechanism. Med Hypotheses 6:1085–1092

Heart-Failure Management: Focus on Heart-Failure Practice Guidelines

Eugene Crystal, Rajneesh Calton

Introduction

Heart failure (HF) is associated with a high burden of mortality and morbidity, reduced quality of life, and increasing healthcare costs [1, 2]. HF is largely a disease of old age, and it is becoming increasingly prevalent with the gradual aging of the global population [3]. HF is a complex syndrome in which abnormal heart function results in, or increases the subsequent risk of clinical symptoms and signs of low cardiac output and/or pulmonary and systemic congestion [4].

Because most evidence-based recommendations for HF management derive from clinical trials involving patients with significant left ventricular systolic dysfunction, the term "heart failure" in various guideline documents has been used to refer to predominant left ventricular systolic dysfunction, unless otherwise reported [5–7]. The increasing recognition of the existence of clinical HF in patients with normal ejection fraction (EF) has led to heightened awareness of the limitations of evidence-based therapy for this important group of patients. A better understanding of the underlying pathophysiological mechanism, combined with the many new treatments developed over the last 20 years, has greatly improved the prognosis of patients with HF, and many patients can now hope for long periods of stable improved symptoms and improved heart function. Nonetheless, an inexorable course of HF can also occur, while many new approaches to treatment continue to develop. Advances in multidisciplinary care, heart failure clinics, polypharmacy, device therapy, and surgical approaches have greatly helped in improving the care of patients with HF [6].

Department of Cardiology, Schulich Heart Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto (ON), Canada

Heart failure is major and growing public health problem. In the USA, approximately 5 million patients have HF, and more than 550,000 patients are diagnosed with first-time HF each year. HF is the primary reason for 12–15 million office visits and 6.5 million hospital days each year [6]. Over one million patients are hospitalized annually for HF as the primary diagnosis [6]. HF treatment also causes a major economic burden on healthcare expenditures. In the USA, in 2005, the estimated total direct and indirect cost of HF was approximately $27.9 billion [6].

The European society of Cardiology (ESC) represents European countries with a population of over 900 million and these countries have at least 10 million patients with HF [7]. There are also patients with myocardial systolic dysfunction without symptoms of HF who also constitute approximately a similar prevalence [8]. The prognosis of HF is uniformly poor if the underlying problem cannot be rectified. Half of patients carrying a diagnosis of HF die within 4 years; in patients with severe heart failure, more than 50% die within 1 year [9].

Management of Heart Failure

Management of HF begins with an accurate diagnosis and requires a rational combination-drug therapy; individualization of care for each patient based on their symptoms, clinical presentation, and disease severity; appropriate mechanical interventions, including revascularization and devices; collaborative efforts among healthcare professionals; and education and cooperation of the patient and their immediate caregivers. Managing patients with HF can be challenging, and practice guidelines provide a great help in caring for such patients. These published guidelines and consensus recommendations provide an evidence-based roadmap to translate knowledge into practice and allow healthcare practitioners to reach the best clinical judgment and decisions for their individual patients.

Presently, three main guidelines for the diagnosis and management of chronic HF in adults are followed internationally. These are: (1) ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in adults: a report of the American College of Cardiology /American Heart Association task force on practice guidelines: Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society [6]; (2) ESC Guidelines: guidelines for the diagnosis and treatment of chronic heart failure (Update 2005). The task force for the diagnosis and treatment of chronic heart failure of the European Society of Cardiology [7];

and (3) Canadian Cardiovascular Society Consensus Conference Recommendations on heart failure 2006: diagnosis and management [5].

All three guidelines are in agreement in defining the class of recommendation and the grade of evidence for any diagnostic procedure or treatment.

- Class I: Evidence or general agreement that a given procedure or treatment is beneficial, useful, and effective.
- Class II: Conflicting evidence or a divergence of opinion about the usefulness or efficacy of the procedure or treatment.
- Class IIa: Weight of evidence is in favor of usefulness or efficacy.
- Class IIb: Usefulness or efficacy is less well-established by evidence or opinion.
- Class III: Evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful.
- Level of evidence A: Data derived from multiple randomized clinical trials or meta-analysis.
- Level of evidence B: Data derive from a single randomized clinical trial or nonrandomized studies.
- Level of evidence C: Consensus of opinion of experts and/or small studies.

Management of HF in general constitutes nonpharmacological methods, pharmacotherapy, device therapy, and surgical procedures. This article compares the recommendations made by different practice guidelines for the management of patients with chronic HF.

Nonpharmacological Interventions

In patients with HF in the presence of systolic left ventricular (LV) dysfunction (LVEF ≤ 40%), all symptomatic patients should be advised about exercise training, salt and fluid restriction, and weight management. Aggressive risk factor reduction should be attempted and lifestyle modification should be advised.

All the guidelines recommend dietary salt restriction (class I, level C). The CCS and ESC guidelines recommend exercise training in HF patients (class I, level C). The ACC/AHA guidelines recommend exercise training in patients with HF as class I, level B indication. The CCS guidelines stress daily weight measurements (class I, level C) while ACC/AHA guidelines advise that the healthcare provider should record the body weight of the patient at each visit. Avoidance of smoking, excessive use of alcohol, and use of illicit drugs is stressed in ACC/AHA and ESC guidelines. Recommendations made in different practice guidelines for nonpharmacological interventions in HF are shown in Table 1.

Table 1. Non-pharmacological management of heart failure (HF): comparison of different practice guidelines

Indication	ACC/AHA guideline (2005)	ESC guideline (2005)	CCS consensus conference on HF recommendations (2006)
Exercise training	Class I, level B	Class I, level C	Class II a, level B
Dietary salt restriction	Class I, level C	Class I, level C	Class I, level C
Daily morning weight monitoring			Class I, level C
Daily fluid restriction		Class I, level C	Class I, level C
Avoid: smoking, excessive alcohol use, and illicit drug use	Class I, level C	Class I, level C	

Pharmacotherapy

There have been many landmark clinical trials and meta-analysis of the use of angiotensin-converting enzyme inhibitors (ACEI) [10] and beta-blockers (BB) [11] in HF, such that these types of drugs have become standard therapy and should be considered in all patients diagnosed with HF. The timing of introduction should be individualized to maximize tolerability and long-term persistence with therapy. In general, acute symptoms should be relieved, but an ACEI or a BB should be introduced as early as the patient's condition allows. All of the practice guidelines are in agreement for strongly recommending (class I, level A) the use of ACEI and BB in patients with HF unless contraindications exist. Tables 2 and 3 list the practice guideline recommendations for the use of ACEIs and BBs in HF patients.

In patients who are already on a combination of ACEI and BB but continue to have heart failure symptoms or hospitalizations, an angiotensin-II-receptor blockers (ARB) should be added [12]. Aldosterone antagonists (spironolactone, eplerenone) are effective in patients with severe post-myocardial-infarction HF or in long-term follow-up, especially in those patients recently hospitalized for HF [13]. Recommendations of practice guidelines is shown in Table 2.

Table 2. Pharmacotherapy of heart failure: comparison of different practice guidelines

Drugs	ACC/AHA guideline (2005)	ESC guideline (2005)	CCS consensus conference on HF recommendations (2006)
ACE inhibitors			
HT and LVH, no symptom of HF	Class IIa, level B		Class IIa, level B
Asymptomatic patients, LVEF ≤ 35%	Class I, level A	Class I, level A	Class I, level A
HF symptoms, LVEF ≤ 40%	Class I, level A	Class I, level A	Class I, level A
Post-AMI, LVEF ≤ 40%, AHF post AMI	Class I, level A	Class I, level A	Class I, level A
ARBs			
Patients who cannot tolerate ACEI; low EF, no symptom of HF	Class I, level A		Class I, level A
ARBs instead of ACEI in AHF with AMI or HF symptoms with LVEF ≤ 40%	Class IIa, level A	Class I, level B	Class I, level B
ARBs added to ACEI for persistent HF symptoms	Class IIb, level B	Class IIa, level B	Class I, level A
ARBs with ACEI when beta-blockers are contraindicated or not tolerated			Class IIa, level B
Aldosterone antagonists			
Severe HF symptoms, LVEF ≤ 30%, and optimized drug therapy	Class I, level B	Class I, level B	Class I, level B
AHF with LVEF ≤ 30% following AMI		Class I, level B	Class IIa, level B

ACEI, Angiotensin-converting-enzyme inhibitors; *ARBs*, angiotensin II receptor blockers; *HF*, heart failure; *LVEF*, left ventricular ejection fraction; *AHF*, acute heart failure; *AMI*, acute myocardial infarction; LVH, left ventricular hypertrophy

Angiotensin-Converting-Enzyme Inhibitors

- ACEI should be used in all patients as soon as safely possible after acute myocardial infarction, and should be continued indefinitely if LVEF is < 40% or if acute HF complicated the myocardial infarction (class I, level A).
- ACEI should be used in all asymptomatic patients with an LVEF < 35% (class I, level A).
- ACEI should be used in all patients with symptoms of HF and an LVEF < 40% (class I, level A).

Angiotensin-Receptor Blockers

- ARBs should be used in patients who cannot tolerate ACEIs, although renal dysfunction and hyperkalemia may recur (class I, level A).
- ARBs should be added to an ACEI for patients with persistent HF symptoms who are assessed to be at increased risk of HF hospitalization, despite optimal treatment with other recommended drugs (class I, level A).
- ARBs may be considered instead of an ACEI for patients with acute MI with acute HF or LVEF < 40% (class I, level B).
- ARBs may also be considered as adjunctive therapy to ACEI when BB are either contraindicated or not tolerated after careful attempt at initiation (class IIa, level B).

Beta-blockers

- All HF patients with an LVEF ≤ 40% should receive a BB proven to be beneficial in large-scale clinical trials (carvedilol, bisoprolol, metoprolol CR/XL) (class I, level A).
- Patients with NYHA class IV symptoms should be stabilized before initiation of a BB (class I, level C).
- Therapy should be initiated at a low dose and titrated to the target dose used in large-scale clinical trials or the maximum tolerated dose if less than the target dose (class I, level B).
- Beta-blockers should not normally be introduced in patients with symptomatic hypotension despite adjustment of other therapies, severe reactive airway disease, symptomatic bradycardia, or significant AV block without a permanent pacemaker. Stable chronic obstructive pulmonary disease is not a contraindication (class I, level B).

Aldosterone Antagonists

- Aldosterone antagonism with spironolactone or eplerenone should be considered for patients with an LVEF < 30% and severe symptomatic chronic HF despite optimization of other recommended treatments (class I, level B), or acute HF with an LVEF < 30% following myocardial infarction (class IIa, level B), if serum creatinine is < 200 μmol/l and potassium is < 5.2 mmol/l.

Vasodilators

- The combination of isosorbide dinitrate and hydralazine should be considered in addition to standard therapy for African-Americans with systolic dysfunction (class IIa, level B), and may be considered for other HF patients unable to tolerate other recommended standard therapy (class IIb, level B). Practice guideline recommendations for the use of vasodilators are given in Table 3.

Diuretics

- A loop diuretic, such as furosemide, is recommended for most patients with HF and congestive symptoms. Once acute congestion is cleared, the lowest minimal dose should be used that is comparable with stable signs and symptoms (class I, level C).
- For patients with persistent volume overload despite optimal, other medical therapy and an increase in loop diuretics, cautious addition of a second diuretic (for example, a thiazide or low-dose metolazone) may be considered as long as it is possible to closely monitor morning daily weight, renal function, and serum potassium (class IIb, level B).

Digoxin

- In patients in sinus rhythm who continue to have moderate to severe persistent symptoms despite optimized HF medical therapy, digoxin is recommended to relieve symptoms and reduce hospitalizations (class I, level A).
- In patients with chronic atrial fibrillation and poor control of ventricular rate despite BB therapy, or when BBs cannot be used, digoxin should be considered (class IIa, level B).

Table 3. Pharmacotherapy of heart failure: comparison of different practice guidelines

Drugs	ACC/AHA guideline (2005)	ESC guideline (2005)	CCS consensus conference on HF recommendations (2006)
Beta-blockers			
All recent or remote MI, regardless of LVEF or HF	Class I, level A	Class I, level A	
Reduced LVEF, no HF Sx	Class I, level C		
HF with LVEF ≤ 4 0%	Class I, level A		Class I, level A
Digoxin			
Current or prior Sx of HF, reduced LVEF, optimized medical therapy	Class IIa, level B	Class IIa, level B	Class I, level A
Any degree of HF with AF		Class I, level B	Class IIa, level B
Vasodilators (nitrates, hydralazine)			
Reduced LVEF, persistent HF Sx on ACEI and BB	Class IIa, level A		Class IIb, level B Afro-Americans: Class IIa, level A
Reduced LVEF, HF Sx, intolerant to ACEI or ARBs	Class IIb, level C	Class IIa, level B	

ACEI, Angiotensin-converting-enzyme inhibitors; *ARBs*, angiotensin II receptor blockers; *BB*, beta-blockers; *HF*, heart failure; *LVEF*, left ventricular ejection fraction; *MI,* myocardial infarction; *Sx,* symptom

CCS guidelines [5] recommend the use of digoxin as a class I indication to reduce hospitalization in patients with sinus rhythm and moderate to severe HF symptoms despite optimized HF medical therapy, while ESC guidelines [7] recommend the use of digoxin as a class I indication for patients with atrial fibrillation (AF) and HF.

Drugs To Be Avoided in Heart-Failure Patients

It is also important to recognize that certain classes of drugs can exacerbate the syndrome of HF and thus should be avoided in most patients [6]. These are:

- Anti-arrhythmic agents: Only amiodarone and dofetilide have been shown not to adversely affect survival.
- Calcium-channel blockers (CCB): only vasoselective CCBs have been shown not to adversely effect survival.
- Nonsteroidal anti-inflammatory drugs.

Focus on Specialized Heart-Failure Clinics

Despite the clear survival benefits supporting the use of pharmacological therapies in the management of HF patients, prognosis associated with recurrent and prolonged hospitalization remains poor. Strategies incorporating post-discharge follow-up by a multidisciplinary team of specially trained staff and/or access to specialized HF clinics reduce mortality and all-cause hospitalizations. A recent review found a significant reduction in all-cause mortality when such multidisciplinary teams were used [14].

Multidisciplinary outpatient management of HF and disease management programs staffed by physicians, nurses, pharmacists, and other healthcare professionals with expertise in HF management should be developed and used for assessment and management of high -risk patients with HF. Multidisciplinary care should include close clinical follow-up, patient and caregiver education, telemanagement or telemonitoring, and home visits by specialized HF healthcare professionals, where resources are available. CCS consensus conference recommendations have stressed the role of multidisciplinary outpatient HF management and disease management programs [5].

Implantation of an ICD To Prevent Sudden Cardiac Death in Patients with Heart Failure

In patients with documented sustained ventricular tachycardia (VT) or ventricular fibrillation (VF), the implantable cardioverter defibrillator (ICD) is highly effective in treating recurrences of these arrhythmias, either by antitachycardia pacing or cardioversion/defibrillation. Implantation of an ICD has been shown to reduce mortality in cardiac-arrest survivors. An ICD is indicated for “secondary prevention” of sudden cardiac death (SCD) due to ventricular tachyarrhythmia in patients with otherwise good clinical func-

tion and prognosis, for which the prolongation of survival is the goal. All the three guidelines are in agreement about ICD implantation in such patients (Table 4). ACC/AHA and ESC guidelines have considered this as a class I, level A recommendation. The CCS guidelines have mentioned that ICDs are the therapy of choice for prevention of SCD and all-cause mortality in patients with a history of sustained VT or VF, cardiac arrest, or unexplained syncope in the presence of left ventricular dysfunction.

Table 4. Implantable cardioverter defibrillator implantation: comparison of different heart-failure practice guidelines

Indication	ACC/AHA guideline (2005)	ESC guideline (2005)	CCS consensus conference on HF recommendations (2006)
Implantable cardioverter defibrillator (ICD)			
CAD, LVEF ≤ 30%, 1 month post-MI, 3 months post-coronary revascularization procedure	Class I, level A	Class I, level A (LVEF < 30–35%)	Class I, level A
NIDCM present for at least 9 months, NYHA class II–III, LVEF ≤ 30%	Class I, level B		Class II a, level B
NIDCM present for at least 9 months, NYHA class II–III, LVEF 31–35%	Class IIa, level B		Class II b, level C
CAD, prior MI, 3 months post-revascularization, LVEF 31–35%, inducible VT/VF on EPS			Class IIa, level B
CAD, prior MI, 3 months post-revascularization, LVEF 31–35% without EPS			Class IIb, level C
HF, reduced LVEF, with history of cardiac arrest, VF or hemodynamically destabilizing VT	Class I, level A		

CAD, Coronary artery disease; *MI*, myocardial infarction; *LVEF*, left ventricular ejection fraction; *NIDCM*, nonischemic dilated cardiomyopathy; *NYHA*, New York Heart Association; *EPS*, electrophysiological study; *VT*, ventricular tachycardia; *VF*, ventricular fibrillation

All of the multicenter trials aimed at the primary prevention of SCD that assessed the usefulness of ICD implantation to reduce all-cause mortality selected patients with low LVEF. The most common LVEF cutoff was 35%, although the MADIT II study had a cutoff of 30% [15]. Most studies did not specifically select patients with symptomatic congestive heart failure (CHF), although the largest study, *Sudden Cardiac Death and Heart Failure Trial* (SCD-HeF Trial), did select patients with current HF symptoms, NYHA class II or III, and a history of HF for more than 3 months [16]. In the SCD-HeF Trial, 2,521 patients with HF and LVEF ≤ 35% were randomized to placebo, amiodarone, or single-lead ICD implantation. After a median follow-up of 45.5 months, there was a significant reduction in mortality in patients with ICD therapy. There was no difference between placebo and amiodarone on survival [16].

All three practice guidelines for HF management are in agreement and have recommended ICD implantation for primary prevention to reduce total mortality by a reduction of SCD in patients with LV dysfunction due to prior myocardial infarction (MI) who are at least 40 days post-MI, have an LVEF ≤ 30–40%, are NYHA functional class II or III, are receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year. A class I, level of evidence A recommendation has been given to this patient subset (Table 4). The ACC/AHA and CCS consensus conference HF guidelines also give separate recommendations for patients with nonischemic dilated cardiomyopathy (Table 4). The ECS HF guidelines do not mention nonischemic cardiomyopathy recommendations separately.

While ICDs are highly effective in preventing death due to ventricular tachyarrhythmia, frequent shocks from the ICD can lead to a reduced quality of life. For symptoms from recurrent discharges triggered by ventricular arrhythmias or AF, anti-arrhythmic therapy, most often amiodarone, may be added [6]. For recurrent ICD discharges from VT despite anti-arrhythmic therapy, catheter ablation may be effective (ACC/AHA guidelines). It is important to note that ICDs have the potential to aggravate HF and have been associated with an increase in HF hospitalizations (ACC/AHA guidelines).

Cardiac Resynchronization Therapy

Patients with HF and LV dysfunction commonly have intra- and interventricular conduction delays that are associated with cardiac mechanical dyssynchrony. These compromise ventricular function and are frequently asso-

ciated with severe symptoms and poor prognosis. CRT uses biventricular pacing to attempt to synchronize the activation of the septum and the LV free wall, and to improve overall LV function [17].

CRT, when added to optimal medical therapy in persistently symptomatic patients, has resulted in significant improvements in quality of life, functional class, exercise capacity, exercise tolerance, EF, and survival in patients randomized to such therapy [17]. Two major trials (COMPANION and CARE-HF) assessed the role of CRT in patients with NYHA class III–IV symptoms on optimal medical therapy, QRS duration ≥ 120 ms, and an LVEF ≤ 35% [18, 19].The CRT group, compared with the medical therapy group, had significantly fewer deaths from any cause and fewer unplanned hospitalization for a major cardiovascular event. As well, the CRT group had better improvement in EF, overall symptoms, and quality of life scores than the medical-therapy-only group [18, 19].

All three guidelines are in agreement with recommending CRT for patients with symptomatic (NYHA III or IV) HF despite optimal medical therapy, who are in normal sinus rhythm and a QRS duration ≥ 120 ms, and a LVEF ≤ 35% (class I, level A) (Table 5).

Table 5. Cardiac resynchronization therapy: comparison of different heart-failure practice guidelines

Indication	ACC/AHA guideline (2005)	ESC guideline (2005)	CCS consensus conference on HF recommendations (2006)
Cardiac resynchronization therapy (CRT)			
HF, NYHA class III-IV despite optimal medical therapy, NSR, QRS ≥ 120 ms, LVEF ≤ 35%	Class I, level A	Class I, level A	Class I, level A
ICD + CRT for patients meeting requirement criteria for ICD		Class IIa, level B	Class IIa, level B

HF, Heart failure; *NYHA*, New York Heart Association; *NSR*, normal sinus rhythm; *ICD*, implantable cardioverter defibrillator

ICD therapy combined with biventricular pacing can be effective for primary prevention to reduce total mortality by a reduction in SCD in patients with NYHA functional class III or IV, who are receiving optimal medical therapy, in sinus rhythm with a QRS complex of ≥ 120 ms, and who have reasonable expectation of survival with a good functional status for more than 1 year. According to the ESC and CCS guidelines, this is a class II A, level B recommendation (Table 5).

Future Directions

The understanding of HF has grown exponentially over the past 20 years and has fuelled many landmark clinical trials that have given definitive answers. The recommendations made in the present guidelines are based on clinical trials that have already been published. There are many trials that are in progress and planning, and these will no doubt provide new information and evidence to guide future recommendations and guidelines [20].

Some of these new and ongoing HF trials are:

- HF-ACTION: Heart Failure - A controlled trial investigating outcomes of exercise training
- AF-CHF: Atrial fibrillation in congestive heart failure
- WARCEF: Warfarin versus aspirin in reduced cardiac ejection fraction
- RED-HF: Reduction of events with darbepoetin alpha in heart failure
- I-PRESERVE: Irbesartanin heart failure with preserved systolic function
- UNLOAD: Use of nitroprusside in left ventricular dysfunction and obstructive aortic valve disease
- STICH: Surgical treatment for ischemic heart failure
- RAFT: Resynchronization /defibrillation for advanced heart failure trial
- REVERSE: Resynchronization reverses remodeling in systolic left ventricular dysfunction
- MADIT-CRT: Multicentre automatic defibrillator implantation cardiac resynchronization therapy trial

Conclusions

The provision of optimal care to patients with HF presents many challenges to the patient, their family or caregivers, the physician, other healthcare providers, and healthcare systems. Practicing guidelines provide support for physicians and other healthcare professionals concerned with the management of HF patients. They also provide advice on how to manage these

patients. Documented and published evidence on diagnosis, efficacy, and safety is the main basis of these guidelines. An organized system of specialist HF care improves symptoms and reduces hospitalization and mortality. Multidisciplinary disease-management programs for patients at high risk for hospital admission or clinical deterioration are recommended to facilitate the implementation of practice guidelines [7].

References

1. Dargie HJ, McMurray JJ (1994) Diagnosis and management of heart failure. BMJ 308:321–328
2. Stewart S, MacIntyre K, Hole DJ et al (2001) More "malignant" than cancer? Five-year survival following a first admission for heart failure. Eur J Heart Fail 3:315–322
3. American Heart Association (2005) Heart disease and stroke statistics: 2005 update. American Heart Association, Dallas
4. Johansen H, Strauss B, Arnold JM et al (2003) On the rise: the current and projected future burden of congestive heart failure hospitalization in Canada. Can J Cardiol 19:430–435
5. Arnold JM, Liu P, Demers C et al (2006) Canadian Cardiovascular Society consensus conference recommendations on heart failure 2006: diagnosis and management. Can J Cardiol 22:23–45
6. Hunt SA, Abraham WT, Chin MH et al (2005) ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in adult – summary article: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to update the 2001 guidelines for the evaluation and management of heart failure). Developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation. Endorsed by the Heart Rhythm Society. Circulation 112:1825–1852
7. Swedberg K, Cleland J, Dargie H et al (2005) ESC guidelines: guidelines for the diagnosis and treatment of chronic heart failure – executive summary (update 2005). The Task Force for the diagnosis and treatment of chronic heart failure of European Society of Cardiology. Eur Heart J 26:1115–1140
8. Cleland JG, Khand A, Cklark A (2001) The heart failure epidemic: exactly how big is it? Eur Heart J 22:623–626
9. Cleland JG, Gemmell I, Khand A et al (1999) Is prognosis of heart failure improving? Eur J Heart Fail 1:229–241
10. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators (1993) Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction and clinical evidence of heart failure. Lancet 342:669–677
11. Merit HF Study Group (1999) Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 353:2001–2007
12. Granger CB, McMurray JJ,Yusuf S et al; CHARM Investigators and Committee (2003) Effect of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin converting enzyme inhibitors: the CHARM alternative trial. Lancet 362:772–776

13. Pitt B, Zannand F, Remme WJ et al; Randomized Aldactone Evaluation Study Investigators (1999) The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 341:709–717
14. McAlister FA, Stewart S, Ferrua S, McMurray JJ (2004) Multidisciplinary strategies for the management of heart failure patients at high risk for admissions: a systematic review of randomized trials. J Am Coll Cardiol 44:810–819
15. Moss AJ, Zareba W, Hall WJ et al; Multicentre Automatic Defibrillator Implantation Trial II Investigators (2002) Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 346:877–883
16. Bardy GH, Lee KL, Mark DB et al; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators (2005) Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med352:225–237
17. McAlister FA, EzeKowitz JA, Wiebe N et al (2004) Systematic review: cardiac resynchronization in patients with symptomatic heart failure. Ann Inter Med 141:381–390
18. Bristow MR, Saxon LA, Boehmer J et al; Comparison of Medical therapy, Pacing And Defibrillation in Heart Failure (COMPANION) Investigators (2004) Cardiac resynchronization therapy with and without an implantable defibrillator in advance chronic heart failure. N Engl J Med 350:2140–2150
19. Cleland JG, Daubert JC, Erdmann E et al; Cardiac Resynchronization Heart Failure (CARE-HF) Study Investigators (2005) The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 352:1539–1549
20. Arnold JM, Howlett JG, Dorian P et al (2007) Canadian Cardiovascular Society Consensus Conference recommendations on heart failure update 2007: prevention, management during intercurrent illness or acute decompensation,and use of biomarkers. Can J Cardiol 23:21–45

Determination of Left Ventricular Contractile Reserve by Dobutamine Stress Echocardiography To Predict the Response to CRT

Carmine Muto, Bernardino Tuccillo

Introduction

Cardiac resynchronization therapy (CRT) has been shown to be a useful therapeutic option to improve the symptoms, functional capacity, and prognosis of patients with severe heart failure (HF). However, 20–30% of patients do not respond to this form of therapy, underscoring the need for additional selection criteria to identify potential responders. The aim of this study was to investigate the value of low-dose dobutamine stress echocardiography (DSE) to predict reverse remodeling after CRT.

Methods

Forty-two patients with HF (33 males, 10 females; age 65 ± 9 years) with left ventricular ejection fraction (EF) < 35%, NYHA class III–IV, and with QRS duration > 120 ms participated in the study. All patients underwent echocardiographic evaluation, including left ventricular volumes and EF before CRT and 6 months after implantation.

A 15% reduction of end-systolic volume after 6 months of CRT defined reverse remodeling. Prior to CRT, intra-left-ventricular asynchrony (LLD) was defined as a delay between the septum and posterior wall ≥ 130 ms, as determined by M-mode echocardiography. A left contractile reserve shown by DSE to be ≤ 20g/kg min was defined as an increase in EF ≥ 10%.

Division of Cardiology, S. Maria di Loreto Hospital, Naples, Italy

Results

After CRT, reverse remodeling was observed in 25 (59.5%) patients (R group) whereas 17 (40.5%) (NR group) did not respond to therapy. At baseline, there were no significant differences between the two groups regarding in end-systolic volume (160 ± 64 ml vs 168 ± 56 ml, n.s.), end-diastolic volume (213 ± 75 ml vs 230 ± 65 ml, n.s.), and EF (26 ± 6% vs 27 ± 7%). Contractile reserve, evaluated by DSE was present in 100% (25/25) of patients in the R group while LLD was present in 92% (23/25).

Among the 17 patients in the NR group, contractile reserve was present in 47.2% (8/17) while a LLD was found in 29.4% (5/17). The percent contractile reserve and the percent LLD were significantly higher in R patients than in NR ones ($p < 0.0001$). Reverse remodeling was significantly related to contractile reserve ($r = 0.63$; $p < 0.00001$) and to LLD ($r = 0.65$; $p < 0.00001$). Multivariate logistic regression including QRS duration showed that contractile reserve (OR: 11.2; CI: 6.2–19.8; $p < 0.001$) and LLD (OR: 18.1; CI: 4.4–16.8; $p < 0.00005$) were independent predictors of reverse remodeling.

Conclusions

Our results show that contractile reserve, as evaluated by DSE, is a useful tool to predict reverse remodeling after CRT. Echocardiographic selection of patients for CRT should thus include the determination of LLD and contractile reserve.

Focus on Optimization of Cardiac Resynchronization Therapy Techniques

Maurizio Lunati[1], Yann Poezevara[2], Andrea Boncompagni[3]

Introduction

Although cardiac resynchronization therapy (CRT) is now a first-line therapy in moderate to severe congestive heart failure patients with broad QRS, a number of treatment modalities remain open issues. Patient selection criteria need to be further specified, as a broader population can probably benefit from CRT. For instance, several clinical trials are currently addressing the role of CRT in patients with narrow QRS, with mild heart failure (HF) symptoms, or with complete AV block to prevent HF development. But even in those patients who meet current selection criteria, we need to further understand some aspects of the treatment modalities to offer maximum benefit from the therapy: Which location for the right ventricular (RV) and left ventricular (LV) pacing leads offers the best resynchronization? How should CRT parameters (AV and VV delays) be programmed to provide maximum hemodynamic benefit? Answers to these questions are crucial to reduce the number of non-responders to CRT, and to maximize the response to CRT by the majority of patients. In this review we will focus on techniques to optimize CRT programming.

Rationale for Optimization of CRT Parameters

It is commonly admitted that roughly one-third to one-fourth of CRT-indicated patients do not respond to the therapy, showing neither improved quality of life nor increased exercise capacity. These were the results from

[1]Cardiology Department, Electrophysiology Unit, Niguarda Ca' Granda Hospital, Milan, Italy; [2]SORIN Group; Les Plessis Robinson Cedex, France; [3]SORIN Group, Milan, Italy

landmark CRT trials (MUSTIC, MIRACLE, CONTAK CD, PATH CHF), which demonstrated the efficacy of CRT on functional capacity, and is generally confirmed by clinical experience. As none of those trials included atrioventricular delay (AVD) optimization, and because right to left ventricle pacing delay (VV delay) was introduced only in later devices, one can conclude that CRT optimization will turn out to be a promising way to improve therapeutic efficacy. However, since those landmark studies, a number of smaller clinical trials have been carried out. Several studies included invasive contractility measurements during different pacing configurations. Auricchio et al. found that AVD was a significant determinant of all LV systolic parameters; also, optimal AVD was found to be highly patient-dependent [1]. Compared to conventional simultaneous biventricular pacing, sequential pacing using VVD was observed to yield incremental benefit from 25 to 35% in terms of contractility [2, 3]. Some authors found that, during CRT delivery, cardiac performance is dependent mainly on an optimized AVD, whereas interventricular delay (VVD) accounts for only about 25% of hemodynamic performance [4]. Considering that programmed VVD affects the time to achieve a global depolarization [5, 6], optimizing CRT should take into account simultaneous AVD and VVD optimization to determine the optimal AVD/VVD combination.

Although data from these later trials need to be confirmed by long-term follow-up studies, there is clinical evidence in favor of optimizing CRT parameters. The difficulty lies, of course, in assessing the combination of parameters tailored to each patient's needs. Moreover, due to HF evolution over time, patients usually need constant monitoring with continuous adjustments of AVD and VVD to obtain the best clinical benefit [7, 8]. In the earliest era of resynchronization, "optimizing CRT" corresponded to selecting the configuration with the narrowest QRS, but further definitive data demonstrated no relationships between QRS duration and dyssynchrony in HF patients [9]. For this reason, over time, many echocardiographic techniques became the gold standard to optimize timing in CRT (optimal AVD and VVD intervals).

Echocardiography

Leaving out the key role of patient selection in therapeutic success, echocardiography techniques represent the most reliable approach used today to optimize CRT devices.

As a rule, echocardiographic Doppler is used to measure mitral inflow or aortic outflow velocities [10] to evaluate different pacing conditions, from

sinus rhythm to biventricular pacing at different AVD and VVD values. This method takes into account the present hemodynamic performance of the cardiac pump, providing, in turn, a direct evaluation of the benefit related to the chosen optimal configuration. Extensive experience in echocardiography has led to the widespread use of this method. However, performance is, unfortunately, very operator-dependent.

Optimal conditions necessarily combine AVD and VVD to obtain the best hemodynamic systolic and diastolic echocardiographic pattern. Several echo measurements should then be evaluated, at each AVD interval for each VVD, resulting (on average) in the need for 30 measurements. Moreover, AVD optimization should be repeated at different pacing rates to obtain an optimal value also during exercise [11, 12]. Last but not least, an optimal AVD-VVD combination is a dynamic concept, implying the need for repeated optimization procedures.

Nonetheless, echocardiographic techniques are time-consuming and burdensome procedures; they require skilled staff and are virtually impossible to perform while the patient exercises [13]. Due to this lack of convenience, it is very common in clinical practice that echocardiography-based CRT is optimized only in non-responders to CRT, as a second chance.

Alternative methods have therefore been developed. These are based on different technologies, with the aim to shorten optimization procedures and to provide the possibility of easy long-term monitoring.

Hemodynamic Sensors

Many hemodynamic sensors, including pressure sensors and "chemical" sensors (pH, temperature) were tested in the past, particularly at the time of rate-response development in pacemakers. Most of them did not overcome the technological challenge posed by the need for an implantable sensor with adequate resistance to fibrosis and limited signal drift (de-calibration) over time. Presently, the only such technology available in the field of CRT is the peak endocardial acceleration (PEA) sensor.

During isovolumetric contraction and relaxation phases, the myocardium generates mechanical vibrations; those vibrations are transmitted through the entire cardiac muscle, independent of ischemia and wall thickness, and can be measured as endocardial acceleration (EA) by an accelerometer sensor placed in contact with the cardiac walls. The peak-to-peak amplitude measured during isovolumetric contraction (PEA-I) corresponds to the first heart sound (FHS) and is highly correlated with heart contractility [14]. In fact, PEA-I is the principal component of PEA signals and, exactly like the

FHS, represents mitral valve closure. Thus, it is very well-correlated with the LV d*P*/d*t* max, in healthy as well as in failing hearts [15] and even during atrial fibrillation [16]. The capability of a sensor embedded in the tip of a right ventricular permanent pacing lead to detect PEA signal is well known [17], but only in the past few years has it been used in the context of a CRT device. This sensor offers the possibility of long-term monitoring of cardiac contractility and can be used to optimize AVD and VVD.

According to the concept of FHS detection over different AV activation sequences, a novel CRT device equipped with PEA sensor implements a proprietary "AVD scanning algorithm" able to compute optimal AVD based upon the evaluation of PEA-I [18]. In this CRT device, the procedure to optimize the AVD is automatically launched every week, without the need of external intervention. Moreover, the system is able to discriminate between the resting and exercise phases of the patient (by means of a standard gravimetric accelerometer): every measured "optimal AVD" is then referred to the corresponding heart rate. This allows the system to build up an "optimal AVD curve" with respect to heart rate, enabling AVD optimization for all heart rates.

PEA can also be used to automatically compute the optimal ventricular pacing configuration (chamber/s and VVD), leading to a global CRT optimal assessment. Evaluation of system performance in this regard (VVD optimization) is currently ongoing.

IEGM-Based Method

A new method to determine an optimal CRT configuration has been recently proposed [19] based on the observation that sequential ventricular pacing with an appropriate VVD can further increase the mechanical efficiency of the heart. This method is based on intracardiac electrograms (IEGM) and consists of estimating optimal VVD. During the latter, the total LV activation time is reduced, leading to synchronization of the activation pattern and of mechanical contraction. The system measures the conduction delays between all the following IEGMs: atrium to sensed IEGM from the LV lead, atrium to sensed IEGM from the RV lead, pacing from the RV to the sensed IEGM from the LV, pacing from the LV to the sensed IEGM from the RV (interventricular conduction delay: pacing from one ventricle to sensing from the other = "correction factor"). The optimal VVD is defined by adding the correction factor to the difference between the atrial and RV IEGM (with final multiplication by 0.5). This method has been tested in acute conditions only and remains to be evaluated in chronic conditions.

Similar to the way described for optimal VVD calculation, the IEGM method can also be applied for optimal AVD setting, by considering the intra-atrial delay, and measured in the same way as previously described for VVD [20].

The main limitation of this approach is that optimization of CRT parameters is based only on conduction times. For the same reason that the QRS width does not well-reflect the mechanical dyssynchrony of the heart, analysis of conduction times does not indicate the improvements in contractility that can be expected from CRT.

Conclusions

Echocardiography is currently considered to be the gold standard for CRT optimization, as it is the most accurate and widespread technique. A proper analysis should include both AVD and VVD optimization and tissue Doppler imaging to evaluate the reduction in intra-ventricular dyssynchrony. However, there is no consensus on the best method to use, and echocardiography can only provides isolated assessment with the patient at rest. For those reasons, it has a limited role in the day-to-day management of CRT patients, which would ideally require CRT optimization during patient daily activities and repeated on a regular basis. To meet these important expectations [21], researchers will need to focus on the development of implantable sensors such as the PEA, which is capable of continuously monitoring patient status and of providing a quick and reliable method for CRT optimization.

References

1. Auricchio A, Stellbrink C, Block M et al (1999) Effect of pacing chamber and atrioventricular delay on acute systolic function of paced patients with congestive heart failure. Circulation 9:2993–3001
2. Perego G, Chianca R, Facchini M et al (2003) Simultaneous vs sequential biventricular pacing in dilated cardiomyopathy: an acute hemodynamic study. Eur J Heart Fail 5:305–313
3. Van Gelder B, Bracke FA, Meijer A et al (2004) Effect of optimizing the VV interval on left ventricular contractility in cardiac resynchronization therapy. Am J Cardiol 93:1500–1503
4. Riedlbauchova L, Kautzner J, Fridl P (2005) Influence of different atrioventricular and interventricular delays on cardiac output during cardiac resynchronization therapy. Pacing Clin Electrophysiol 28(Suppl 1):S19-S23
5. Auricchio A, Fantoni C, Regoli F et al (2004) Characterization of left ventricular activation in patients with heart failure and left bundle-branch block. Circulation 109:1133–1139

6. Sogaard P, Egeblad H, Pedersen AK et al (2002) Sequential versus simultaneous biventricular resynchronization for severe heart failure. Circulation 106:2078–2084
7. Porciani MC, Dondina C, Macioce R et al (2006) Temporal variation in optimal atrioventricular and interventricular delay during cardiac resynchronization therapy. J Card Fai 12:715–719
8. O'Donnel D, Nadurata V, Hamer A et al (2005) Long-term variation of cardiac resynchronization therapy devices. Pacing Clin Electrophysiol 28(Suppl 1):S24-S26
9. Bleeker GB, Schalij MJ, Molhoek SG et al (2004) Relationship between QRS duration and left ventricular dyssynchrony in patients with end-stage heart failure. J Cardiovasc Electrophysiol 15:544–599
10. Burri H, Sunthorn H, Shah D, Lerch R (2006) Optimization of device programming for cardiac resynchronization therapy. Pacing Clin Electrophysiol 29:1416–1425
11. Scharf C, Li P, Muntwyler J et al (2005) Rate-dependent AV delay optimization in cardiac resynchronization therapy. Pacing Clin Electrophysiol 28:279–284
12. Verbeek XA, Vernooy K, Peschar M et al (2003) Intra-ventricular resynchronization for optimal left ventricular function during pacing in experimental left bundle branch block. J Am Coll Cardiol 42:558–567
13. Porciani MC, Dondina C, Macioce R et al (2005) Echocardiographic examination of atrioventricular and interventricular delay optimization in cardiac resynchronization therapy. Am J Cardiol 95:1108–1110
14. Plicchi G, Marcelli E, Parlapiano M, Bombardini T (2002) PEA I and PEA II based implantable haemodynamic monitor: pre clinical studies in sheep. Europace 4:49–54
15. Plicchi G, Marcelli E, Bombardini T, Gaggini G (2002) PEA I and PEA II based implantable system for monitoring acute ventricular failure. Pacing Clin Electrophysiol 28(4 Part II):691
16. Bombardini T, Gaggini G, Marcelli E et al (2000) Peak endocardial acceleration reflects heart contractility also in atrial fibrillation. Pacing Clin Electrophysiol 23:1381–1385
17. Rickards AF, Bombardini T, Corbucci G, Plicchi G (1996) An implantable intracardiac accelerometer for monitoring myocardial contractility. The Multicenter PEA Study Group. Pacing Clin Electrophysiol 19(12 Pt 1):2066–2071
18. Ritter P, Padeletti L, Gillio-Meina L, Gaggini G (1999) Determination of the optimal atrioventricular delay in DDD pacing. Comparison between echo and peak endocardial acceleration measurements. Europace 1:126–130
19. Min X, Meine M, Baker JH 2nd et al (2007) Estimation of the optimal VV delay by an IEGM-based method in cardiac resynchronization therapy. Pacing Clin Electrophysiol 30ì (Suppl 1): S19-S22
20. Gold MR, Niazi I, Giudici M et al (2007) A prospective comparison of AV delay programming methods for hemodynamic optimization during cardiac resynchronization therapy. J Cardiovasc Electrophysiol 18:1–7
21. Braunschweig F, Kjellstrom B, Gadler F, Linde C (2004) Optimization of cardiac resynchronization therapy by continuous hemodynamic monitoring. J Cardiovasc Electrophysiol 15:94–96

Evaluation of the Clinical State of Cardiac Resynchronization Therapy Patients by Continuous Heart-Failure Monitoring

Henri Benkemoun, Bertrand Colombo, Jean Sacrez, Philippe Lagrange, Philippe Cabrol, Gabriel Robert, Marc Moulichon

Introduction

Heart failure is a major and growing public health problem, affecting more than 22 million people worldwide. Despite effective drug therapies, the morbidity and mortality associated with heart failure remain unacceptably high. Increasing numbers of heart-failure patients are receiving device-based therapy, either cardiac resynchronization therapy (CRT) alone or cardiac resynchronization therapy with an implantable cardioverter-defibrillator (CRT-ICD). Over 60,000 patients around the world were supplied with a CRT system in 2006 alone.

In the USA, heart failure is the most common cause for hospitalization among patients over 65 years of age [1–3]. In many developed countries besides the USA, heart failure is one of the most costly diseases in health care budgets, with 70% of the expenses going to the treatment of decompensation due to acute heart failure [4]. The factors contributing to hospital readmission as a result of heart failure include noncompliance (33%), inadequate follow-up (20%), and the patient's failure to seek medical attention when experiencing worsening symptoms (20%) [5].

Although regular monitoring of heart-failure patients is recommended in management programs [6], none of these measures has shown conclusive impact on morbidity associated with this condition [7, 8].The ability to better monitor the clinical status of heart-failure patients may provide an early warning of decompensation, help to reduce hospitalization rates, and improve patient quality-of-life. The latest generation CRT devices offer tools to detect changes in clinical status (symptoms or clinical parameters) and to

Cardiologie, Clinique Saint Pierre, Perpignan, France

provide this information to medical staff. Both sides of this new approach of diagnosis and evaluation of CRT patients by continuous monitoring of heart failure are aimed at detecting changes in clinical status and providing the tools with which to communicate them.

Tools To Detect Changes in Clinical Status (Symptoms or Clinical Parameters)

Automated Monitoring of Intrathoracic Impedance by an Implantable Device

Patients with heart failure are frequently hospitalized for fluid overload. Measuring intrathoracic impedance in patient with a special CRT-ICD device implanted in the left pectoral region is a reliable method to identify fluid overload [9]. Intrathoracic impedance decreases before each decompensation by an average of 12.3% over an average of 18 days. Impedance reduction begins 15.3 days before the onset of worsening symptoms. There is an inverse correlation between intrathoracic impedance and pulmonary wedge pressure, and between intrathoracic impedance and net fluid loss during hospitalization.

Regular monitoring of intrathoracic impedance may provide an early warning of impending decompensation. The algorithm proposed for the detection of intrathoracic impedance reduction produces 1.5 false-positive detections per patient-year of monitoring.

Heart-Rate Variability Measured by an Implanted CRT Device

Long-term, continuous heart-rate variability (HRV) can be measured from an implantable CRT device [10]. Continuous HRV is measured as the standard deviation of 5-min median atrial-atrial intervals (SDAAM) sensed by the device. SDAAM < 50 ms when averaged over 4 weeks is associated with an increased mortality risk. Moreover, SDAAM was found to be persistently lower in patients who required hospitalization. SDAAM decreases a median of 16 days before hospitalization for decompensation due to acute heart failure and returns to baseline after treatment. Automated detection of decreases in SDAAM has a sensitivity of 70% in detecting cardiovascular hospitalization, with 2.4 false-positives per patient-year of follow-up.

These reports indicate that continuous long-term SDAMM is a useful tool in the clinical management of patients with chronic heart failure. Neurohormonal activation, as suggested by a decrease in SDAAM, occurs several days to weeks before patients decompensate enough to require hospi-

talization. This finding provides insight into the autonomic mechanisms of heart-failure physiopathology. In addition, autonomic markers, when continuously measured by implanted CRT devices, offer meaningful information that may be useful in the day-to-day management of heart failure patients.

Other Parameters Measured by CRT Devices

Body-weight scale, reflecting fluid status and blood pressure, can be measured by the patients and integrated into the data transmitted to the clinical center. Patient activity, as measured by the activity sensor of the CRT device, as well as quality of life issues, atrial fibrillation burden, percentage of CRT delivered, and premature ventricular complex are other relevant parameters that can be evaluated.

Tools To Communicate

Different systems and approaches are used to transmit information to the general practitioner and/or the heart-failure specialist. Data from the device collected are communicated automatically or not and continuously or not, depending on the extent of patient compliance. Some systems use a call center to answer patients' questions. In the future, remote access for pro-active care will be technically possible.

Conclusions

The new CRT devices are expected to improve patient care with respect to preventing decompensation induced by acute heart failure. Additional benefits include reduced hospitalizations and heart-failure cost burden and improvements in the patient's quality-of-life. The optimal sensor to detect changes in clinical status and the best way to transmit the collected data are still being debated. Ultimately, the best tool to detect heart failure using a CRT device may be an association of different sensors that monitor each other. The energy spent to collect and send the data is a key point and poses a challenge to medical engineering. Evaluation of the clinical state of CRT patients by continuous heart failure monitoring will eventually become the responsibility of the physician. These considerations imply that, on the one hand, clinicians must change their perception of treating heart-failure patients and, on the other, industry has to not only supply clinicians with more specific and sensitive tools but also educate them regarding their use.

References

1. Wang L, Lahtinen S, Lentz L et al (2005) Feasibility of using an implantable system to measure thoracic congestion in an ambulatory chronic heart failure canine model. Pacing Clin Electrophysiol 28:404–411
2. Mc Alister FA, Ezekowitz JA, Wiebe N et al (2004) Systematic review: cardiac resynchronization in patients with symptomatic heart failure. Ann Intern Med 141:381–390
3. Bristow MR, Saxon LA, Boehmer J et al (2004) Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 350:2140–2150
4. Stewart S, Jenkins A, Buchan S et al (2002) The current cost of heart failure to the National Health Service in the UK. Eur J Heart Fail 4:361–371
5. Vinson JM, Rich MW, Sperry JC et al (1990) Early readmission of elderly patients with heart failure. J Am Geriatr Soc 38:1290–1295
6. Hunt SA, Baker DW, Chin MH et al (2001) ACC/AHA Guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. Circulation 104:2996–3007
7. Goldberg LR, Piette JD, Walsh MN et al (2003) Randomized trial of a daily electronic home monitoring system in patients with advanced heart failure: the Weight Monitoring in Heart Failure (WHARF) trial. Am Heart J 146:705–712
8. Louis AA, Turner T, Gretton M et al (2003) A systematic review of telemonitoring for the management of heart failure. Eur J Heart Fail 5:583–590
9. Yu C, Wang L, Chau E et al (2005) Intrathoracic impedance monitoring in patient with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization. Circulation 112:841–848
10. Adamson PB, Smith AL, Abraham WT et al (2004) Continuous autonomic assessment in patients with symptomatic heart failure: prognostic value of heart rate variability measured by implanted cardiac resynchronization device. Circulation 110:2389–2394

Predicting Heart Failure Events in CRT Patients: Future Challenges

Roberto Mantovan[1], Danilo Contardi[2], Vittorio Calzolari[1], Martino Crosato[1], Zoran Olivari[1]

Background

Advanced heart failure (HF) and related acute decompensations have become the single most costly medical syndrome in cardiology. HF leads to frequent re-hospitalizations: in the US alone, yearly HF hospitalizations number more than 1 million [1]. A recent analysis carried out in all European countries led to the conclusion that 75% of all HF-related costs have to be attributed to HF hospitalizations [2].

Although HF is a syndrome that trends to become chronic, it does not evolve gradually. In HF patients, phases of relative stability alternate with acute exacerbations that frequently lead to HF hospitalizations [3]. Thus, the ability to "predict" acute events implies an ability to improve patients' quality of life (QoL) and prognosis.

Many clinical and instrumental variables are limited (or of limited usefulness) in predicting HF evolution, as they are often influenced by psychological and subjective factors (dyspnea, QoL, NYHA class) or only able to describe the clinical status at follow-up (echocardiographic exam, effort test, 6' WT, etc.). There are indeed useful variables to define a worsening profile (edema, body weight) but the "predictive delay" is often very short (2–3 days).

Thus predicting HF events remain a challenge to HF specialists. In this brief report, we focus our attention on HF patients with indications for cardiac resynchronization therapy (CRT). In addition, we provide an overview of the potential/real application of several sensors on-board CRT devices that allow the early identification of acute HF events.

[1]Cardiovascular Department, S. Maria dei Battuti Hospital, Treviso, Italy; [2]SORIN Group, Clinical Department, Milan, Italy

The prediction of acute HF events in the population of patients indicated for CRT has been facilitated by the availability of common sensors technologies in CRT devices. Among them, we discuss the few sensors used in pilot experiences or which have given interesting preliminary results.

Heart Rate Variability

Several reports have been recently published about the usefulness of heart rate variability (HRV) in determining the prognosis of HF patients. A first significant positive experience was reported by Adamson [4] in a 1-year follow-up of 370 CRT patients of NYHA class III/IV. The prognostic value of HRV in terms of RR variability measured by the CRT device was demonstrated through SDAAM, defined as the average value of the standard deviation of 5-min RR interval clusters. A markedly depressed HRV was significantly associated with "major HF events" (HF hospitalizations or death due to HF). More recently, the HF-HRV Registry [5] reported a significant association between HRV and clinical outcome in a population of 1,421 CRT patients. Whether the reverse relationship (reduced HRV and worse clinical profile) also holds remains to be demonstrated. An Italian observational report on a large CRT-ICD population (INSYNC ICD Registry) [6] found the same trend of HRV over time (as measured by implanted CRT-ICDs) in patients of different NYHA classes, but at significantly higher levels in NYHA class II patients (Fig. 1).

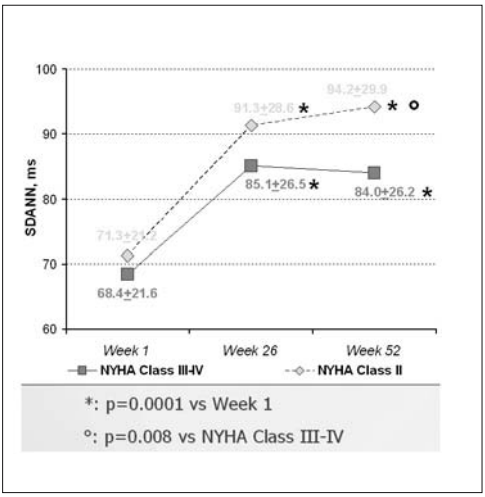
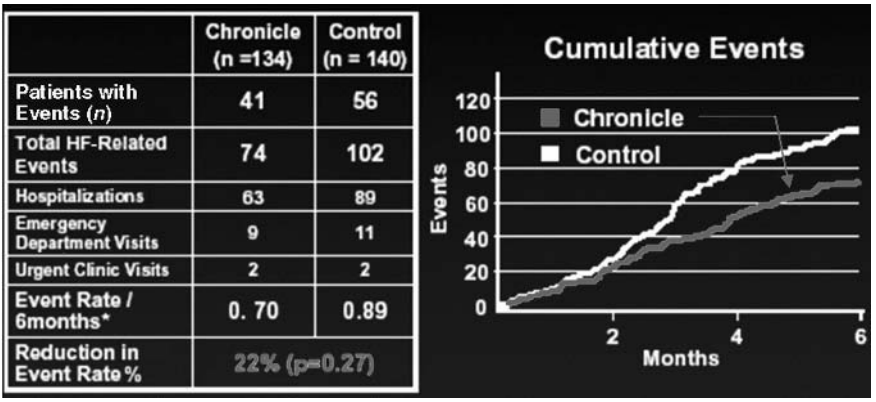


Fig. 1. Trend of SDAAN (specific measure of HRV defined as the average value of the standard deviation of 5-min RR interval clusters) in 509 CRT patients over a 1-year follow-up. The same profiles were obtained over time, but at different levels of variability according to the different NYHA class (significantly higher for class II than for class III/IV)

Implantable Hemodynamic Sensor

Several years ago, an implantable hemodynamic monitoring system, the Chronicle (Medtronic), was realized and implanted in small cohorts of HF patients. The subcutaneously implanted device (similar to a cardiac pacemaker) was connected to an implantable lead placed in the right ventricular outflow tract and was equipped with a hemodynamic sensor able to estimate left ventricular pre-load by measuring pulmonary artery pressures. The technical feasibility of this approach was successfully tested [7]. Furthermore "in deep" safety and efficacy aspects were also tested. The Compass HF randomized efficacy trial [8] showed that this implantable system, together with a home monitoring network that directly alerts the physician when an "event" is foreseen, was able to reduce HF events by 22% vs controls on a 6-month follow-up basis (Fig. 2).

Chronicle systems have been confirmed to provide objective hemodynamic and associated clinical data, both in real-time via a programmer and by telephone hook-up to a central computer site where data can be viewed via the Internet. With the use of monitoring parameters, appropriate and timely interventions can be initiated to ensure optimal patient outcome. The impact of this technology, however, on the mortality and morbidity of patients with HF has not yet been established. Further testing in larger clinical trials specifically designed to evaluate patient outcome and QoL is therefore needed. Nevertheless, preliminary results are encouraging, such that implantable monitoring may be a step in the management of patients with HF that moves beyond traditional care-delivery systems.



	Chronicle (n =134)	Control (n = 140)
Patients with Events (*n*)	41	56
Total HF-Related Events	74	102
Hospitalizations	63	89
Emergency Department Visits	9	11
Urgent Clinic Visits	2	2
Event Rate / 6months*	0. 70	0.89
Reduction in Event Rate %	22% (p=0.27)	

Fig. 2. Efficacy objective of the Compass heart HF randomized trial: reduction of heart failure (HF) events by prediction. A hemodynamic, implantable monitoring system (Chronicle) vs controls: event rate at short-term follow-up. *Hypothesized event rate=1.2

Fluid Overload Sensor

Significant results were obtained with the Optivol (Medtronic) diagnostic system, which is currently indicated in patients in whom CRT-D is indicated. Optivol performs daily measurements of intrathoracic impedance in order to estimate fluid overload in that region, as that finding is often one of the earliest signs of worsening HF. The concept behind the Optivol sensor is very simple, but powerful: the lower the intrathoracic impedance, the higher the fluid overload.

To date, the most interesting data were reported by Yu [9] in a study of 33 HF patients, NYHA class III/IV, who were observed for 20 months. The sensitivity of the Optivol sensor (correct detection of true HF events) was 76.9%, with a predictive delay of 15.3 ± 10.6 days. However, the specificity (rejection of false HF events) of the system was not satisfactory, since an average of 1.5 inappropriate visits/patient per year of observation was determined.

Transvalvular Impedance Sensor

Only limited animal studies have been carried out for bio-impedance sensors. An abstract was recently published that described the implantation of a pacemaker (Sophos, Medico) in sheep. The system was equipped with special algorithms to derive intracardiac impedance values. The authors claimed [10] that the sensor was able to accurately detect changes in right ventricular volumes and to directly compute the contractility-derived rate during inotropic (isoproterenol) stimulation. So far, however, no convincing human test results have been published.

Workload and Ventilatory Dynamics

Taking advantage of already available sensors technologies in cardiac implantable devices, some researchers have attempted to use the close relationship between physical activity and ventilatory dynamics [11], which is thought to be very relevant in the context of progressively failing hearts.

A recent retrospective evaluation concerned patients implanted with a CRT-pacemaker who were included in the DESIRE clinical trial (n = 49 HF patients in NYHA class III/IV, with narrow QRS < 150 ms). In this trial, information regarding capacitive accelerometer and minute ventilation was obtained from two commonly used sensors and fed to an expert system. A day by day "functional status flag" was thus obtained in which -1 = worsening, 0 = stable, and +1 = improving. Accordingly, the system, called "Diag-

Phy" (physiological diagnosis), was able to store an alert in PM memory. All stored alerts were retrospectively compared to real HF events reported in the clinical files of the respective patients. This permitted evaluation of: (1) the performance of Diag-Phy in terms of sensitivity, specificity, negative/positive predictive values (NPV/PPV); and (2) the predictive delay of Diag-Phy, defined as the time-distance (days) between the alert and the real event.

The impressive results, still retrospective, were recently published [12]: 25 real HF events (documented by clinical files) were reported in 16 of 49 patients. The sensitivity/specificity of the expert system was, respectively, 88 and 95%, whereas the PPV/NPV was, respectively, 71 and 98%. The predictive delay, measured by true events, was 14 ± 10 days (min = 3, max = 30 days). The authors of the study concluded that an analysis of the daily variations in minute ventilation and physical activity offers a simple and reliable method to predict acute HF events, and thus to reduce HF-related hospitalizations (see example in Fig. 3).

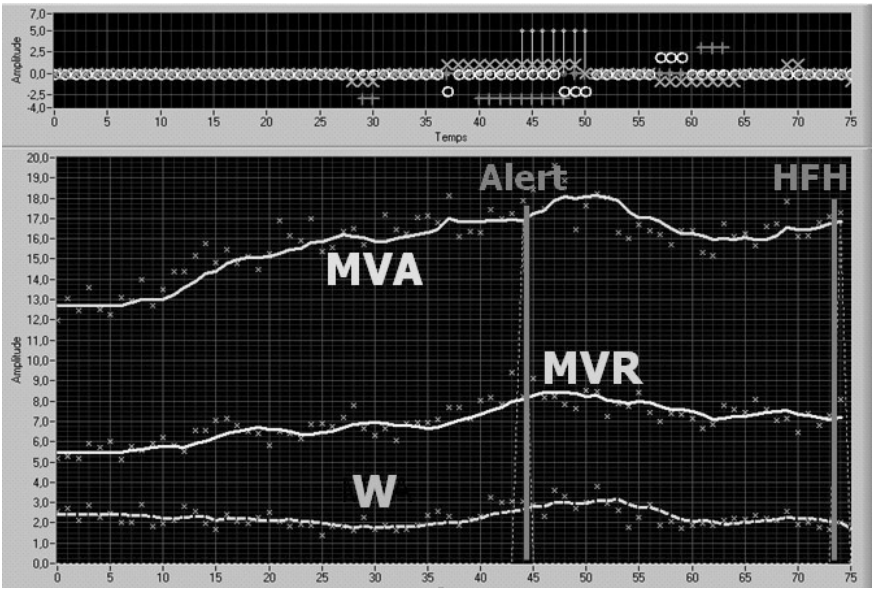


Fig. 3. Trend over time (day by day) of ventilatory dynamics (*MVR*, minute ventilation at rest; *MVA* maximum minute ventilation) and physical activity (*W*, patient's workload measured by accelerometer sensor). The patient in this example was hospitalized (*HFH*) due to progressive dyspnea and signs of heart failure (HF). This event could have been predicted by the expert system with a 30-days "predictive" delay (*Alert*)

Future Perspectives

Several hemodynamic sensors, with very different approaches, limitations, and efficacies, have been tested to date. Of those technologies potentially applicable to CRT devices, BEST (SORIN Group) is a very well-known acceleration sensor able to measure mechanical heart vibrations when placed in contact with the heart walls. The signal generated by the sensor is referred to as the PEA (peak endocardial acceleration), and it is based on a technology developed by the manufacturer more than 15 years ago. The sensor mimics phonocardiography in that it measures the amplitude and timing of heart vibrations induced by the opening and closing of the cardiac valves (Fig. 4). The different components of the PEA signal have been investigated during the last 10 years, leading to the conclusion that PEA-I (principal component, expression of the mitral valve closure) is very well correlated with left ventricular d*P*/d*t* in both healthy and failing hearts [13]. This is the reason why PEA-I is considered to be a reliable monitor of cardiac inotropic status (intrinsic contractility), one of the major variables that describe the mechanics of the heart.

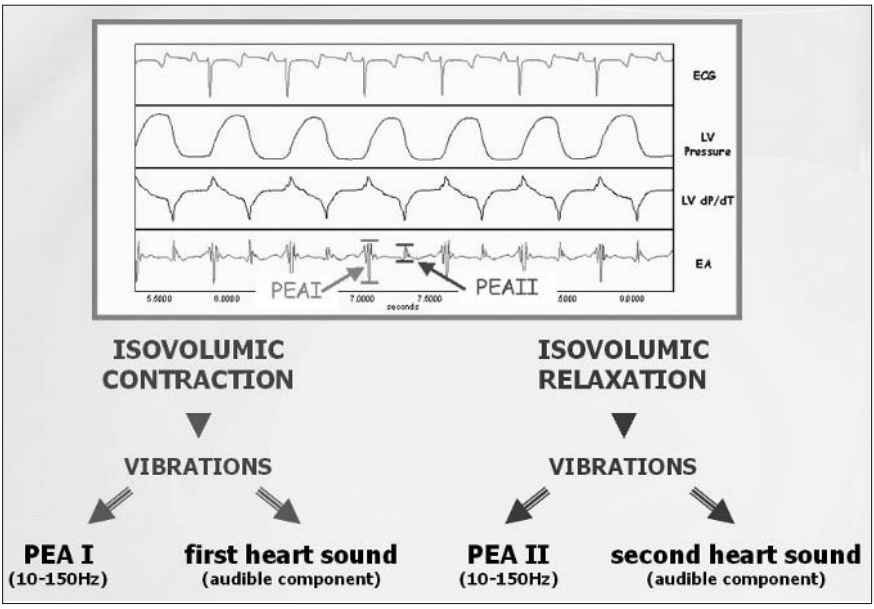


Fig. 4. Correspondence between peak endocardial acceleration (PEA) signal components and left ventricular pressure. The sensor tracks the vibrations induced by the isovolumetric phases of cardiac contraction. The PEA-I component is significantly correlated with the left ventricular pressure gradient (*LV dP/dt*)

Researchers today are directing their efforts towards the integration of predictive technologies with hemodynamic sensors in order to develop approaches that can be used in routine clinical practice.

Future ICD platforms will be aimed at predicting HF events by means of expert systems able to process several signals on a daily basis: respiratory variables (Optivol, Diag-Phy, transthoracic impedance), autonomic variables (HRV, others), cardiac contractility (PEA signal, intracardiac impedance), and left ventricular pre-load estimation (e.g., the Chronicle experience). The real issue is to fine-tune the expert system in order to correctly classify and prioritize the information coming from multiple sensors, mainly to avoid false-positives (which lead to a high rate of inappropriate visits to the respective implant centers). For this reason, one of the required features of such systems is "auto-learning" (i.e., the system tunes itself automatically). In this context, fuzzy logic and neural networks may act as optimal partners in future monitoring systems.

Conclusions

Several implantable sensors are able today to accurately track the evolution over time of cardiac, metabolic, and ventilatory variables, which provide the basis for identifying (possibly at a very early stage) trends toward the occurrence of an acute HF event.

Considering the sudden instability of HF patients, instead of obtaining a clinical image when they present for follow-up, current CRT-Ds can take advantage of the enormous diagnostic value of the sensor-generated information to continuously describe the clinical profile of HF patients from follow-up to follow-up.

True hemodynamic implantable sensors together with auto-learning software (and, of course, remote monitoring networks) are the last barriers to making monitoring systems totally autonomous regarding their ability to predict HF events at early stages, with the aim of reducing HF-related hospitalizations and their tremendous impact on health-care costs, patient QoL, and prognosis.

Clinical trials to evaluate this technology are on-going, and the preliminary observations have been very promising.

References

1. Levy D, Kenchaiah S, Larson MG et al (2002) Long-term trends in the incidence of and survival with heart failure. N Engl J Med 347:1397–1402

2. Swedberg K, Cleland J, Dargie H et al (2005) Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). Eur Heart J 26:1115–1140
3. Jain P, Massie BM, Gattis WA et al (2003) Current medical treatment for the exacerbation of chronic heart failure resulting in hospitalization. Am Heart J 145(2 Suppl):S3-S17
4. Adamson PB, Smith AL, Abraham WT et al (2004) Continuous autonomic assessment in patients with symptomatic heart failure: prognostic value of heart rate variability measured by an implanted cardiac resynchronization device. Circulation 110(16):2389–2394
5. Gilliam FR III, Kaplan AJ, Black J et al (2007) Changes in heart rate variability, quality of life, and activity in cardiac resynchronization therapy patients: results of the HF-HRV registry. Pacing Clin Electrophysiol 30(1):56–64
6. Gasparini M, Lunati M, Santini M et al (2006) Long-term survival in patients treated with cardiac resynchronization therapy: a 3-year follow-up study from the InSync/InSync ICD Italian Registry. Pacing Clin Electrophysiol 29(Suppl 2):S2-S10
7. Steinhaus D, Reynolds DW, Gadler F et al; Chronicle Investigators (2005) Implant experience with an implantable hemodynamic monitor for the management of symptomatic heart failure. Pacing Clin Electrophysiol 28(8):747–753
8. Anonymous (2005) Compass-HF Trial finds continuous monitoring of intracardiac pressure associated with significant reduction in heart failure hospitalization. Available at: http://www.medscape.com/viewarticle/501568 (last access July 29, 2005)
9. Yu CM, Wang L, Chau E et al (2006) Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization. Circulation 112(6):841–848
10. Chirife R, Di Gregorio F, Gonzales JL et al (2006) Hemodynamic assessment using a transvalvular impedance sensor. Initial animal experience with implanted Sophos TM pacemaker. Europace Suppl 1, abs 216/2
11. Bonnet JL, Geroux L, Cazeau S (1998) Evaluation of a dual sensor rate responsive pacing system based on a new concept. French Talent DR Pacemaker Investigators. Pacing Clin Electrophysiol 21(11 Pt 2):2198–2203
12. Landolina M, Page E, Galley D et al (2006) Minute Ventilation and patient's activity may predict acute heart failure events in CRT patients. Heart Rhythm Suppl 3(5), abs P4/95
13. Plicchi G, Marcelli E, Bombardini T, Gaggini G (2002) PEA I and PEA II based implantable system for monitoring acute ventricular failure. Pacing Clin Electrophysiol 24(Part II):691

Use of Fluid Accumulation Monitoring in HF Patients

Saverio Iacopino[1], Rossella Alemanni[1], Antonella Talerico[1], Gennaro Fabiano[1], Sergio Canonaco[2], Francesco Borrello[1]

Introduction

Decompensated heart failure (HF) is the leading cause of hospital admissions for US Medicare patients. Early detection of intrathoracic fluid accumulation may reduce the morbidity and mortality associated with cardiac decompensation. Much of the medical costs incurred by decompensated HF patients are related to hospitalization and rehospitalization [1]. Therefore, monitoring pulmonary fluid status may be valuable in detecting early decompensation, and the following adjustment of medical therapy may prevent hospitalization. The new generation of cardiac resynchronization therapy devices, biventricular implantable cardioverter-defibrillators (ICDs; Medtronic, Minneapolis, MN, USA), permit intrathoracic impedance measurements and thus the detection of changes in pulmonary fluid status. The feasibility of the InSync Sentry device was recently reported by Yu et al. [2], who demonstrated an inverse correlation of intrathoracic impedance and pulmonary capillary wedge pressure with fluid balance. Furthermore, in these devices, an audible alarm (the OptiVol alert) can be triggered when a decrease in intrathoracic impedance indicates pulmonary fluid accumulation secondary to left-sided HF. Accordingly, these new devices may detect HF in the preclinical phase, which may allow the adjustment of therapy and thereby obviate the need for HF-related hospitalization. Therefore, the aim of this study was to evaluate the clinical value of this alarm for patients with decompensated HF.

[1]Cardiovascular Department, Electrophysiology Unit, Sant'Anna Hospital, Catanzaro; [2]Medtronic Italia, Sesto San Giovanni (MI), Italy

Methods

The series consisted of 106 consecutive patients with severe HF who received InSync Sentry or Concerto biventricular ICDs. Patients were selected according to the traditional criteria for cardiac resynchronization therapy: advanced HF (New York Heart Association class III or IV), depressed left ventricular (LV) ejection fraction (< 35%), and prolonged QR duration (> 120 ms). Patients with atrial fibrillation or previously implanted pacemakers were included. The study protocol was as follows: before device implantation, the patient's clinical status was assessed and echocardiography was performed to measure LV ejection fraction. During follow-up, standard outpatient clinic visits and biventricular ICD printouts were scheduled every 3 months. Patients were instructed to visit the hospital in case of OptiVol alerts.

Device Implantation

A coronary sinus venogram was obtained, after which the LV pacing lead was inserted. A 9-Fr guiding catheter was used to position the LV lead (Attain OTW 4193-88, Attain Bipolar OTW 4194-88, Attain Starfix 4195, Medtronic) in the coronary sinus. The preferred position was a lateral or posterolateral vein [3]. The right atrial and ventricular leads were positioned conventionally. All leads were connected to the InSync Sentry or Concerto biventricular ICD.

Intrathoracic Impedance Monitoring

In OptiVol fluid-status monitoring, intrathoracic impedance is measured every 20 min from 12 a.m. to 5 p.m. using an electrical-impulse vector that travels between a lead in the right ventricle of the heart and the pulse generator. As a result, the electrical impulse passes through lung tissue. Comparison of the daily average impedance values with a reference impedance line allows the assessment of a trend line in the OptiVol fluid index chart. OptiVol fluid-status monitoring is initiated 30 days after device implantation to allow wound healing. As fluid accumulates in a patient's lungs, the OptiVol fluid index increases. If the condition is not resolved, and the OptiVol index crosses a predefined threshold, an observation will be triggered. If enabled, an OptiVol alert will also be audible from the implanted device at a programmed time. If the fluid build-up has resolved and the trend of the daily impedance value is at or greater than the reference imped-

ance values, the OptiVol fluid index returns to zero. The OptiVol threshold can be programmed at device implantation or at follow-up device checks. In our analysis, the threshold was programmed at the default value of 60 Ω per day, on the basis of clinical data for optimal sensitivity and low false-positive rates [4].

Clinical and Biventricular ICD Monitoring

During follow-up, clinical status and biventricular ICD check-up were performed every 3 months in the outpatient clinic. Based on the biventricular ICD printouts, the OptiVol index trend and thoracic impedance were determined. Additional visits were planned in case of OptiVol alerts. In patients who presented with an OptiVol alert, current hemodynamic status was evaluated with respect to patient history, drug use, physical examination, laboratory tests, and chest radiography. An alert was considered as true-positive and follow-up visits were planned if significant HF needing medical adjustment was confirmed.

Statistical Analysis

Continuous data are presented as mean ± SD; dichotomous data are presented as numbers and percentages. The data were compared using the unpaired Student's *t* test for continuous variables and Fisher's exact test for proportions. For all tests, $p < 0.05$ was considered statistically significant.

Results

The baseline characteristics of the 106 patients included in this study (76 men; mean age 66 ± 12 years) are listed in Table 1. Device and lead implantation were successful in all patients and without major complications. All OptiVol thresholds were set at 60 Ω per day, and an audible alarm was enabled in all patients. During follow-up (mean 15 ± 5 months), 21 patients presented with 32 OptiVol alerts. One patient presented with an alert 1 year after implantation due to subclavian vein thrombosis. The mean time between implantation and OptiVol alert was 269 ± 117 days. The mean maximal OptiVol fluid index was 109 ± 32 Ω per day. In only 13 alerts, clinical signs and symptoms of HF requiring medication adjustment were present, whereas in the remaining alerts these clinical signs and symptoms were absent ($p < 0.05$). Only one patient with true-positive alerts had to be admit-

ted for intravenous therapy. It is important to note that no patients were admitted for acute decompensation after OptiVol alerts. The maximum OptiVol index was significantly greater in patients with symptoms of HF than in those without such symptoms (136 ± 39 vs 108 ± 41 Ω per day, $p < 0.05$). Evaluation of the biventricular ICD printouts did not result in the detection of inappropriate elevation of the OptiVol fluid index.

Table 1. Patient characteristics ($n = 106$)

Variable	Value
Age (years)	66 ± 12
Men/women	76/30
New York Heart Association functional class	2.6 ± 0.6
Etiology	
Ischemic	75 (70%)
Nonischemic	31 (30%)
QRS duration (ms)	153 ± 37
Sinus rhythm	96 (90.6%)
Atrial fibrillation	8 (7.5%)
Paced	2 (1.9%)
Left ventricular ejection fraction (%)	24 ± 6
Left ventricular end-diastolic volume (ml)	214 ± 75
Left ventricular end-systolic volume (ml)	161 ± 77
Medication	
Diuretics	102 (96%)
Angiotensin-converting-enzyme inhibitors	99 (93%)
β-Blockers	83 (78%)
Spironolactone	56 (52%)
Digoxin	36 (33%)

Discussion

Decompensated HF is associated with high morbidity, mortality, and treatment costs [1]. The ability to monitor pulmonary fluid status may permit the early identification of decompensated HF, which in turn may reduce the number of hospitalizations and improve patients' quality of life. Intrathoracic fluid-status monitoring was first tested in the Medtronic Impedance Diagnostics in Heart Failure Trial (MID-HeFT) [2]. A considerable delay between the onset of symptoms and the initiation of therapy was found. Evangelista et al. [5] reported a mean delay from the onset of worsening symptoms to hospital admission of 3 days, and almost 30% of the patients had delays > 5 days.

The present findings demonstrate that OptiVol intrathoracic impedance measurement may be a useful tool to prevent worsening HF symptoms. The proposed threshold for the OptiVol fluid alert of 60 Ω per day is very sensitive, but at the cost of low specificity, because more than half of the alerts were false-positives. The maximum OptiVol index was significantly greater in patients with symptoms of HF than in patients without these symptoms. Consequently, increasing the threshold for the OptiVol alert provided a better balance between sensitivity and specificity to predict decompensated HF.

In conclusion, with a cut-off value for the OptiVol threshold of 60 Ω per day, a reasonable balance between sensitivity and specificity is obtained. Our results confirm the clinical value of the Optivol alert for patients with decompensated HF. These findings are relevant to the increasing number of patients with HF who are being considered for device therapy.

References

1. Thom T, Haase N, Rosamond W et al (2006) Heart disease and stroke statistics – 2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 113:e85-e151
2. Yu CM, Wang L, Chau E et al (2005) Intrathoracic impedance monitoring in patients with heart failure: correlation with fluid status and feasibility of early warning preceding hospitalization. Circulation 112:841–848
3. Alonso C, Leclercq C, Victor F et al (1999) Electrocardiographic predictive factors of long-term clinical improvement with multisite biventricular pacing in advanced heart failure. Am J Cardiol 84:1417–1421
4. Stadler RW, Wang L, Yu CM et al (2003) Automated detection of decreases in intrathoracic impedance to predict CHF hospitalization. Pacing Clin Electrophysiol 26:16
5. Evangelista LS, Dracup K, Doering LV (2000) Treatment-seeking delays in heart failure patients. J Heart Lung Transplant 19:932–938

Performing Carotid Sinus Massage

Roberto Maggi, Michele Brignole

Introduction

Carotid sinus syndrome is a frequent cause of syncope, especially in the elderly. The initial evaluation for this condition consists of a patient history, physical examination, standard electrocardiogram (ECG) and systemic blood pressure measurement in the supine and upright positions. If the origin of syncope remains uncertain, carotid sinus massage (CSM) together with the tilt test becomes the method of choice to unmask neuromediated syncopes.

Performing Carotid Sinus Massage

Continuous ECG monitoring must be carried out during the test. Continuous beat-to-beat noninvasive blood pressure monitoring is also important, as the vasodepressor response is rapid and cannot be adequately detected with devices that do not measure continuous blood pressure. After baseline measurements, the right carotid artery is firmly massaged for 5–10 s at the anterior margin of the sternocleidomastoid muscle at the level of the cricoid cartilage. After 1–2 min, if the massage on one side fails to yield a "positive" response, a second massage is performed on the opposite side. If an asystolic response is evoked, then the contribution of the vasodepressor component (which may otherwise be hidden) is assessed by repeating the massage after intravenous administration of atropine (1 mg or 0.02 mg/kg body weight). The response to CSM is generally classified as cardioinhibitory (i.e., asys-

Arrhythmologic Centre, Department of Cardiology, Ospedali del Tigullio, Lavagna (GE), Italy

tole), vasodepressive (fall in systolic blood pressure), or mixed. The mixed response is diagnosed by the association of an asystole of ≥ 3 s and a decline in systolic blood pressure of ≥ 50 mmHg on rhythm resumption from the baseline value (Table 1).

In general, CSM is performed by one of two different methods:

- In the first, the massage is performed for a short time (usually 5 s) during which the patient is in the supine position, and the result is defined as positive if an asystole ≥ 3 s and/or a fall in systolic blood pressure ≥ 50 mmHg are induced [1–5]. Pooled data from four studies performed in elderly patients with syncope showed a positive response rate of 35% (235 of 663 patients) [1–4]. However, previous studies found that the diagnosis may be missed in about one-third of patients if only supine massage is performed [5, 6].
- In the second method, the "method of symptoms," CSM is performed for 10 s with the patient in the supine position and then again for another 10 s with the patient in the upright position. The test is defined as positive if during the massage the spontaneous symptoms are reproduced in association with cardioinhibition and/or vasodepression [7–11]. In an intrapatient comparison study [9], a higher positivity rate (49 vs 41%) in patients with syncope and a lower positivity rate (5 vs 15%) in patients without syncope were obtained with the "method of symptoms" than with the first method. In a large population of 1,719 consecutive patients

Table 1. Carotid sinus massage: classification of the positive responses

- Carotid sinus massage, baseline: asystole ≥ 3 s with reproduction of spontaneous symptoms
- Carotid sinus massage after atropine: no further symptoms[a]

Mixed form

- Carotid sinus massage, baseline: asystole ≥ 3 s and fall in systolic blood pressure ≥ 50 mmHg with reproduction of spontaneous symptoms.
- Carotid sinus massage after atropine: milder symptoms due to systolic blood pressure fall ≥ 50 mmHg

Dominant vasodepressor form

- Carotid sinus massage, baseline: reproduction of the spontaneous symptoms due to systolic blood pressure fall ≥ 50 mmHg without asystole
- Carotid sinus massage after atropine: unchanged

[a]In this case, the vasodepressor reflex is absent or, if present, the patient is asymptomatic

with syncope unexplained after the initial evaluation (mean age 66 ± 17 years), carotid sinus hypersensitivity was found in 56% and syncope was reproduced in 26% [12]. The positivity rate increased with age, ranging from 4% in patients < 40 years to 41% in patients > 80 years. The test was positive only in the upright position in 49% of patients.

Whatever method is used, the importance of administering the massage with the patient in the upright position, usually using a tilt table, has been recognized [5, 6, 12, 13]. In addition to yielding a higher positivity rate compared with supine massage only, upright massage allows for better evaluation of the magnitude of the vasodepressor component and for better reproduction of symptoms. The vasodepressor component of the reflex was underestimated in the past, but is actually present in most patients who exhibit an asystolic response [13]. Correct determination of the vasodepressor component of the reflex is of practical importance for the choice of therapy. Indeed, pacemaker therapy has been shown to be less effective in mixed forms with an important vasodepressor component rather than in dominant cardioinhibitory forms [1, 14]. The syndrome is misdiagnosed in half of the patients if CSM is not performed in the upright position.

The main complications of CSM are neurological [15]. In three studies, neurological complications were reported in seven of 1,600 patients (5,000 massages), with an incidence of 0.45% [12]; in 11 of 4,000 patients (16,000 massages), with an incidence of 0.28% [16]; and in three of 1,719 patients, with an incidence of 0.17% [12]. Even if neurological complications are rare, carotid massage should be avoided in patients with previous transient ischemic attacks or strokes within the past 3 months (except if carotid Doppler studies have excluded significant stenosis) or in patients with carotid bruits [15]. Rarely, CSM may elicit self-limited atrial fibrillation of little clinical significance [17, 1]. Since asystole induced by the massage is self-terminating shortly after the end of the massage, resuscitative measures are not usually needed.

Recommendations According to the Guidelines on Syncope of the European Society of Cardiology

Indications and Methodology

Carotid sinus massage is recommended in patients > 40 years of age with syncope of unknown etiology after the initial evaluation. If there is a risk of stroke due to carotid artery disease, massage should be avoided. Electrocardiographic monitoring and continuous blood pressure measurement during

carotid massage are mandatory. Duration of massage for a minimum of 5 and a maximum of 10 s is recommended. Carotid massage should be performed with the patient both supine and erect.

Diagnosis

The procedure is considered positive if syncope is reproduced during or immediately after massage in the presence of asystole > 3 s and/or a fall in systolic blood pressure ≥ 50 mmHg. A positive response is diagnostic of the cause of syncope in the absence of any other competing diagnosis.

Diagnostic Value of Carotid Sinus Massage

There is considerable disagreement regarding the diagnosis of carotid sinus syndrome (CSS); its reported prevalence ranges from 1 to 60% [1–4, 8–10, 19–21]. This discrepancy, which creates confusion and may lead to underestimation of the real importance of CSS, is probably due to different interpretations of the results of CSM and the different indications for the test in the clinical setting. This controversy may partly be resolved by considering "spontaneous" and "induced" CSS separately. Thus, "spontaneous CSS" can be defined as syncope that, by its history, seems to occur in close relationship with accidental mechanical manipulation of the carotid sinuses and which can often be reproduced by CSM. Spontaneous CSS is rare and accounts for only about 1% of all causes of syncope [19–21]. By contrast, "induced CSS" is more broadly defined and can be assumed to be present even though a close relationship between manipulation of the carotid sinus and the occurrence of syncope is not demonstrated. Thus, induced CSS is diagnosed in patients who are found to have an abnormal response to CSM. Regarded in this way, CSS is much more frequent, with 26–60% of patients affected by unexplained syncope [1–4, 9–11]. Moreover, CSS may be responsible for many cases of syncope or unexplained "falls" in older persons. Objections could be raised that the latter definition lacks specificity and that several false-positive cases could be misinterpreted as CSS, when the real cause of syncope is different. However, this does not seem to be true; indeed, some observational and controlled studies have shown that pacing therapy is able to reduce syncopal relapses in patients with induced CSS [8, 20, 22–24]. In other words, the results of therapy indirectly validate the utility and efficacy of extending the indications for performing CSM according to the "method of symptoms."

Unlike vaso-vagal syncope, which is present in young people, the prevalence of positive CSM progressively increases with age, suggesting a phys-

iopathological role of age-related degenerative processes in the genesis of the abnormal reflex. Since CSS is rare in persons under the age of 40, CSM could be limited to people older than 40 years.

The association with orthostatic blood pressure drop is more common than might otherwise be considered and suggests that an impairment of the mechanism of adaptation to the upright position is frequently involved. CSM is able to unmask this type of abnormality, which would not otherwise be revealed by the standard orthostatic hypotension testing performed during initial evaluation of syncope [6].

In conclusions, the systematic administration of "method of symptoms" CSM testing reveals that CSS is a frequent cause of syncope, especially in the elderly. Its rate is probably underestimated when the massage is not systematically performed in patients with syncope of uncertain origin after initial evaluation.

CSS is misdiagnosed in half of the cases if the massage is not performed with the patient in the upright position. The "method of symptoms" approach is safe, with a complication rate similar to that of CSM performed according to the "short time" method.

Correlation between Carotid Sinus Massage and Spontaneous Syncope

Recently, our group prospectively evaluated whether a cardioinhibitory carotid sinus hypersensitivity (CSH) was correlated (and therefore could predict) the clinical outcome and the mechanism of implantable loop recorder (ILR)-documented spontaneous syncope [25]. The correlation of spontaneous syncopal episodes with an abnormal ILR finding can be regarded as a reference standard when an arrhythmia is suspected to have a role in the genesis of syncope.

The study included 18 consecutive patients with suspected recurrent neurally mediated syncope and a positive cardioinhibitory response during CSM (maximum pause 5.5 ± 1.6 s) who had subsequent documentation of a spontaneous syncope by means of an ILR. The patients were compared with a 2:1 age- and sex-matched group of 36 patients with a clinical diagnosis of recurrent neurally mediated syncope and negative response to CSM, tilt testing, and ATP test. Asystole > 3 s was observed at the time of the spontaneous syncope in 16 (89%) of the CSH patients and in 18 (50%) of the control group ($p = 0.007$). Sinus arrest was the most frequent finding among CSH patients but not among controls (72 vs 28%, $p = 0.003$). After ILR documentation, 14 CSH patients with asystole received dual-chamber pacemaker implantation; during 35 ± 22 months of follow-up, two syncopal episodes recurred in two

patients (14%) and presyncope occurred in another two patients (14%). Syncope burden decreased from 1.68 (95%, confidence interval 1.66–1.70) episodes per patient per year before to 0.04 (0.038–0.042) after pacemaker implant (98% relative risk reduction).

In this study we found that a long asystole, mainly due to sinus arrest, was the most frequent finding at the time of spontaneous syncope in patients with cardioinhibitory CSH. In patients with a clinical diagnosis of suspected neurally mediated syncope, the finding of a cardionihibitory response during carotid sinus massage predicted, with a probability of 89%, that a long asystolic reflex was also present at the time of the spontaneous syncope. The finding of progressive sinus bradycardia followed by ventricular asystole (types 1A and 1B of the ISSUE classification [26] was consistent with the etiology of neurally mediated syncope. In the absence of a cardioinhibitory CSH, the electrocardiographic findings at the time of spontaneous neurally mediated syncope were heterogeneous, with bradycardia or asystole accounting for only approximately one-half of the syncope events [26].

The finding of asystolic syncope during spontaneous episodes forms the background for the potential benefit of cardiac pacing in CSH patients. Indeed, according to our study, cardiac pacing resulted in a 98% reduction of the syncope burden during 3 years of follow-up.

References

1. Mc Intosh SJ, Lawson J, Kenny RA (1993) Clinical characteristics of vasodepressor, cardioinhibitory and mixed carotid sinus syndrome in the elderly. Am J Med 95:203–208
2. Graux P, Mekerke W, Lemaire N et al (1989) Le syndrome du sinus carotidien. Apport de la monitorisation de la pression arterielle a l'exploration electrophysiologique endocavitaire. Arch Mal Coeur 82:193–199
3. Huang SKS, Ezri MD, Honser RG, Denes P (1988) Carotid sinus hypersensitivity in patients with unexplained syncope: clinical, electrophysiologic, and long-term follow-up observation. Am Heart J 116:989–996
4. Volkmann H, Schnerch B, Kuhnert H (1990) Diagnostic value of carotid sinus hypersensitivity. Pacing Clin Electrophysiol 13:2065–2070
5. Parry SW, Richardson D, O'Shea D et al (2000) Diagnosis of carotid sinus hypersensitivity in older adults: carotid sinus massage in the upright position is essential. Heart 83:22–23
6. Brignole M, Sartore B, Prato R (1983) Role of body position during carotid sinus stimulation test in the diagnosis of cardioinhibitory carotid sinus syndrome. G Ital Cardiol 14:69–72
7. Thomas JE (1969) Hyperactive carotid sinus reflex and carotid sinus syncope. Mayo Clin Proc 44:127–139
8. Brignole M, Menozzi C, Lolli G et al (1992) Long-term outcome of paced and non paced patients with severe carotid sinus syndrome. Am J Cardiol 69:1039–1043

9. Brignole M, Menozzi C (1992) Carotid sinus syndrome: diagnosis, natural history and treatment. Eur J Cardiac Pacing Electrophysiol 4:247–254
10. Brignole M, Menozzi C, Gianfranchi L et al (1991) Carotid sinus massage, eyeball compression and head-up tilt test in patients with syncope of uncertain origin and in healthy control subjects. Am Heart J 122:1644–1651
11. Brignole M, Menozzi C, Gianfranchi L et al (1991) Neurally mediated syncope detected by carotid sinus massage and head-up tilt test in sick sinus syndrome. Am J Cardiol 68:1032–1036
12. Puggioni E, Guiducci V, Brignole M et al (2002) Results and complications of the carotid sinus massage performed according to the "Methods of Symptoms". Am J Cardiol 89:599–601
13. Gaggioli G, Brignole M, Menozzi C et al (1995) Reappraisal of the vasodepressor reflex in carotid sinus syndrome. Am J Cardiol 75:518–521
14. Brignole M, Menozzi C, Lolli G et al (1991) Validation of a method for choice of pacing mode in carotid sinus syndrome with or without sinus bradycardia. Pacing Clin Electrophysiol 14:196–203
15. Munro N, McIntosh S, Lawson J et al (1994) The incidence of complications after carotid sinus massage in older patients with syncope. J Am Geriatr Soc 42:1248–1251
16. Davies AG, Kenny RA (1998) Neurological complications following carotid sinus massage. Am J Cardiol 81:1256–1257
17. Franke H (1963) Uber das karotissinus-syndrome und den sogennanten hyperactiven karotissinus reflex. Fridrich-Kave Schattaueur, Stuttgart
18. Brignole M, Alboni P, Benditt DG et al (2004) Guidelines on management (diagnosis and treatment) of syncope – Update 2004. Europace 6:467–537
19. Kapoor W, Snustad D, Peterson J et al (1986) Syncope in the elderly. Am J Med 80:419–427
20. Mathias CJ, Deguchi K, Schatz I (2001) Observation on recurrent syncope and presyncope in 641 patients. Lancet 357:348–353
21. Ammirati F, Colivicchi F, Santini M (2000) Diagnosing syncope in clinical practice. Eur Heart J 21:935–940
22. Morley CA, Perrins EJ, Chan SL, Sutton R (1983) Long-term comparison of DVI and VVI pacing in carotid sinus syndrome. In: Steinbach K (ed) Proceedings of the VII World Symposium on Cardiac Pacing. Steinkopff Verlag, Darmstadt, pp 929–935
23. Stryjer D, Friedensohn A, Schlesinger Z (1986) Ventricular pacing as the preferable mode for lomg-term pacing in patients with carotid sinus syncope of the cardioinhibitory type. Pacing Clin Electrophysiol 9:705–709
24. Blanc JJ, Boshat J, Penther Ph (1984) Hypersensibilité sino-carotidienne. Evolution à moyen terme en fonction du traitement et de ses symptomes. Arch Mal Coeur 77:330–336
25. Maggi R, Menozzi C, Brignole M et al (2007) Cardioinhibitory carotid sinus hypersensitivity predicts an asystolic mechanism of spontaneous neurally-mediated syncope. Europace (in press)
26. Brignole M, Moya A, Menozzi C et al (2005) Proposed electrocardiographic classification of spontaneous syncope documented by an implantable loop recorder. Europace 7:14–18

Performing Tilt Testing and Physical Countermaneuvers Training

Giuseppina M. Francese, Michele M. Gulizia

Introduction

Vasovagal syncope is a common clinical condition and has an estimated lifetime prevalence of 35% [1–3]. Although the disorder is episodic in nature, it can be considered a chronic disorder since symptoms often occur over many years due to recurrent episodes of (pre)syncope [1, 2], with deleterious effects on patients' quality of life [4]. A correct initial evaluation (history, physical examination, supine and upright systolic blood pressure measurement, ECG) in accordance with European Society of Cardiology Syncope Guidelines [5] facilitates a diagnosis of suspected or certain neurally mediated syncope. In this case, additional, specific diagnostic tests should be performed. Different diagnostic examinations are used in actual clinical practice to identify the syncope mechanism. These include carotid sinus massage (CSM), tilt-table testing, and implantable loop recorder. In patients > 40 years of age, CSM can identify an abnormal response. This so-called carotid sinus hypersensitivity is characterized by a ventricular pause lasting ≥ 3 s and a fall in systolic blood pressure of ≥ 50 mmHg. However, carotid sinus hypersensitivity is not diagnostic of carotid sinus syndrome (CSS); rather, reproducibility is a crucial diagnostic element. If the latter is to be obtained, the patient should undergo tilt-table testing under secure conditions in order to prevent his or her injury from a fall.

Cardiology Department, Garibaldi-Nesima Hospital, Catania, Italy

Tilt-Table Testing

The gold standard diagnostic examination for neurally mediated syncope has always been the tilt-table test. From 1986 to 1995, different test execution protocols were proposed [6–10]. In 1994, Raviele et al. [11] proposed the use of intravenous nitroglycerin infusion. With this protocol, 21 of 40 (53%) patients with syncope of unknown origin had positive responses, with a specificity of 92%. Ten of 40 patients (25%) had progressive hypotension without bradycardia. The latter was classified as an exaggerated response consisting of an excessive hypotensive effect of the drug. More recently, Raviele et al. [12] used sublingual nitroglycerin instead of an intravenous infusion. After 45 min of baseline tilting, 0.3 mg of sublingual nitroglycerin was administered. With this protocol the overall rate of positive responses in patients with syncope of unknown origin was 51%, with a specificity of 94%. The main advantage of sublingual nitroglycerin is that venous cannulation is not needed for patient testing. Recently, many clinicians have used a shortened protocol consisting of 400 μg of nitroglycerin spray administered sublingually after a 20-min baseline phase. This method is known as the "Italian Protocol". Other drugs used as provocative agents during tilt testing include isosorbide dinitrate [13], edrophonium [14], clomipramine [15], and adenosine. In 1992, Sutton et al. [16] assessed the different hemodynamic responses evoked by tilt-table testing and developed a classification that has been successively modified (Table 1) [17]. In order to use the tilt test effectively in

Table 1. New Vasovagal Syncope International Study (VASIS) classification. Adapted from [17]

Type 1	Mixed. Heart rate falls at the time of syncope but the ventricular rate does not fall to < 40 bpm or falls to < 40 bpm for < 10 s. Blood pressure falls before the heart rate falls
Type 2A	Cardioinhibition without asystole. Heart rate falls to a ventricular rate < 40 bpm for > 10 s but asystole of > 3 s does not occur. Blood pressure falls before the heart rate falls
Type 2B	Cardioinhibition with asystole. Asystole occurs for > 3 s. Blood pressure fall coincides with or occurs before the heart rate fall
Type 3	Vasodepressor. Heart rate does not fall > 10% from its peak at the time of syncope
Exception 1	Chronotropic incompetence. No heart rate rise during tilt testing (i.e., < 10% from the pre-tilt rate)
Exception 2	Excessive heart rate rise. An excessive rise in heart rate both at the onset of the upright position and throughout its duration before syncope (i.e., > 130 bpm)

the evaluation of therapeutic options, two conditions are needed: (1) a high reproducibility of the test and (2) responses to the test that are predictive of outcome at follow-up. The overall reproducibility of an initial negative response (85–94%) is higher than the reproducibility of an initial positive response (31–92%). In addition, data from controlled trials showed that approximately 50% of patients with a baseline positive tilt test became negative when the test was repeated with treatment or with placebo [18]. Moreover, acute studies were not predictive of the long-term outcome of pacing therapy [19]. These data showed that tilt testing aimed at assessing the effectiveness of different treatments has important limitations (level A).

While the head-up tilt test is a safe procedure and the rate of complications is very low, in some patients the tilt-table test is negative even when neurally mediated syncope is strongly suspected. In these circumstances and when the interval between recurrences is measured in months or years, consideration should be given to implantable ECG loop recorder (ILR). This device is placed subcutaneously under local anesthesia, and has a battery life of 18–24 months. It has a solid-state loop memory, and the current version can store up to 42 min of continuous ECG. Retrospective ECG allows activation of the device after consciousness has been restored. The ILR may ultimately become the reference standard, to be adopted when an arrhythmic cause of syncope is suspected but not sufficiently proven to allow an etiological treatment. Recently, ISSUE 2 study results have been published [20]. That study examined the effectiveness of a new strategy for managing patients with suspected neurally mediated syncope, apart from those with carotid sinus syndrome. The strategy requires early implantation of an ILR, irrespective of tilt-testing results, and delay of therapy until after ILR documentation of recurrent syncope and establishment of a mechanism for the spontaneous syncope. ISSUE2 also demonstrated that the mechanism of spontaneous syncope as documented by ILR is poorly correlated with the results of tilt-table testing and not predicted by the results of an ATP test. Therefore, these tests are of poor or no value in guiding specific therapy [21]. In another study [22], Brignole et al. reported that older patients with unexplained syncope are more likely than younger ones to have an indication for an ILR. In these older patients, ILR has a higher diagnostic value and arrhythmia are more likely detected and successfully treated. In asystolic neurally mediated syncope documented by ILR, ISSUE-2 demonstrated that the pacemaker was effective in reducing the 1-year first syncope recurrence rate from 33% before implantation (ILR phase 1) to 5% after implantation (phase 2). Moreover, the control non-asystolic group continued to have a 41% recurrence rate after the first recurrence of syncope, thus supporting that the

pacemaker-mediated reduction was due to the beneficial effect of the pacemaker itself and not to other factors. However, a formal controlled trial is needed to confirm these findings.

Physical Counterpressure Maneuvers

Vasovagal syncope is preceded by prodromal symptoms in about two-thirds of patients. During the prodromal phase, blood pressure falls markedly. This fall usually precedes the decrease in heart rate, which may be absent at least at the beginning of this phase. Hypotension is caused by vasodilatation in the skeletal muscles due to inhibition of sympathetic vasoconstrictive activity. In normal and hypertensive subjects, isometric handgrip exercises are able to induce a significant blood pressure increase, which is mediated largely by endogenous catecholamine release. Muscle sympathetic nerve discharge and vascular resistance increase during handgrip exercises by healthy subjects. Physical counterpressure maneuvers have previously been shown to be effective in stabilizing blood pressure in patients with autonomic failure. Recently, Krediet et al. [23, 24] published reports on controlling or aborting impending vasovagal syncope by leg crossing and muscle tensing. Brignole et al. [25] found a comparable effect of isometric arm counterpressure maneuvers. Several physical countermaneuvers have been proposed in the management of orthostatic hypotension [26], such as the handgrip (maximal voluntary contraction of a rubber ball taken in the dominant hand for the maximum tolerated time or till complete disappearance of symptoms), arm-tensing (maximum tolerated isometric contraction of the two arms achieved by gripping one hand with the other and contemporarily abducting the arms for the maximum tolerated time), and leg crossing (combined with maximum tensing of leg, abdominal, and buttock muscles for the maximum tolerated time). A randomized, controlled trial of physical countermaneuvers [27] showed that education and physical counterpressure maneuvers performed at the time of appearance of symptoms of impending syncope are effective in reducing syncopal recurrences in young patients affected by vasovagal syncope. This implies that isometric arm contraction is able to abort syncope in most cases, even when the patient remains in the standing position. The practical consequence is that when symptoms of impending syncope occur the patient will have enough time to apply counterpressure treatment before losing consciousness. In some cases, treatment will definitely abort the vasovagal reaction, or at least delay syncope for the duration of the maneuver, thus allowing enough time to initiate other maneuvers to abort syncope (e.g., supine posture). The physical counterpressure trial also found that

patients were able to enact a counterpressure maneuver in 98% of cases and to relieve symptoms in 99% of these.

Counterpressure maneuvers can be regarded as a first-line treatment in association with other conventional measures recommended by the international guidelines for treating vasovagal syncope, namely, reassurance regarding the benign nature of the condition, training in the recognition of premonitory symptoms, avoidance of triggering events, the adoption of maneuvers to abort the episode (e.g., supine posture), and avoidance of volume depletion and prolonged upright posture. ISSUE 3 is a new, multi-center, prospective, randomized, controlled double-blind study aimed at assessing the effectiveness of pacemaker therapy for prevention of asystolic neurally mediated syncope. This study, in which physical counterpressure maneuvers will be evaluated in older patients, will last until December 2010 [22].

References

1. Colman N, Nahm K, Ganzeboom KS et al (2004) Epidemiology of reflex syncope. Clin Auton Res 14(Suppl 1):i9-i17
2. Ganzeboom KS, Colman N, Reitsma JB et al (2003) Prevalence and triggers of syncope in medical students. Am J Cardiol 91:1006–1008
3. Sheldon RS, Sheldon AG, Connolly SJ et al (2006) Age of first faint in patients with vasovagal syncope. J Cardiovasc Electrophysiol 17:1–6
4. Rose MS, Koshman ML, Spreng S, Sheldon R (2000) The relationship between health-related quality of life and frequency of spells in patients with syncope. J Clin Epidemiol 53:1209–1216
5. Brignole M, Alboni P, Benditt D et al (2004) Guidelines on management (diagnosis and treatment) of syncope - Update. Europace 6:467–537
6. Kenny RA, Ingram A, Bayliss J, Sutton R (1986) Head-up tilt: a useful test for investigating unexplained syncope. Lancet 1:1352–1355
7. Almquist A, Goldenberg IF, Milstein S et al (1989) Provocation of bradycardia and hypotension by isoproterenol and upright posture in patients with unexplained syncope. N Engl J Med 320:346–351
8. Kapoor WN, Brant N (1992) Evaluation of syncope by upright tilt testing with isoproterenol. A nonspecific test. Ann Intern Med 116:358–363
9. Morillo CA, Klein GJ, Zandri S, Yee R (1995) Diagnostic accuracy of a low-dose isoproterenol head-up tilt protocol. Am Heart J May 129:901–906
10. Natale A, Aktar M, Jazayeri M et al (1995) Provocation of hypotension during head-up tilt testing in subjects with no history of syncope or presyncope. Circulation 92:54–58
11. Raviele A, Gasparini G, Di Pede F et al (1994) Nitroglycerin infusion during upright tilt: a new test for the diagnosis of vasovagal syncope. Am Heart J 127:103–111
12. Raviele SA, Menozzi C, Brignole M et al (1995) Value of head-up tilt testing potentiated with sublingual nitroglycerin to assess the origin of unexplained syncope. Am J Cardiol 76:267–272
13. Ammirati F, Colivicchi F, Biffi A et al (1998) Head-up tilt testing potentiated with low-dose sublingual isosorbide dinitratte: a simplified time-saving approach for the evaluation of unexplained syncope. Am Heart J 135:671–676

14. Voice RA, Lurie KG, Sakaguchi S et al (1998) Comparison of tilt angles and provocative agents (edrophonium and isoproterenol) to improve head-upright tilt-table testing. Am J Cardiol 81:346–351
15. Theodorakis G, Markianos M, Zarvalis E et al (2000) Provocation of neurocardiogenic syncope by clomipramine administration during the head-up tilt test in vasovagal syncope. J Am Coll Cardiol 36:174–178
16. Sutton R, Petersen M, Brignole M et al (1992) Proposed classification for tilt induced vasovagal syncope. Eur J Cardiac Pacing Electrophysiol 3:180–188
17. Brignole M, Menozzi C, Del Rosso A et al (2000) New classification of haemodynamics of vasovagal syncope: beyond the VASIS classification. Analysis of the presyncopal phase of the tilt test without and with nitroglycerin challenge. Europace 2:66–76
18. Moya A, Permanyer-Miralda G, Sagrista-Sauleda J et al (1995) Limitations of head-up tilt test for evaluating the efficacy of therapeutic interventions in patients with vasovagal syncope: results of a controlled study of etilefrine versus placebo. J Am Coll Cardiol 25:65–69
19. Raviele A, Brignole M, Sutton R et al (1999) Effect of etilefrine in preventing syncopal recurrence in patients with vasovagal syncope: a double-blind, randomized, placebo-controlled trial. The Vasovagal Syncope International Study. Circulation 99:1452–1457
20. Brignole M, Sutton R, Menozzi C et al (2006) Early application of an implantable loop recorder allows a mechanism-based effective therapy in patients with recurrent suspected neurally-mediated syncope. Eur Heart J 27:1085–1092
21. Brignole M, Sutton R, Menozzi C et al (2006) Lack of correlation between the responses to tilt testing and adenosine triphosphate test and the mechanism of spontaneous neurally mediated syncope. Eur Heart J 27:2232–2239
22. Brignole M, Menozzi C, Maggi R et al (2006) The usage and diagnostic yield of the implantable loop-recorder in detection of the mechanism of syncope and in guiding effective antiarrhythmic therapy in older people. Europace 7:273–279
23. Krediet CT, van Dijk N, Linzer M et al (2002) Management of vasovagal syncope: controlling or aborting faints by leg crossing and muscle tensing. Circulation 106:1684–1689
24. Krediet CT, de Bruin IG, Ganzeboom KS et al (2005) Leg crossing, muscle tensing, squatting, and the crash position are effective against vasovagal reactions solely through increases in cardiac output. J Appl Physiol 99:1697–1703
25. Brignole M, Croci F, Menozzi C et al (2002) Isometric arm counterpressure maneuvers to abort impending vasovagal syncope. J Am Coll Cardiol 40:2053–2059
26. Bouvette CM, McPhee BR, Opfer-Gehrking TL, Low PA (1996) Role of physical countermaneuvers in the management of orthostatic hypotension: efficacy and biofeedback augmentation. Mayo Clin Proc 71:847–853
27. van Dijk N, Blanc JJ, Quartieri F et al (2006) Randomized trial of optimal conventional therapy versus optimal conventional therapy plus counterpressure manoeuvres in patients with neurally-mediated syncope. J Am Coll Cardiol 48:1652–1657

Implanting a Loop Recorder

Michele Brignole

Holter Monitoring in Syncope

Episodes of syncope over the course of a 24-h Holter monitoring are rare. The vast majority of patients have a syncope-free interval, which can be measured in weeks, months, or years, but not days; therefore, symptom-ECG correlation is seldom achieved with Holter monitoring. In an overview [1] of the results of eight studies of ambulatory monitoring in syncope, only 4% of patients (range between 1 and 20%) had a correlation of symptoms with arrhythmia. The true yield of conventional ECG monitoring in syncope may be as low as 1–2% in an unselected population.

An asymptomatic arrhythmia detected by Holter monitoring is often used to make a diagnosis by inference. However, in the absence of symptom-ECG correlation, ECG findings may be inappropriately maximized, leading to unnecessary therapy, e.g., pacemaker implantation in a patient with vasomotor syncope. Alternatively, symptoms may be inappropriately minimized by physicians if Holter monitoring fails to yield any evidence of an arrhythmia.

Holter monitoring in syncope may be of greater value if symptoms are very frequent (> 1 per week). Daily single or multiple episodes of loss-of-consciousness might increase the likelihood of symptom-ECG correlation. Nonetheless, experience in these patients suggests that many have psychogenic blackouts. Undoubtedly, in such patients, true negative findings of Holter monitoring may be useful in confirming the underlying cause.

Arrhythmologic Centre, Department of Cardiology, Ospedali del Tigullio, Lavagna (GE), Italy

External Loop Recorder in Syncope

Conventional event recorders are external devices equipped with fixed electrodes, through which an ECG can be recorded by direct application to the chest wall. Provided the patient is able to comply at the time of symptom occurrence, a high-fidelity recording can be made.

Recordings can be prospective, retrospective (loop recorders), or both. Prospective external event recorders are of limited value in syncope because the patient must be able to apply the recorder to the chest during the period of unconsciousness and activate recording. Retrospective ECG allows activation of the device after consciousness has been restored.

External retrospective loop recorders, by contrast, show a higher diagnostic yield in syncope. In one study [2], in 25% of enrolled patients syncope or pre-syncope was recorded during the monitoring period, which lasted up to 1 month. However, since patients usually do not comply with external retrospective loop recorders for more than a few weeks, symptom-ECG correlation cannot be achieved when the syncopal recurrence rate is less frequent. In a recent study [3], the external loop recorder was not useful for diagnosis of syncope in patients with 3 ± 4 episodes (more than 2) of syncope during the previous 6 months, no overt heart disease, and a negative tilt test. External loop recorders in syncope may be valuable if symptoms are frequent (> 1 per month).

Implantable Loop Recorder in Syncope

The implantable loop recorder is placed subcutaneously under local anesthesia, and has a battery life of 18–24 months. With this device, high-fidelity ECG recordings can be made. Retrospective ECG allows activation of the recorder after consciousness has been restored. Automatic activation is also available if predefined arrhythmias should happen to occur.

In a preliminary clinical experience, implantable loop recorders were used diagnostically in patients whose syncope still could not be explained at the end of full conventional work-ups. Symptom-ECG correlation was achieved in 88% of a small series of highly selected patients, within a mean of 5 months of implantation [4]. In a larger series [5], correlation between symptoms (syncope or pre-syncope) and ECG was achieved in 59% of 85 patients within a mean of 10 months of implantation. Syncope-ECG correlation was achieved in 27% of patients and presyncope-ECG correlation in 32%; presyncope was much less likely to be associated with an arrhythmia

than syncope and did not prove to be an accurate surrogate for syncope in establishing a diagnosis. Pooled data from four studies [4–7] for a total of 247 patients with unexplained syncope at the end of a complete conventional investigation showed a correlation between syncope and ECG in 84 patients (34%); of these, 52% had bradycardia or asystole at the time of the recorded event, 11% had tachycardia, and 37% had no rhythm variation.

In another study [8] 60 patients with unexplained syncope were randomized to "conventional" testing with external loop recorders and tilt and electrophysiological testing or to prolonged monitoring with the implantable loop recorder. The results showed that implantation of the loop recorder during an initial phase of the work-up was more likely than conventional testing to provide a diagnosis (52 vs 20%). However, patients at high risk of life-threatening arrhythmias as well as those with an ejection fraction < 35% were excluded.

Based on the preliminary experience involving patients with unexplained syncope, monitoring with the implantable loop recorder may become the reference standard. This approach could be implemented when an arrhythmic cause of syncope is suspected but not sufficiently proven to allow etiologically directed treatment. There are several areas of interest that merit further clarification:

- Patients in whom epilepsy was suspected but in whom treatment has proven ineffective [9].
- Patients with recurrent and unexplained syncope and without structural heart disease, when an understanding of the exact mechanism of spontaneous syncope may alter the therapeutic approach [6].
- Patients who have a diagnosis of neurally mediated syncope, when an understanding of the exact mechanism of spontaneous syncope may alter the therapeutic approach [6].
- Patients with bundle branch block in whom a paroxysmal AV block is likely, despite a complete negative electrophysiological evaluation [10].
- Patients with definite structural heart disease and/or non-sustained ventricular tachyarrhythmias in whom a ventricular tachyarrhythmia is likely despite a completed negative electrophysiological study [11].
- Patients with unexplained falls [12].

The implantable loop recorder carries a high up-front cost of approximately € 1,500. However, if symptom-ECG correlation can be achieved in a substantial number of patients, then analysis of the cost per symptom-ECG yield might demonstrate that the implanted device is more cost-effective than a conventional investigation [8].

Diagnosis

Whatever the type of ECG monitoring used (Holter, external or implantable loop recorder) the diagnostic criteria are similar: ECG monitoring is diagnostic when a correlation between syncope and an electrocardiographic abnormality (brady- or tachyarrhythmia) is detected. Conversely, ECG monitoring excludes an arrhythmic cause when there is a correlation between syncope and no rhythm variation. In the absence of such correlations, additional testing is recommended, with the possible exception of ventricular pauses longer than 3 s when the patient is awake, or periods of Mobitz II or 3rd degree atrioventricular block in the awake patient, or rapid paroxysmal ventricular tachycardia [13].

Presyncope may not be an accurate surrogate for syncope in establishing a diagnosis; therefore, therapy should not be guided by presyncopal findings.

ECG Monitoring in Syncope: Where in the Work-up?

The role of ECG monitoring in syncope cannot be defined in isolation. Physicians may be guided by the results of the patient's clinical history and physical examination as well as objective testing, for example, by tilt testing. Knowledge of what transpires during a spontaneous syncopal episode is the gold standard for syncope evaluation. For this reason, it is likely that implantable monitors will become increasingly important in the evaluating syncope and that their use will be incorporated into the diagnostic flow instead of or before many other conventional investigations are carried out.

References

1. Kapoor WN (1992) Evaluation and management of the patient with syncope. JAMA 268:2553–2560
2. Linzer M, Pritchett ELC, Pontinen M et al (1990) Incremental diagnostic yield of loop electrocardiographic recorders in unexplained syncope. Am J Cardiol 66:214–219
3. Schuchert A, Maas C, Kretzschmar C et al (2003) Diagnostic yield of external loop recorders in patients with recurrent syncope and negative tilt table test. Pacing Clin Electrophysiol 26:1837–1840
4. Krahn A, Klein G, Norris C, Yee R (1995) The etiology of syncope in patients with negative tilt table and electrophysiologic testing. Circulation 92:1819–1826
5. Krahn AD, Klein GJ, Yee R et al (1999) Use of an extended monitoring strategy in patients with problematic syncope. Reveal Investigators. Circulation 99:406–410
6. Moya A, Brignole M, Menozzi C et al (2001) Mechanism of syncope in patients with isolated syncope and in patients with tilt-positive syncope. Circulation 104:1261–1267

7. Nierop P, Vam Mechelen R, Elsacker A et al (2000) Heart rhythm during syncope and presyncope. Pacing Clin Electrophysiol 23:1532–1538
8. Krahn A, Klein GJ, Yee R et al (2001) Randomized Assessment of Syncope Trial. Conventional diagnostic testing versus a prolonged monitoring strategy. Circulation 104:46–51
9. Zaidi A, Clough P, Cooper P et al (2000) Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. J Am Coll Cardiol 36:181–184
10. Brignole M, Menozzi C, Moya A et al (2001) The mechanism of syncope in patients with bundle branch block and negative electrophysiologic test. Circulation 104:2045–2050
11. Menozzi C, Brignole M, Garcia-Civera R et al (2002) Mechanism of syncope in patients with heart disease and negative electrophysiologic test. Circulation 105:2741–2745
12. Kenny RA, Richardson DA, Steen N et al (2001) Carotid sinus syndrome: a modifiable risk factor for nonaccidental falls in older adults (SAFE PACE). J Am Coll Cardiol 1:1491–1496
13. Brignole M, Alboni P, Benditt D et al (2004) Guidelines on management (diagnosis and treatment) of syncope – Update 2004. Europace 6:467 14. Brignole M, Alboni P, Benditt D et al (2004) Guidelines on management (diagnosis and treatment) of syncope – Update 2004 - Executive summary and recommendations. Eur Heart J 25:2054

Noninvasive Sudden Death Risk Stratification: Heart Rate Variability and Turbulence, and QT Dynamicity

Antonio Vincenti, Stefano Pedretti

Heart-Rate Variability

General Considerations

Variability in sinus-rhythm pacemaker activity over time is a major physiological characteristic of heart-rate behavior, and many cardiovascular and metabolic conditions result in a change in heart rate variability. The numerous studies of time- and frequency-dependent variability have improved our knowledge of the physiological and pathological patterns of heart-rate variability (HRV). The standard deviation of 24-h mean RR value (SDNN), and measurement of the total variance (or power) in the change of RR at high (HF) and low (LF) frequencies are commonly used to estimate HRV. Power-spectrum analysis (i.e. recording the distribution of power as a function of the frequency at which it occurs) requires the transformation of time-series data by means of advanced mathematical algorithms, generally the fast Fourier transform (FFT) (Fig. 1), which is particularly useful in disclosing the harmonic components of variability.

A high SDNN, high HF, and low LF/HF ratio are generally considered the hallmarks of parasympathetic prevalence in autonomic balance; conversely, low SDNN (< 100 ms), high LF, and a high LF/HF ratio (> 6) indicate sympathetic prevalence [1].

Some studies have reported that the LF band is also influenced by parasympathetic components. This is particularly evident in advanced congestive heart failure (CHF), in which a low LF value is often observed. Consequently, LF and the LF/HF ratio are less reliable in CHF patients [2, 3].

Arrhythmology Unit, Cardiac/Thoracic/Vascular Department, San Gerardo Hospital, Monza, Italy

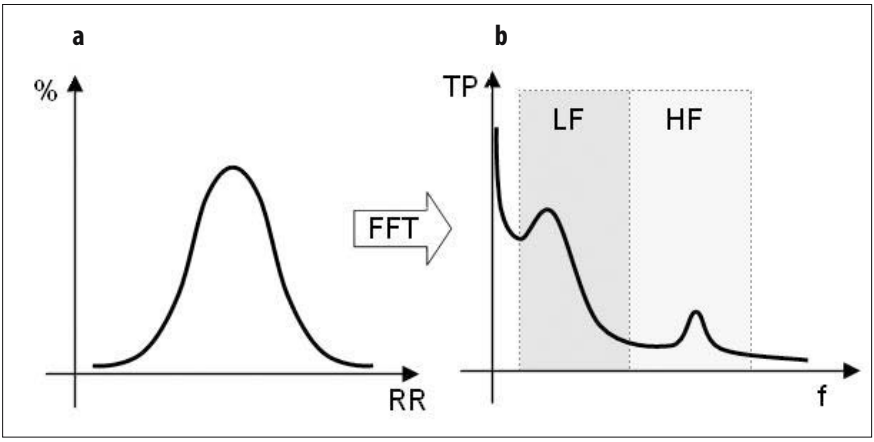


Fig.1. a Time domain representation of RR series, as proportion of beats in function of RR duration. **b** FFT of RR time series, (short term sampling), showing two high-density area in the HF and LF band

More recently, multidisciplinary research investigations have sought to clarify the behavior, mechanisms, and clinical relevance of "nonlinear components" of HRV. Complex algorithms used elsewhere in the scientific field to describe "chaos phenomena" have proven to be also relevant for HRV with respect to the recursive, non-linear (fractal) behavior of heart beats [4]. Poincaré analysis, in which each normal-to-normal RR interval is plotted against the subsequent normal-to-normal interval, is a simple representation of this aspect of HRV. Another approach to estimating non-linear phenomena of HRV consists of examining the proportionality of RR variance in samples of different dimensions. Computational analysis yields a log-log linear relationship between sample size and variability. The slope of this relationship (called the fractal scaling component, α_1) ranges between 0.5 (completely unpredictable variability) and 1.5 (brownian variability). An α_1 value close to 1 is the hallmark of the presence of a physiological, fractal-like signal, which means perfect proportionality between the scale of the RR phenomena and the variance (what happens on a large scale seems to be repeated on a small scale in a similar fashion) [5].

HRV and Survival

Evidence of the prognostic value of low SDNN in unselected patients with previous myocardial infarction (MI) dates to results from the MPIP trial, in

1986 [6]. Later, the UK-Heart study [7] confirmed that in patients with CHF who had a moderate risk profile (mean ejection fraction = 0.41), a value of SDNN < 100 ms was associated with increased all-cause mortality, while SDNN < 50 ms indicated a very poor prognosis.

The independent prognostic value of HRV in post-MI patients has been confirmed in other studies, including those focusing on patients with preserved or reduced ventricular systolic function [8–10]. The prognostic value of HRV, when determined long after the occurrence of MI, is less clear. However, the *Cardiac Arrhythmia Pilot Study* (CAPS), the pilot study for the *Cardiac Arrhythmia Suppression Trial* (CAST), reported that HRV measured within 1 year post-MI continues to predict mortality during an approximately 2-year follow-up [11].

Recently reviewed data from the DEFINITE trial (non-ischemic dilated cardiomyopathy, ejection fraction < 36%) [12] showed a high value of SDNN in risk stratification, since patients in the upper tertile (SDNN >113 ms) had a 0% mortality during follow-up compared to those in the lower levels (SDNN 81–113 ms: 7%; SDNN < 81 ms: 10%). Of note, about one in four patients was excluded from the analysis due to atrial fibrillation or a high incidence (> 25%) of ventricular ectopic beats (VEBs); in this cohort, mortality was the highest (17%; $p = 0.03$).

HRV and Arrhythmic Risk

The value of HRV in assessing the risk of sudden cardiac death (SCD) is less well-defined. Reduced 24-h SDNN was present as a significant risk factor for SCD in one study but not in others (including UK-Heart) [7, 14, 15]. There is no evidence that low SDNN maintains predictive values after adjustment for covariates [16]. With respect to frequency domain analysis, one study supported an independent value of low LF [< 3.3 ln(ms^2)] in predicting SCD in CHF, but only when derived from analysis (day-time) over a long period of time [15]. Conversely, other studies reported that night-time low LF was an independent predictor of SCD [17].

Nonlinear Methods

Concerning non-linear methods, univariate and multivariate analyses provided evidence that an abnormal Poincaré plot distribution is indicative of a worse prognosis in CHF and SCD [14]. In another study, a low α_1 value (< 0.9) was predictive of all-cause mortality in CHF [18].

Heart-Rate Turbulence

General Considerations

By definition, heart-rate turbulence (HRT) refers to the physiological short-term instability of sinus rhythm that follows the occurrence of a VEB [19]. In normal subjects, HRT evolution is biphasic, with an initial shortening and subsequent widening of the RR cycle; the whole phenomenon generally lasts for 15–20 sinus beats. The physiological mechanism of HRT is believed to be the baroreflex response to VEB and pause-determined hemodynamic perturbations [20–22]. Classically, HRT is represented by a tachogram (Fig. 2) and quantified by two parameters:

- *Turbulence onset (TO)*, which is given by the formula:
  $TO = 100 \times [(RR_{+1} + RR_{+2}) - (RR_{-2} + RR_{-1})]/(RR_{-2} + RR\text{-}1)$
  where a physiological initial acceleration in beats +1 and +2 results in a negative TO; a positive TO is considered pathological.
- *Turbulence slope (TS)*, which describes the maximum rate of RR increase obtained by performing a linear regression in multiples of five consecutive beat samples (from beat +1 to beat +15); the steepest regression slope is by definition TS. The cut-off value for normal TS is > 2.5 ms/beat.

HRT is inversely correlated to initial heart rate [23–25], which may reduce the reliability of absolute TO and TS values in unselected patients. TS is also structurally linked to the number of ectopic beats and thus indirectly to time-series length, since HRT is determined after averaging all RR values, leading to smoothing of HR perturbations [26]. TS is inversely correlated to the square root of the number of VEBs [27].

The influence of the VEB coupling interval (CI) on HRT magnitude is still a matter of debate, since published data reported an inverse correlation between CI and HRT in some cases [28, 29]. However, for other authors this was confirmed only in subjects with a left ventricular ejection fraction > 0.40 [30], whereas still others found no correlation [24]. A few methods to obtain more reliable HRT values have been proposed. These include:

- Re-scaling the tachogram by normalizing it either to a heart rate of 80 bpm before analysis [31] or to a combination of a cycle length of 800 ms, duration of the time series, and number of VEBs [26].
- Quantification of the heart-rate dependence of TS by linear regression, as proposed by Schmidt et al. [32] with the term “turbulence dynamicity” (TD) (Fig. 3).
- Measuring HRT during ventricular programmed stimulation [33].

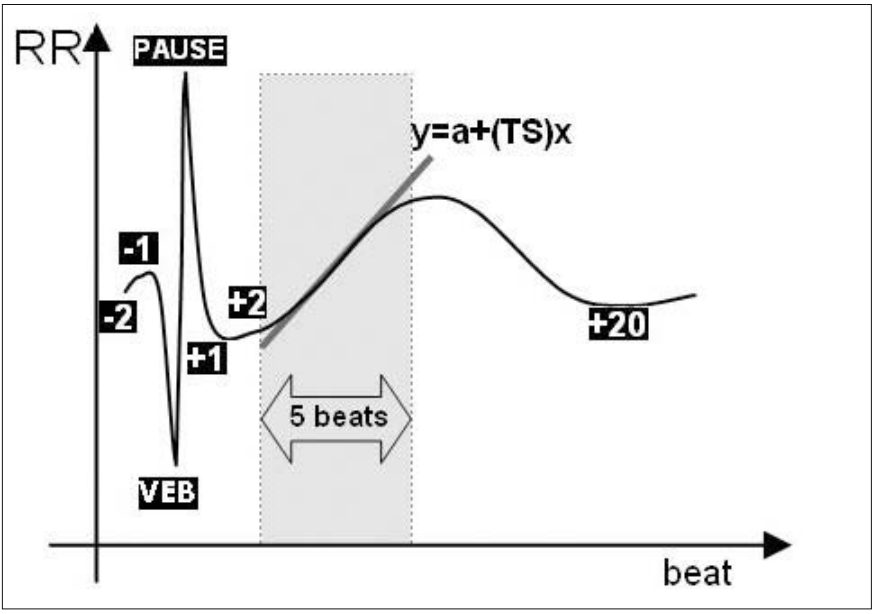


Fig. 2. Tachogram representing HRT evolution, with beats nomenclature. The steepest 5-beat regression that gives TS value is also shown

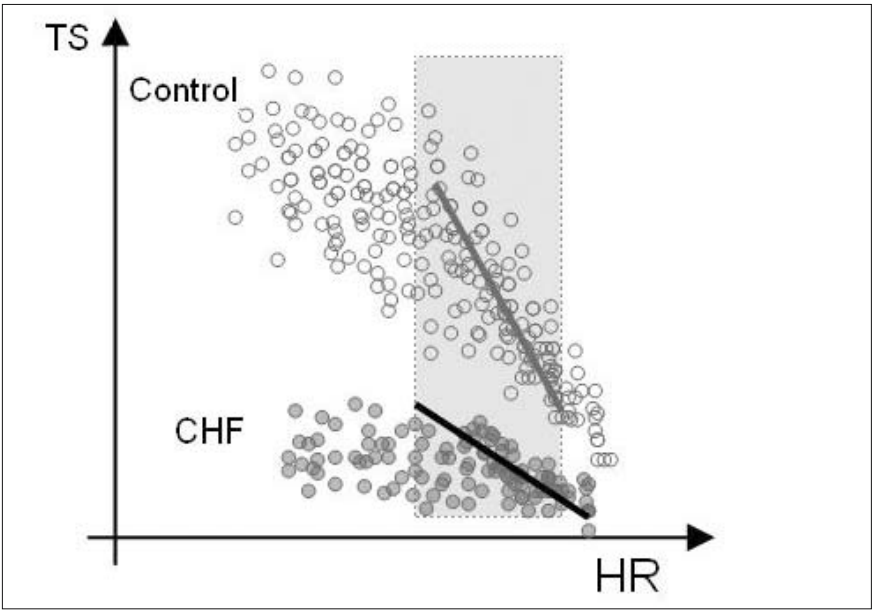


Fig. 3. Schematic representation of TS/HR relation; the most negative slope of the linear regression obtained with variable 10 bpm windows is by definition TD. Adapted from [34]

Furthermore, certain clinical conditions and therapeutic regimens have been associated with worse HRT values, including previous myocardial infarction and reduced left ventricular systolic function [35]. Statin therapy seems to improve TS, while the effects of beta-blockers therapy are controversial. HRT is also reduced in diabetic patients with autonomic dysfunction [36–38].

HRT analysis shares with HRV some advantages: both are easily elaborated from Holter monitoring data, noninvasive, and low-cost. HRV has a methodological limit in heart-beat series with high rates of ectopic occurrences, whereas this is not the case for HRT. Neither is valuable in patients with atrial fibrillation. According to current opinion, once atrial fibrillation patients are excluded, HRT can be determined in 90% of subjects [31].

Prognostic Value of HRT in Post-infarction

The overall prognostic value of HRT with respect to post-infarction mortality was described by post-hoc analysis of a few clinical trials. In the EMIAT trial, multivariate analysis showed an independent prognostic value of TO, TS, history of myocardial infarction, mean heart rate > 75 bpm, and ejection fraction (EF). In the MPIP trial, only TS and EF were independent predictors. In both trials, the combination of TO and TS was the most powerful predictor of outcome.

Data from the CAST trial [39] showed that TS was the best predictor of total mortality, irrespective of EF; after adjustment for covariates, only TS and HRV were independent indicators, with HRV still dependent on TS [33].

The ISAR-HRT trial [40], involving 1,455 subjects with previous MI and age below 76 years, was the first prospective study to evaluate HRT. The results showed that a combination of altered TO and TS was as powerful as EF as a prognostic indicator (RR = 6). The presence of pathological TO-TS and EF < 30% identified a cohort with the highest mortality rate (40% in 2 years). A 44% sensibility and 23% positive predictive value (PPV) were declared for the HRT study in post-MI patients with EF < 0.30, or > 0.30 in the presence of diabetes or age > 65 years. TO and TS showed better tradeoffs for sensibility/specificity than SDNN or EF.

Concerning SCD in post-MI patients, the role of HRT is less well-established.

In the ATRAMI trial, which enrolled also patients with EF > 0.40, abnormal TS and TS-TO combined allowed the classification of high-risk subjects (respectively, RR = 4.1 and RR = 6.9), with additional value given to stratification according to SDNN and the baroreflex sensitivity index. Positive predictive value of abnormal TS was 12.5% with a sensibility of 40%, which was

better than baroreceptors sensitivity (PPV = 7.8%) [41].

The FINGER trial [42] prospectively evaluated 2,130 patients with recent (< 2 weeks) MI for a mean follow-up of 1,012 days. Cardiovascular mortality at the end of follow-up was 5%, of which sudden death accounted for half. After multiparametric noninvasive evaluation, only TS and nonsustained ventricular tachycardia (NSVT) during Holter monitoring were independent predictors of SCD, but this effect was abolished in the low EF subgroup (< 0.35), i.e., the group in which SCD predictors are highly desirable for therapeutic purposes.

Prognostic Value of HRT in CHF

In the UK-HEART trial [7], only TS was predictive of death for patients with acute decompensation, but not of total mortality. In a recent publication on symptomatic CHF patients, TS was predictive of death for progressive decompensation, but not for SCD [43], since TO and TS were significantly higher in patients who died suddenly.

Evidence of the predictive value of HRT in non-ischemic cardiomyopathy is limited. Zareba reported an independent value of TS and EF in predicting mortality in a small cohort, although SDNN was a more powerful mortality stratifier [44].

It has also been reported that in a group of CHF patients with a prevalent non-ischemic etiology, pathological TO or TS were correlated with a worse prognosis (cardiovascular death and hospitalization for heart failure), but were not statistically different in subjects who experienced major ventricular arrhythmias in the follow-up. In that group, late potentials, T-wave alternans analysis, and QT dispersion were altered [45].

QT Dynamicity

General Considerations

The term "QT dynamicity" refers to the physiological adaptation of electrical repolarization to variations of the cardiac cycle in time, both under steady-state and dynamic conditions. Some adaptive mechanisms are intrinsic to the regulation of the electrophysiologic cycle in myocytes, which leads to a linear regression between the QT and RR cycle (QT/RR relationship). Indeed, QT/RR function does not fully describe the complex physiological adaptation. Instead, several physiological non-steady-state phenomena, such as autonomic drive, HRV, and physical exercise, confer additional variance to

the QT/RR relationship. When considered as a time delay to the QT adaptation, this variability is termed "QT hysteresis."

Many pathological conditions can alter the complex relationship between QT and cycle length, possibly leading to major rhythm disturbances, including SCD. This explains the clinical interest in this phenomenon, in addition to its use in SCD risk stratification.

QT/RR Regression

In recent years, a linear regression of QT with respect to the RR of the preceding cycle, as obtained from 24-h ECG registrations, has been the subject of clinical interest for use in arrhythmic risk stratification. An increased slope indicates hypercorrection of repolarization, which eventually exposes to excessively long QT during bradycardia and increases excitable gap during tachycardia.

Nevertheless, the QT/RR slope is particularly prone to intra- and inter-subjects variability, which limits its standardization and use in clinical trials and practice [46]. Moreover, scientific evidence on the stratification power of QT/RR slope is limited. An analysis of QT/RR in subjects enrolled in the EMIAT trial showed steeper regression in patients who died due to arrhythmic causes than in controls, when evaluated in the morning hours [47].

QT Hysteresis

In normal subjects, physiologic HRV is coupled with QT variability after a temporal delay. This phenomenon, known as "hysteresis," is highly variable between subjects and may last up to 3 min during cardiac pacing.

Chauan et al. [48] reported sex differences in the QT-interval dynamics during exercise and recovery in healthy subjects. In women, there is greater QT-interval shortening during accelerating heart rates and greater QT-interval prolongation during decelerating heart rates. This results in greater QT-interval hysteresis, possibly contributing to the higher prevalence of drug-induced torsade de pointes in women.

Beat-to-Beat Variability of Repolarization

This process, often termed "QT variability," refers to cyclic variations in repolarization over time, either coupled or not to HRV. An automated QT

variability algorithm based on a time series (e.g., Holter monitoring) has been proposed [49]. It provides time-domain values, such as QT variance (QTV, in ms^2) and QTV as the log ratio between QTV and HRV (QTV index, QTVI). A power-spectrum analysis of QT variability discloses the grade of overlap between QT and HR spectra (coherence).

In that same study [49], patients with dilated cardiomyopathy were shown to have greater QT variance than control subjects (60.4 ± 63.1 vs 25.7 ± 24.8 ms^2, $p < 0.0001$) and QTVI (-0.43 ± 0.71 vs -1.29 ± 0.51, $p < 0.00010$-0.00012), the latter being directly correlated with NYHA functional class. When matched with a reduced heart rate variance (6.7 ± 7.8 vs 10.5 ± 10.4 bpm^2, $p = 0.01$), the coherence between heart rate and QT-interval fluctuations at physiological frequencies was lower in DCM patients than in control subjects (0.28 ± 0.14 vs 0.39 ± 0.18, $p < 0.0001$).

A more recent re-evaluation of MADIT-II trial data found that median normalized QTV and QTVI were significantly higher in patients who experienced VT/VF in the follow-up than in patients with clinically silent disease, and conferred a higher events risk even after adjustments for covariates [34].

References

1. De Maria M, Marconi M (2004) Stratificazione del rischio di morte improvvisa aritmica dopo infarto miocardico: ruolo degli esami strumentali invasivi e non invasivi. Giornale Italiano di Aritmologia e Cardiostimolazione 7(3)
2. Lombardi F, Mortara A (1998) Heart rate variability and heart failure. Heart 80:213–214
3. Lombardi F (2000) Chaos theory, heart rate variability, arrhythmic mortality. Circulation 101:8–10
4. Perkiomaki JS, Makikallio TH, Huikuri HV (2005) Fractal and complexity measures of heart rate variability. Clin Exp Hypertens 27:149–158
5. Goldberger AL, Amaral LA, Hausdorff JM et al (2002) Fractal dynamics in physiology: alterations with disease and aging. Procl Natl Acad S USA 99:2466–2472
6. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ (1987) Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 59:256–262
7. Nolan J, Batin PD, Andrews R et al (1998) Prospective study of heart rate variability and mortality in chronic heart failure: results of the United Kingdom Heart Failure Evaluation and Assessment of Risk Trial (UK-Heart). Circulation 98:1510–1516
8. Zuanetti G, Neilson JM, Latini R et al (1996) Prognostic significance of heart rate variability in post-myocardial infarction patients in the fibrinolytic era. The GISSI-2 results. Circulation 94: 432–436
9. Malik M, Camm AJ, Jansse MJ et al (2000) Depressed heart rate variability identifies postinfarction patients who might benefit from prophylactic treatment with amiodarone: a substudy of EMIAT (The European Myocardial Infarct Amiodarone Trial). J Am Coll Cardiol 35:1263–1275

10. Camm AJ, Pratt CM, Schwartz PJ et al (2004) Mortality in patients after a recent myocardial infarction: a randomized, placebo-controlled trial of azimilide using heart rate variability for risk stratification. Circulation 109:990–996
11. Bigger JT, Fleiss JL, Rolnitzky LM, Steinman RC (1993) Frequency domain measures of heart period variability to assess risk late after myocardial infarction. J Am Coll Cardiol 21:729–736
12. Rashba EJ, Estes NAM, Wang P et al (2006) Preserved heart rate variability identifies low-risk patients with nonischemic dilated cardiomyopathy: results from the DEFINITE trial. Heart rhythm 3:281–286
13. Bilchick KC, Fetics B, Djoukeng R et al (2002) Prognostic value of heart rate variability in chronic congestive heart failure (Veterans Affairs' Survival Trial of Antiarrhythmic Therapy in Congestive Heart Failure). Am J Cardiol 90:24–28
14. Brouwer J, van Veldhuisen DJ, Man in 't Veld AJ et al (1996) Prognostic value of heart rate variability during long-term follow-up in patients with mild to moderate heart failure. The Dutch Ibopamine Multicenter Trial Study Group. J Am Coll Cardiol 28:1183–1189
15. Galinier M, Pathak A, Fourcade J et al (2000) Depressed low frequency power of heart rate variability as an independent predictor of sudden death in chronic heart failure. Eur Heart J 21:475–482
16. Sandercock GRH, Brodie DA (2006) The role of heart rate variability in prognosis for different modes of death in chronic heart failure. Pacing Clin Electrophysiol 29:892–904
17. Guzzetti S, La Rovere MT et al (2005) Different spectral components of 24 h heart rate variability are related to different modes of death in chronic heart failure. Eur Heart J 26:357–362
18. Makikallio TH Huikuri H et al (2001) Fractal analysis and time- and frequency-domain measures of heart rate variability as predictors of mortality in patients with heart failure. Am J Cardiol 87:178–182
19. Watanabe MA, Schmidt G (2004) Heart rate turbulence: a 5-year review. Heart Rhythm 1:732–738)
20. Wichterle D, Melenovsky V et al (2002) Mechanism involved in heart rate turbulence. Card Electrophysiol Rev 6:262–266
21. Mrowka R, Persson PB (2000) Blunted arterial baroreflex causes "pathological" heart rate turbulence. Am J Physiol Regulatory Integrative Comp Physiol 279:R1171-R1175
22. Dejan D et al (2006) Effects of atropine and pirenzepine on heart rate turbulence. Ann Noninv Electrophysiol 11:34–37
23. Bauer A, Schneider R et al (2001) Heart rate turbulence dynamicity. Eur Heart J 22(Suppl):436
24. Schwab JO, Coch M, Veit G et al (2001) Post-extrasystolic heart rate turbulence in healthy subjects: influence of gender and basic heart rate. Circulation 104:II-490, 2324
25. Watanabe MA, Marine JE et al (2002) Effects of ventricular premature stimulus coupling interval on blood pressure and heart rate turbulence. Circulation 106:325–330
26. Hallstrom AP, Stein PK et al (2004) Structural relationships between measures based on heart beat intervals: potential for improved risk assessment. IEEE Transactions on Biomedical Engineering 51:1414–1420
27. Francis J, Watanabe MA (2005) Heart rate turbulence: a new predictor for risk of sudden cardiac death. Ann Noninv Electrophysiol 10:102–109

28. Bauer A, Barthel P et al (2001) Impact of coupling interval on heart rate turbulence. Eur Heart J 22(Suppl):438
29. Indik JH, Ott P et al (2002) Heart rate turbulence and fractal scaling coefficient in response to premature atrial and ventricular complexes and relationship to the degree of prematurity. J Am Coll Cardiol 39(Suppl A)
30. Savelieva I, Wichterle D et al (2002) Different effects of atrial and ventricular prematurity on heart rate turbulence: relation to left ventricular function. Pacing Clin Electrophysiol 25:II-608
31. Watanabe MA (2003) Heart rate turbulence: a review. Indian Pacing Electrophys J 3:10
32. Bauer A, Barthel P (2002) Dynamics of heart rate turbulence as independent risk predictor after dynamic myocardial infarction. Pacing Clin Electrophysiol 25:II-608
33. Hallstroma AP Steinb PK et al (2005) Characteristics of heart beat intervals and prediction of death. Int J Cardiol 100:37–45
34. Haigney MC, Moss AJ et al (2004) QT interval variability and spontaneous ventricular tachycardia or fibrillation in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II patients. J Am Coll Cardiol 44:1481–1487
35. Cygankiewicz I, Wranicz JK et al (2003) Clinical covariates of abnormal heart rate turbulence in coronary patients. Ann Noninv Electrophysiol 8:289–295
36. Schmidt G Malik M et al (2000) Heart rate turbulence in post-MI patients on and off beta-blockers. Pacing Clin Electrophysiol 23:II-619
37. Jeron A, Holmer S et al (2003) Association of the heart rate turbulence with classic risk stratification parameters in postmyocardial infarction patients. Ann Noninv Electrophysiol 8:296–301
38. Lin LY, Hwang JJ et al (2004) Restoration of heart rate turbulence by titrated beta-blocker therapy in patients with advanced congestive heart failure: positive correlation with enhanced vagal modulation of heart rate. J Cardiovasc Electrophysiol 15:752–756
39. Echt DS, Liebson PR et al (1991) Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The cardiac arrhythmia suppression trial. N Engl J Med 324:781–788
40. Barthel P et al (2003) Risk stratification after acute myocardial infarction by heart rate turbulence. Circulation 108:1221–1226
41. Malik M, Schmidt G et al (1999) Heart rate turbulence is a post-infarction mortality predictor which is independent of and additive to other recognised risk factors. Pacing Clin Electrophysiol 22:II-741
42. Makikallio TH, Barthel P et al (2005) Prediction of sudden cardiac death after acute myocardial infarction: role of Holter monitoring in the modern treatment era. Eur Heart J 26:762–769
43. Moore RK et al (2006) Heart rate turbulence and death due to cardiac decompensation in patients with chronic heart failure. Eur J Heart Fail 8:585–590
44. Zareba W, Karcz M et al (2002) Heart rate turbulence, variability, and dynamics in nonischemic dilated cardiomyopathy. Circulation 106(Suppl):2977
45. Koyama J, Watanabe J et al (2002) Evaluation of heart-rate turbulence as a new prognostic marker in patients with chronic heart failure. Circ J 66:902–907
46. Sredniawa B et al (2005) Methods of assessment and clinical relevance of QT dynamics. Indian Pacing Electrophysiol J 5:221–232
47. Milliez P, Coumel P et al (2005) Usefulness of ventricular repolarization dynamicity in predicting arrhythmic deaths in patients with ischemic cardiomyopathy (from the European Myocardial Infarct Amiodarone Trial). Am J Cardiol 95:821–826

48. Chauan VS, Krahn AD et al (2002) Sex differences in QTc interval and QT dispersion: dynamics during exercise and recovery in healthy subjects. Am Heart J 144(5):858–864
49. Berger RD, Kasper EK et al (1997) Beat-to-beat QT interval variability novel evidence for repolarization lability in ischemic and nonischemic dilated cardiomyopathy. Circulation 96:1557–1565

Noninvasive Risk Stratification of Sudden Death: T-Wave Alternans

Roberto F.E. Pedretti, Simona Sarzi Braga, Raffaella Vaninetti, Antonio Laporta, Sergio Masnaghetti, Rossella Raimondo, Mario Salerno, Francesco Santoro

Introduction and Background

Sudden cardiac death (SCD) accounts for approximately 400,000 deaths each year in the USA and remains a health problem of epidemic proportions. Most SCDs are caused by fatal ventricular arrhythmias, i.e., ventricular tachycardia (VT) and ventricular fibrillation (VF), in patients with and without known structural heart diseases [1, 2]. Identifying patients at risk for these arrhythmias remains a major challenge since < 2% of patients who have sudden cardiac arrest are resuscitated and survive hospital discharge. Given the large number of patients potentially at risk for developing ventricular arrhythmias, any strategy for treating them prophylactically requires efficient and effective risk stratification. A number of recently completed randomized clinical trials showed that an implantable cardioverter defibrillator (ICD) can prevent SCD in selected high-risk patients. These trials have used different methods for identifying patients at risk for SCD. The *Multicenter Automatic Defibrillator Implantation Trial* (MADIT) and the *Multicenter Nonsustained Tachycardia Trial* (MUSTT) identified patients with left ventricular (LV) dysfunction and nonsustained VT who had VT induced by programmed ventricular stimulation [3, 4]. These two studies demonstrated that implantation of an ICD can reduce the risk of death in this group of high-risk patients. In contrast, in the *Coronary Artery By-pass Graft* (CABG) *Patch Trial,* which identified a group of high-risk patients with LV dysfunction and an abnormal signal-averaged electrocardiogram who were undergoing elective CABG surgery, implantation of an ICD did not reduce all-cause mortality [5]. Also, the *Defibrillator in Acute Myocardial*

Division of Cardiology, IRCCS Fondazione Salvatore Maugeri, Scientific Institute of Tradate, Tradate (VA), Italy

Infarction Trial (DINAMIT) did not show a survival benefit from an ICD in patients who had a reduced left ventricular ejection fraction (LVEF) and impaired cardiac autonomic function, 6–40 days after a myocardial infarction (MI) [6]. When viewed together, the CABG Patch Trial, DINAMIT, MADIT, and MUSTT raise important issues about our understanding of high-risk patients, and that not all high-risk patients benefit from ICD therapy. Based on these trials, the only patients in whom the prophylactic implantation of an ICD proved beneficial were those identified by documented spontaneous nonsustained or inducible sustained ventricular arrhythmias.

The publication of MADIT II radically changed our ability to identify those patients who may derive benefit from the implantation of a prophylactic ICD [7]. MADIT II aimed to evaluate the effects of an ICD on survival in patients with prior MI (≥ 1 month before enrollment) and severe impairment of LVEF (< 30%). The study population comprised 1,232 patients from 76 centers mainly in the USA. Patients were randomized with a 3:2 ratio to ICD (742 patients) or conventional medical therapy (490 patients); the end-point of the study was all-cause mortality. The main clinical and demographic characteristics as well as medical therapy were not significantly different in the two groups of patients. At a mean follow up of 20 months, mortality was 19.8% in the medically treated group and 14.2% in the ICD group. Hazard ratio for the risk of death from all-causes was 0.69 (95% IC, 0.51–0.93; p = 0.016), with a risk reduction of 31% in patients implanted with an ICD compared with those treated with medical therapy. Kaplan-Meier survival curves diverged at 9 months from the enrollment, showing a mortality reduction of 12 and 28% at 1 and 2 years, respectively. Based on these results, the prophylactic implant of an ICD improved survival in patients with prior MI and severely impaired LV function.

More recently, three studies further supported the clinical relevance for ICD implantation in different groups of patients, who in all cases were selected by clinical data and LVEF, without additional noninvasive/invasive risk markers.

The *Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation* (DEFINITE) *Trial* included 458 patients with nonischemic dilated cardiomyopathy, LVEF < 36%, and premature ventricular complexes or nonsustained VT [8]; the mean LVEF was 21%. Two hundred and twenty nine patients were randomly assigned to receive standard medical therapy and another 229 standard medical therapy plus ICD. At a mean follow-up of 29 months, there were 68 deaths: 28 in the ICD group and 40 in the standard-therapy group (hazard ratio 0.65; 95% CI 0.40–1.06; p = 0.08). The mortality rate at 2 years

was 14.1% in the standard-therapy group and 7.9% in the ICD group. There were 17 sudden deaths from arrhythmia: three in the ICD group as compared with 14 in the standard-therapy group (hazard ratio 0.20; 95% CI 0.06–0.71; $p = 0.006$). The study investigators concluded that in patients with severe, nonischemic dilated cardiomyopathy ICD implantation significantly reduced the risk of sudden death from arrhythmia and was associated with a non significant reduction in the risk of death from any cause.

The *Comparison of Medical Therapy, Pacing, and Defibrillation* (COMPANION) *in Heart Failure Trial* tested the hypothesis that prophylactic cardiac-resynchronization therapy (CRT) with or without a defibrillator backup would reduce the risk of death and hospitalization among patients with advanced congestive heart failure (CHF) and intraventricular conduction delay [9]. A total of 1,520 patients with advanced CHF (New York Heart Association class III or IV) of either ischemic or nonischemic etiology, QRS interval ≥ 120 ms, PR interval > 150 ms, and end-diastolic LV diameter > 60 mm were randomly assigned in a 1:2:2 ratio to receive optimal pharmacological therapy alone or CRT or CRT plus ICD therapy. The primary end-point was the time to death from or hospitalization for any cause. Compared with optimal pharmacological therapy alone, both CRT and CRT plus ICD significantly reduced the primary end-point (hazard ratio 0.81 and 0.80; $p = 0.014$ and 0.01 respectively). CRT reduced the risk of the secondary end-point of death from any cause by 24% ($p = 0.059$), CRT plus defibrillator-backup reduced the risk by 36% ($p = 0.003$). In conclusion, in patients with advanced CHF and prolonged QRS interval, combined electrical therapy (CRT+ICD) significantly reduced all-cause mortality.

The *Sudden Cardiac Death in Heart Failure Trial* (SCD-HeFT) [10] compared the impact on all-cause mortality of three different treatments in patients affected by mild to moderate CHF (NYHA class II, III) of either ischemic or nonischemic etiology, with LVEF ≤ 35%: placebo, amiodarone (200–400 mgr per day), ICD. The primary end-point of the study was all-cause mortality. At 60 months of follow-up, no significant difference was observed between the amiodarone and placebo groups; conversely, a clear reduction in all-cause mortality was observed in patients treated with an ICD compared with placebo group patients (hazard ratio 0.77, $p = 0.007$). These preliminary data strongly supported the use of ICD in this group of CHF patients. Moreover, further evidence about the inefficacy of amiodarone in reducing deaths from any causes was provided, confirming previous clinical trials (EMIAT and CAMIAT) that tested this drug in patients after MI [11, 12].

Guidelines and Recommendations

On the basis of the recent recommendations of the American Heart Association/American College of Cardiology/European Society of Cardiology regarding SCD [13], an ICD should be implanted (class I) in "MADIT-MUSTT like" patients and in patients with ischemic or nonischemic cardiomyopathy who have a LVEF ≤ 30 to 35%, are in NYHA functional class II–III and receiving optimal medical therapy, and with an expectation of survival in a good functional status > 1 year. An ICD may also be recommended in those patients who are in NYHA functional class I because of a prior MI (IIa) or a nonischemic dilated cardiomyopathy (IIb).

Focus on Risk Stratification

Prior to the above mentioned studies, the aim of noninvasive risk stratification was to identify patients at high enough risk to warrant treatment as aggressive as an ICD (sensitivity was sacrificed in order to maximize positive predictive accuracy). This approach was based on the assumption that ICDs are expensive, associated with certain risks, and thus should be reserved for patients who are extremely likely to need them. Noninvasive risk-stratifying tests were judged based on their positive predictive accuracy. Nowadays, the results of these recent studies are associated with a transition to a completely different type of thinking: a much wider group of patients has been omitted in an attempt to maximize sensitivity. This new approach is based on the assumption that ICDs can be implanted more easily, less expensively, and with less risk, and should not be reserved only for the highest risk patients. The focus of noninvasive risk stratifying testing is thus on maximizing negative predictive accuracy.

In the following T-wave alternans (TWA) analysis, a recent and promising noninvasive risk marker is reviewed.

T-Wave Alternans

T-wave alternans is a beat-to-beat fluctuation in the amplitude or morphology of the T wave that alternates every other beat and has been closely associated with ventricular arrhythmias and SCD. More recently, using sensitive signal-processing techniques, the detection of microvolt-level, virtually unapparent TWA was found to be a potent predictor of life-threatening ventricular arrhythmias in several subgroups of patients.

Many studies demonstrated macroscopic TWA in different clinical condi-

tions that are associated with malignant ventricular arrhythmias, including long QT syndrome, acute myocardial ischemia and infarction, Prinzmetal's angina, and electrolyte derangements [14–20]. TWA is caused by primary alternations in the repolarization phase of the action potential [21, 22]. Moreover, above a critical heart-rate threshold, repolarization potentials from adjacent regions of the ventricle alternate with those of opposite phase, that is discordant alternans, causing spatial gradients of repolarization and yielding an electrophysiologic substrate for functional block, reentry, and VF. When electrical uncoupling by a structural barrier is present, there is a higher probability of discordant alternans at lower critical heart-rate threshold which, by inducing a maximum spatial gradient of repolarization, may cause unidirectional block, reentry, and sustained monomorphic VT. In either case, TWA suggests the presence of electrophysiologic properties of the myocardium that are associated with the genesis of ventricular arrhythmias.

Clinical Studies

The original studies of TWA comprised different subgroups of very high-risk patients. The results of the first study, published in 1994 by Rosenbaum et al., were obtained from a group of patients who underwent electrophysiological (EP) studies because of nonfatal sustained ventricular tachyarrhythmias, syncope or, in a minority of cases, supraventricular arrhythmias [23]. A strong relationship was found between the presence of TWA evaluated during atrial pacing and the inducibility of ventricular tachyarrhythmias during EP testing as well as 20-month arrhythmia-free-survival. Subsequent similar studies confirmed the association between TWA measured during bicycle exercise and both inducible and spontaneous ventricular arrhythmias in patients who underwent EP study and also in ICD recipients [24–26]. It is also important to note that good reproducibility of TWA testing results and TWA heart-rate threshold was demonstrated during both atrial pacing and exercise-induced sinus tachycardia [27].

A number of small studies in patients with congestive HF (CHF) suggested that TWA is associated with an increased risk of ventricular arrhythmias and sudden death. Klingenheben et al. evaluated 107 CHF patients without history of sustained ventricular arrhythmias over a mean follow-up period of 15 months [27, 28]. Patients had a mean LVEF of 28%, coronary artery disease in 67% of cases, and received angiotensin converting enzyme (ACE) inhibitors and beta-blockers in 93 and 42% of cases, respectively. In this study, TWA was a strong and significant predictor of arrhythmic events.

Remarkably, none of the patients with a negative TWA test had an arrhythmic event, indicating a very high negative predictive value. We obtained similar results in a study of 46 patients with CHF, NYHA class III in 35%, mean LVEF 29%, and ischemic etiology 61% [29]; at a mean follow-up of 1.6 years, a significant relationship with cardiac death was found: seven of 23 (30%) patients with positive TWA died during follow-up. Interestingly, also in our study, none of the 13 patients who had negative TWA died or had malignant ventricular arrhythmias.

The prognostic value of TWA was also confirmed in patients with dilated nonischemic cardiomyopathy. Hohnloser et al. studied 137 patients with dilated cardiomyopathy, mean age 55 years, and LVEF 29% [30]. Their results were similar to those found in CHF patients of both etiologies. More recently, Costantini et al. [31] reported preliminary results of a study that included 282 patients with a LVEF ≤ 40% and dilated nonischemic cardiomyopathy. The study tested the hypothesis that a negative TWA would identify patients at low risk of death. The primary end-point of the study was actuarial all-cause mortality at 2 years. TWA testing was normal (negative) in 95 patients (34%), and abnormal (positive or indeterminate) in 187 patients (66%). None of the patients with a normal TWA test and 12 patients with an abnormal TWA test (8.6%) died ($p \leq 0.02$), further supporting the very high negative predictive value of a negative TWA.

Results of the *Marburg Cardiomyopathy Study* contradicted the above-mentioned promising results [32]. In that study, arrhythmia risk stratification was performed prospectively in 343 patients with idiopathic dilated cardiomyopathy, including analysis of LVEF, signal-averaged ECG, arrhythmias on Holter ECG, QTc dispersion, heart-rate variability (HRV), baroreflex sensitivity (BRS), and TWA. During a mean follow-up of 52 months, major arrhythmic events occurred in 46 patients (13%). On multivariate analysis, LVEF was the only significant arrhythmia risk predictor in patients with sinus rhythm, with a relative risk of 2.3 per 10% decrease of ejection fraction (95% CI, 1.5–3.3; $p = 0.0001$), whereas beta-blocker therapy was associated with a trend toward lower arrhythmia risk (RR, 0.6; 95% CI, 0.3–1.2; $p = 0.13$). Thus, in this study TWA as well as other noninvasive risk markers did not seem to be helpful for arrhythmia risk stratification. However some criticisms should be noted: (1) Interpretation of TWA results was not based on a "negative and non-negative" classification [33]; in fact, of 38 arrhythmic events, 31 (81%) occurred in the 191 (16%) patients with a non-negative result compared to seven of 72 (10%) patients with a negative TWA ($p = 0.06$). (2) More importantly, as reported by the same authors, the use of beta-blockers in this study was not uniform and many patients did not have this

type of therapy at study entry, when risk stratification was performed, but received it during follow-up (52 vs 73%). (3) Beta-blockers were withheld for 24 h before TWA testing whenever possible because the development of TWA is critically dependent on heart rate. This may have increased the proportion of false-positive results, with a possible unapparent change of TWA from positive to negative during the follow-up period. (4) The rate of events was very low, about 3% per year, making the follow-up significantly longer (4.3 years) than the follow-up available in the other TWA studies (in general, 2 years).

On the basis of these conflicting results, further studies are needed in order to define the prognostic value of this promising marker in patients with nonischemic cardiomyopathy. A large multicenter prospective study, the *ALPHA Study* (*T-Wave Alternans in Patients with Heart Failure*), is currently ongoing in Italy. Its aim is to assess the prognostic power of TWA in a large cohort of patients with nonischemic dilated cardiomyopathy, NYHA class II–III, and a LVEF ≤ 40% [34].

T-wave alternans has also been demonstrated to be an effective tool for identifying high-risk patients after MI. Ikeda et al. evaluated the prognostic significance of TWA between 2 and 10 weeks after an acute MI in a large cohort of 850 consecutive unselected patients [35]. During a mean follow-up 25 months, only TWA and LVEF ≤ 40% were significant multivariate predictors for primary events, defined as SCD or resuscitated VF [relative hazard 5.9 ($p = 0.007$) and 4.4 ($p = 0.005$), respectively]. In contrast, in a study of 379 patients post-MI, Tapanainen et al. reported that TWA was not associated with increased mortality [36]. This study was flawed, however, because the TWA study was performed too early after MI (8.1 ± 2.4 days), when TWA is believed to be unstable and unreliable.

Interestingly, two recent studies strongly supported the potential role of TWA in the risk stratification of "MADIT-II like" patients. In 129 post-MI patients, all with a LVEF < 30%, TWA testing was prospectively assessed [37]. At 24 months of follow-up, no SCD or sudden cardiac arrest occurred among patients who tested TWA-negative, compared with an event rate of 15.6% among the remaining patients. More recently, a study evaluated the ability of microvolt TWA to identify groups at high and low risk of dying among HF patients who met MADIT II criteria for ICD prophylaxis [38]. Primary endpoint was 2-year all-cause mortality. Of the 177 MADIT II-like patients included in the study, 32% had a QRS duration > 120 ms and 68% had an abnormal (positive or indeterminate) microvolt TWA test. During an average follow-up of 20 months, 20 patients died and patients with an abnormal TWA test were compared to those with a normal (negative) test. The hazard ratios

for 2-year mortality was 4.8 ($p = 0.020$) and the actuarial mortality rate was substantially lower among patients with a normal TWA test (3.8%), with a corresponding false-negative rate of 3.5%. Notably, in this study TWA testing was a better predictor than QRS complex duration – an index recommended in the USA for the selection of MADIT-II patients suitable for ICD therapy – in identifying groups of patients at high or low risk of death.

Recently, Chow et al. [39] noted that mortality reduction with ICD implantation differs according to TWA status in patients with ischemic cardiomyopathy and no prior history of ventricular arrhythmia, with implications for risk stratification and health policy. This study consisted of a prospective cohort of 768 patients with LVEF ≤ 35% and no prior sustained ventricular arrhythmia, of which 392 (51%) received ICDs. The mean follow-up time was 27 ± 12 months. A non-negative TWA test result identified 514 (67%) patients. After multivariate adjustment, ICDs were associated with lower all-cause mortality in TWA-non-negative patients (hazard ratio 0.45, $p = 0.003$) but not in TWA-negative patients (hazard ratio 0.85, $p = 0.73$). The number needed to treat with an ICD for 2 years to save one life was nine among TWA-non-negative patients and 76 among TWA-negative patients.

Another interesting aspect was evaluated by Ikeda et al. [40], who conducted a collaborative study to evaluate the predictive power of TWA in patients with preserved LVEF after MI. This study enrolled 1,041 post-infarction patients with a LVEF ≥ 40% in whom TWA testing was performed an average 48 days after the infarction. During a follow-up of 32 ± 14 months, 38 patients (3.7%) died of non-arrhythmic cause and were not considered for analysis. Of the 1,003 evaluable patients, 18 (1.8%) had sudden death or a life-threatening arrhythmic event. TWA was positive in 169 (17%) patients, negative in 747 (74%), and indeterminate in 87 (9%). A positive TWA test was the most significant predictor, with a hazard ratio of 19.7 ($p < 0.0001$). This marker had the highest sensitivity and negative predictive value for events. Therefore, the investigators conclude that TWA could be used for risk-stratification in the low-risk population of post-infarction patients with preserved LVEF.

Conclusions

In conclusion, an abnormal TWA test is associated with a significant increase of cardiac death and life-threatening ventricular arrhythmias in patients with left ventricular dysfunction of both ischemic and nonischemic etiology. Moreover, patients with a normal TWA test appear to have a very good prognosis, as shown by the high negative predictive value of the test. The results

suggest that TWA can be effectively used to identify a subgroup of patients who are unlikely to benefit from ICD therapy despite heart failure and left ventricular dysfunction.

References

1. Myerburg RJ, Interian AJ, Mitrani RM et al (1997) Frequency of sudden cardiac death and profiles of risk. Am J Cardiol 80:10F-19F
2. Zipes DP, Wellens HJ (1998) Sudden cardiac death. Circulation 98:2334–2351
3. Moss AK, Hall WJ, Cannom DS et al (1996) Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 335:1993–1940
4. Buxton AE, Hafley G (1999) A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 341:1882–1890
5. Bigger JT (1997) Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. Coronary Artery Bypass Graft (CABG) Patch Trial Investigators. N Engl J Med 337:1569–1575
6. Hohnloser SH, Kuck KH, Dorian P et al; DINAMIT Investigators (2004) Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 351:2481–2488
7. Moss AJ, Zareba W, Hall WJ et al for the Multicenter Automatic Defibrillator Implantation Trial II Investigators (2002) Prophylactic implantation of a defibrillator in patients with myocardial infarction and a reduced ejection fraction. N Engl J Med 346:877–883
8. Kadish A, Dyer A, Daubert JP et al; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators (2004) Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 350:2151–2158
9. Bristow MR, Saxon LA, Boehmer J et al; Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) Investigators (2004) Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 350:2140–2150
10. Bardy GH, Lee KL, Mark DB et al; SCD-HeFT Investigators (2005) Amiodarone or implantable cardioverter defibrillator for congestive heart failure. N Engl J Med 352:225–237
11. Julian DG, Camm AJ, Frangin G et al (1997) Randomised trial of effect of amiodarone on mortality in patients with left-ventricular dysfunction after recent myocardial infarction: EMIAT. European Myocardial Infarct Amiodarone Trial Investigators. Lancet 349:667–674
12. Cairns JA, Connolly SJ, Roberts R, Gent M (1997) Randomised trial of outcome after myocardial infarction in patients with frequent or repetitive ventricular premature depolarisations: CAMIAT. Canadian Amiodarone Myocardial Infarction Arrhythmia Trial Investigators. Lancet. 349:675–682
13. Anonymous (2006) ACC/AHA/ESC guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. A report of

the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for practice guidelines. Circulation 114:1088–1132
14. Schwartz PJ, Malliani A (1975) Electrical alternans of the T-wave: clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q-T sindrome. Am Heart J 89:45–50
15. Puletti M, Curione M, Righetti G, Jacobellis G (1980) Alternans of the ST segment and T wave in acute myocardial infarction. J Electrocardiol 13:297–300
16. Hohnloser SH, Huikuri HV, Schwartz PJ et al (1999) T wave alternans in post myocardial infarction patients (ACES Pilot Study). J Am Coll Cardiol 33:144A
17. Kleinfeld MJ, Rozanski JJ (1977) Alternans of the ST segment in Prinzmetal's angina. Circulation 55:574–577
18. Cheng TC (1983) Electrical alternans. An association with coronary artery spasm. Arch Intern Med 143:1052–1053
19. Reddy CV, Kiok JP, Khan RG, El-Sherif N (1984) Repolarization alternans associated with alcoholism and hypomagnesemia. Am J Cardiol 53:390–391
20. Shimoni Z, Flatau E, Shiller D et al (1984) Electrical alternans of giant U waves with multiple electrolyte deficits. Am J Cardiol 54:920–921
21. Pastore JM, Girouard SD, Laurita KR et al (1999) Mechanisms linking T-wave alternans to the genesis of cardiac fibrillation. Circulation 99:1385–1394
22. Watanabe MA, Fenton FH, Evans SJ et al (2001) Mechanisms for discordant alternans. J Cardiovasc Electrophysiol 12:196–206
23. Rosenbaum DS, Jackson LE, Smith JM et al (1994) Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 330:235–241
24. Estes NAM III, Michaud G, Zipes DP et al (1997) Electrical alternans during rest and exercise as predictors of vulnerability to ventricular arrhythmias. Am J Cardiol 80:1314–1318
25. Gold MR, Bloomfield DM, Anderson KP et al (2000) A comparison of T-wave alternans signal-averaged electrocardiography and programmed ventricular stimulation for arrhythmia risk stratification. J Am Coll Cardiol 36:2247–2253
26. Hohnloser SH, Klingenheben T, Li YG et al (1998) T-wave alternans as a predictor of recurrent ventricular tachyarrhythmias in ICD recipients: prospective comparison with conventional risk markers. J Cardiovasc Electrophysiol 9:1258–1268
27. Hohnloser SH, Klingenheben T, Zabel M et al (1997) T wave alternans during exercise and atrial pacing in humans. J Cardiovasc Electrophysiol 8:987–993
28. Klingenheben T, Hohnloser SH, Cohen RJ et al (2000) Predictive value of T-wave alternans in patients with congestive heart failure. Lancet 356:651–652
29. Sarzi Braga S, Vaninetti R, Laporta A et al (2004) T-wave alternans is a predictor of death in patients with congestive heart failure. Int J Cardiol 93:31–38
30. Hohnloser SH, Klingenheben T, Bloomfield D et al (2003) Usefulness of microvolt T-wave alternans for prediction of ventricular tachyarrhythmic events in patients with dilated cardiomyopathy: results from a prospective observational study. J Am Coll Cardiol 41:2220–2224
31. Costantini O, Kaufman ES, Bloomfield DM et al (2004) Patients with a nonischemic cardiomyopathy and a negative T-wave alternans stress test are at a low risk of death. American Heart Association Scientific Session, New Orleans, LA, Nov 7–10
32. Grimm W, Christ M, Bach J et al (20039 Noninvasive arrhythmia risk stratification in idiopathic dilated cardiomyopathy: results of the Marburg Cardiomyopathy Study. Circulation 108:2883–2891

33. Kaufman ES, Bloomfield DM, Steinman RC et al (2006)9 " Indeterminate" microvolt T-wave tests predict high risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. J Am Coll Cardiol 48:1399–1404
34. Salerno-Uriarte JA, Pedretti RF, Tritto M et al (2004) The ALPHA study (T-wave alternans in patients with heart failure): rationale, design and endpoints. Ital Heart J 5:587–592
35. Ikeda T, Saito H, Tanno K et al (2002) T-wave alternans as a predictor for sudden cardiac death after myocardial infarction. Am J Cardiol 89:79–82
36. Tapanainen JM, Still AM, Airaksinen KE, Huikuri HV (2001) Prognostic significance of risk stratifiers of mortality, including T-wave alternans, after acute myocardial infarction. Results of a prospective follow-up study. J Cardiovasc Electrophysiol 12:645–652
37. Hohnloser SH, Ikeda T, Bloomfield DM et al (2003) T-wave alternans negative coronary patients with low ejection and benefit from defibrillator implantation. Lancet 362:125–126
38. Bloomfield DM, Steinman RC, Namerow PB et al (2004) Microvolt T-wave alternans distinguishes between patients likely and patients not likely to benefit from implanted cardiac defibrillator therapy: a solution to the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II conundrum. Circulation 110:1885–1889
39. Chow T, Kereiakes DJ, Bartone C et al (2007) Microvolt T-wave alternans identifies patients with ischemic cardiomyopathy who benefit from implantable cardioverter-defibrillator therapy. J Am Coll Cardiol 49:50–58
40. Ikeda T, Yoshino H, Sugi K et al (2006) Predictive value of microvolt T-wave alternans for sudden cardiac death in patients with preserved cardiac function after acute myocardial infarction: results of a collaborative cohort study. J Am Coll Cardiol 48:2268–2274

Risk Stratification for Sudden Death in Hypertrophic Cardiomyopathy

Domenico Catanzariti, Massimiliano Maines, Giuseppe Vergara

Early studies suggested that hypertrophic cardiomyopathy (HCM), an inherited and primary disease of cardiac muscle characterized by a thickening of the left ventricular (LV) walls, was a relatively uncommon but malignant disorder. The annual mortality rates were reported to be 2–4% in adults and 6% in adolescents and children, the majority of deaths being sudden. Recently it has been found that HCM is, in fact, more common than originally assumed, with a prevalence estimated from echocardiographic population screening of 0.2%. It is also now clear that HCM is much more benign, with an annual mortality rate in large unselected non-referred series of approximately 1.5%. More than half of these deaths are sudden while the remainder are largely caused by heart failure and stroke [1–3]. This relatively low incidence creates a challenge for risk stratification. Furthermore, most individuals with HCM are asymptomatic and the first manifestation may be sudden cardiac death (SCD), related to ventricular arrhythmia with potential triggers including ischemia, outflow obstruction, and atrial fibrillation.

In recent years, the identification of various noninvasive indicators associated with SCD has allowed patients to be stratified according to their risk of developing this complication. A consensus document of the ACC and ESC has categorized the known risk factors for SCD as "major" and "possible" in individual patients [4]. Major risk factors for SCD in HCM are: (1) Cardiac arrest (ventricular fibrillation, VF); (2) spontaneous sustained ventricular tachycardias (VT); (3) family history of premature SCD; (4) unexplained syncope; (5) LV thickness ≥ 30 mm; (6) abnormal exercise blood pressure; and (7) non-sustained spontaneous VT. Possible risk factors in individual patients are: atrial fibrillation [5]; myocardial ischemia; LV outflow obstruc-

Cardiology Division, S. Maria del Carmine Hospital, Rovereto (TN), Italy

tion [6]; high-risk mutation; and intense competitive physical exertion. By contrast, the absence of risk factors identifies a low-risk group. In this respect, the low positive predictive accuracy of the previously recognized major risk factor of SCD is a major limitation.

Hospital-based HCM patients with a combination of two or more sudden death risk factors have been recently identified as higher risk group, although an extreme single factor may identify young patients exposed to a relevant risk in very long term follow-up. Such patients represent an additional subgroup at high risk. However, intermediate risk has been related to the presence of only one of the major risk factors. A more precise assessment of SCD risk stratification should be undertaken in relation to community-based HCM patients. Prospective registries could be helpful in this type of assessment although individuals who have undergone implantable cardioverter defibrillator (ICD) implantation will modify risk assessment stratification and follow-up clinical end-points (e.g., ICD-based VTs as clinical surrogates of SCD).

Recently, the guidelines of the AIAC (acronym of the Italian Association of Cardiac Pacing and Arrhythmia Specialists) regarding ICD implantation were published [7]. Indications for ICD implantation in HCM were determined according to stratification based on incorporation of either single strong risk factors or multiple risk factors, with the aim of improving the positive predictive accuracy of the algorithm. Such efforts to obtain an effective risk stratification algorithm are motivated by the consideration that ICD represents a very efficacious tool for preventing SCD in HCM [8].

In the case of HCM, the available data are less consistent; the patient series are small; and the length of follow-up is short. In clinical studies for ICD in HCM patients, the main reason for device implantation is secondary prevention following aborted SCD or sustained VT. Nevertheless, the results of a retrospective multicenter study containing a large number of patients, in which the benefit of ICD implantation was shown in both primary and secondary prevention of SCD, suggested that the indications for ICD implantation should be expanded in HCM.

Various authors have recommended ICD implantation for primary prevention in patients with HCM and two or more risk factors for SCD, and even in some patients with only a strong single risk factor. However, also assuming a slightly less restrictive position regarding the more widespread use of ICDs, the economic costs and risks in this young population of either repeated device substitutions or lead-related malfunctions should be considered. Thus, it is important to correctly identify candidates, since this mode of treatment is not without complications.

Risk factors

Secondary Prevention of Cardiac Arrest

A history of cardiac arrest or episodes of sustained VT are predictors of high risk representing an absolute indication for ICD implantation and secondary prevention of SCD.

Family History of Sudden Death

A multiple family history with two or more premature (< 45 years) SCDs is considered a strong single risk factor justifying ICD implantation. However, this is infrequent (5% of patients), and a history of a single premature SCD is a more common situation (25% of patients). In these patients, risk assessment and the subsequent decision for ICD implantation are more uncertain. Such a decision is based on the identification of additional risk factors, such as syncope. Regardless, all patients with a single family history of SCD should be informed of device-related problems, as well as the limitation of each risk stratification in HCM.

Extreme LV Hypertrophy

Extreme hypertrophy of the LV wall (> 30 mm) is a strong predictor of SCD in young patients with HCM and is associated with an estimated long term risk of SCD of about 20% at 10 years and of > 40% at 20 years. Serious consideration should be given to implantation of an ICD in those young patients with extreme hypertrophy, independently of the presence of other risk factors, due to the clinically significant impact on SCD prevention of ICD implantation during long-term (over many decades) risk exposure [9].

Syncope

Syncope challenges the accurate clinical and prognostic evaluation of patients, due to the multiple potential mechanisms responsible for syncopal episodes in HCM (supraventricular or ventricular tachyarrhythmias as well as bradyarrhythmias, dynamic obstruction, diastolic dysfunction, myocardial ischemia, and vasovagal mechanisms). In clinical series involving multiparametric assessment of SCD risk in hospital-based HCM patients, unexplained syncope has been combined with a multiple familiar history of SCD as a high risk factor for SCD [10].

Accurate evaluation of the clinical profile of each patient is important in order to precisely identify the role of each single syncopal episode, although clinical perceptions and experience are also essential in this assessment. Recent (< 1 year), recurrent syncope, either during effort or a non-neurally mediated episode at rest, is generally considered a marker of increased risk in young patients and a possible indication for ICD implantation.

Non-sustained Ventricular Tachycardia

In young patients (< 35 years), brief runs of non-sustained VT (three or more beats) on Holter monitoring are associated with a significant increase in the risk for SCD. In very young patients (children and adolescents), non-sustained VT is rare and indicative of high risk. In other patients, multiple (e.g., more than two episodes in 6 months) or prolonged runs of non-sustained VT may be of particular concern and raise the issue of ICD implantation, even in the absence of other risk factors. If not recurrent, then brief episodes of non-sustained VT are not considered significant risk factors in community-based patients, in the absence of additional risk factors [11].

Abnormal Blood Pressure Response to Exercise

Hypotensive blood pressure response during upright exercise suggests an increased risk for SCD and may be included in the overall risk profile, particularly in patients < 50 years of age. In adults, the absence of a hypotensive response to exercise is reassuring, although in young patients the absence of additional risk factors is also needed.

Electrophysiologic Study

Electrophysiologic study seems to be not clinically relevant for risk assessment, as unspecific responses are also induced in patients with very low risk. This examination does not have any role in the stratification of SCD risk in the vast majority of cases.

Low Clinical Risk Profile

Patients with mild LV hypertrophy (wall thickness < 20 mm) and without any additional risk factors (included in the list of “major” risk factors) can

be considered at low risk and have a mean life expectancy similar to that of the general population [12].

Clinical Reassessment

Patients are annually re-evaluated periodically during follow-up or as considered necessary by the patient's doctor on the basis of either clinical suspicion or change of risk-factor burden.

References

1. Spirito P, Seidman CE, McKenna WJ, Maron BJ (1997) The management of hypertrophic cardiomyopathy. N Engl J Med 336:775–785
2. Maron BJ 2002)Hypertrophic cardiomyopathy. A systematic review. JAMA 287:1308–1320
3. Elliott P, McKenna WJ (2004) Hypertrophic cardiomyopathy. Lancet 363:1881–1891
4. Maron BJ, McKenna WJ, Danielson GK et al (2003) American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy. A report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. J Am Coll Cardiol 42:1687–1713
5. Olivotto I, Cecchi F, Casey SA et al (2001) Impact of atrial fibrillation on the clinical course of hypertrophic cardiomyopathy. Circulation 104:2517–2524
6. Maron MS, Olivotto I, Betocchi S et al (2003) Effect of left ventricular outflow tract obstruction on clinical outcome in hypertrophic cardiomyopathy. N Engl J Med 348:295–303
7. AIAC (2005) Linee guida all'impianto di PM e ICD. Giornale Italiando di Aritmologia e Cardiostimolazione 8(4):54–66; available at: www.aiac.it
8. Maron BJ, Shen WK, Link MS et al (2000) Efficacy of implantable cardioverter defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. N Engl J Med 342:365–373
9. Spirito P, Bellone P, Harris KM et al (2000) Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. N Engl J Med 342:1778–1785
10. Elliott PM, Poloniecki J, Dickie S et al (2000) Sudden death in hypertrophic cardiomopathy: identification of high risk patients. J Am Coll Cardiol 36:2212–2218
11. Monserrat L, Elliott PM, Gimeno JR et al (2003) Non-sustained ventricular tachycardia in hypertrophic cardiomyopathy: an independent marker of sudden death risk in young patients. J Am Coll Cardiol 42:873–879
12. Spirito P, Autore C (2006) Management of hypertrophic cardiomyopathy. BMJ 332:1251–1255

Managing Hypertrophic Cardiomyopathy: Screening in Young Subjects

Maurizio Santomauro[1] on behalf of the AIAC Task Force of Risk Management, Gianluca Botto[2], Corrado Diaco[2], Michele M. Gulizia[3], Giuseppe Marceca[4], Francesco Melandri[5], Franco Naccarella[6], Carla Riganti[7], Massimo Santini[8]

Introduction

Myocardial diseases (MDs) include an infrequently occurring heterogeneous group of potentially lethal abnormalities in children and young adults. Recent epidemiological studies have shown that dilated and hypertrophic cardiomyopathies are the most frequent morphological substrata of cardiomyopathy in children [1, 2]. Furthermore, MDs have been associated with unexpected sudden death (SD) in apparently healthy people < 35 years old [3–9]. Acute myocarditis and hypertrophic cardiomyopathy are the leading causes of SD in this age group. In addition, arrhythmogenic right ventricular cardiomyopathy/dysplasia has been recognized as a relatively frequent cause of SD in southern European countries [4, 9, 10]. In some cases, SD is the first manifestation of disease, although sometimes the child or young adult has had some symptom during their lifetime [11, 12]. The actual incidence and distribution of cardiac SD by sex and age group in well-defined populations are poorly characterized, and only a few observational studies have assessed this problem in children and young adults. Most studies have been done in selected samples or in reference centers, with the consequent bias making it impossible to provide epidemiological data. A population-based observational retrospective study was carried out in children and young adults < 35 years old in the Italian province of Campania between 1998 and 2005 with the aims of assessing the epidemiological and clinical data on MD mortality and determining the causes of SD and non-sudden death (NSD).

[1]Department of Cardiovascular and Internal Medicine, Faculty of Medicine and Surgery, Federico II University, Naples; [2]Department of Cardiology, S. Anna Hospital, Como; [3]Division of Cardiology, Garibaldi–Nesima Hospital, Catania; [4]Scuola di Specializzazione Medicina del Lavoro, La Sapienza University, Rome; [5]Cardiology Unit, Nuovo Ospedale Civile, Sassuolo (MO); [6]Cardiovascular Epidemiology Unit, Cardiology Department AUSL, Bologna; [7]Direzione Sanitaria, AOU Federico II, Naples; [8]Cardiovascular Department, San Filippo Neri Hospital, Rome, Italy

Patients and Methods

The study was done in Campania (approximate population 5,100,000), which has a homogeneous population. Foreigners form 1.7% of the total. Individuals between the ages of 1 and 35 years who died due to an MD during the period from January 1998 to December 2005 were included in this study. The cases were classified as SD or NSD as follows: SD was defined as death occurring naturally (non-violently), unexpectedly, and instantaneously, or less than 1 h from the onset of premonitory symptoms or collapse, in a person in an apparently good state of health, not admitted to the hospital, and while carrying out habitual activities at the time of the fatal event [6, 13]. In line with Italian legislation, a forensic autopsy is required for deaths due to violence or when crime is suspected. The latter include sudden unexpected natural deaths in non-hospitalized children and young people. In NSD, legislation requires a medical death certificate signed by the physician who was treating the patient for a previously known disease. In Italy, in the case of the death of a child or young adult outside the hospital, a preliminary investigation is done and, assuming that there are signs of violent death or an unexpected SD (for forensic purposes unexpected SD involves a potentially criminal activity), a forensic autopsy is requested and the medical death certificate is annulled. Consequently, all medical death certificates and forensic autopsy reports are coded according to the underlying cause of death in the Mortality Registry of the Campania Region, following the International Classification of Diseases (ICD-9).

To achieve the aim of this work, Mortality Registry data were analyzed and the files in Campania were checked for the period 1998 to 2005, inclusive. All SDs occurring in people age 1 to 35 years old were examined. In all cases, a complete autopsy and toxicological and histopathological studies had been carried out. The cardiac conduction system was studied via a simplified method previously described [14]. Clinical data and the circumstances surrounding the death were also reviewed. This information was obtained from the reports of physicians and forensic doctors. It was not possible to review physicians' reports on NSD patients.

Statistical Analysis

The total incidence rates and those for each sex and age group were calculated according to the population census data for Campania province for the years 1998 and 2005. For non-census years, year interpolations were calculated for the population for each sex and age group, assuming a linear yearly increase or decrease in the population.

The relative risk (RR) (and its 95% confidence interval [CI] of SD due to MD compared to NSD was calculated for the total series and for the different age and sex groups. Similarly, the RR (and its 95% CI) of SDs and NSDs were compared between sex and between age groups (1–14 and 15–35 years old). The Fisher exact test was used to calculate the difference in distribution of the absolute frequency of SD regarding the activity carried out at the time of death (physical vs another activity) between the SD due to MD groups and SD due to other causes. The significance level was set at $p < 0.05$.

Results

According to Mortality Registry data, there were 25,320 deaths in people between the ages of 1 and 35 years (16,880 males and 8,440 women) in Campania from 1998 to 2005. The cause of death was MD in 39 cases. In 30 cases, a forensic autopsy for SD was carried out. In the other nine cases, the appropriate medical death certificate was issued as no evidence indicative of SD due to suspected crime was found by the Forensic Pathology Service; these were therefore included in the NSD group. Of the 39 cases of death due to MD, 29 were male and 10 female; the average age was 27.40 ± 7.17 years. All were Caucasian. The mortality rate due to MD was 0.55/100,000 inhabitants/year. This was higher for males than for females, and for subjects 15–24 and 25–35 years of age than for children 1–14 years old. The RR of SDs was significantly higher than that of NSDs, especially between adolescents and young males.

Analysis of the Registry data showed 270 cases of SD in people between the ages of 1 and 35 years; 39 of these were due to the following MDs: myocarditis, dilated cardiomyopathy, arrhythmogenic cardiomyopathy, hypertrophic cardiomyopathy, and idiopathic concentric left ventricular hypertrophy (CLVH). Myocarditis was the most frequent cause of SD (35.5%) followed by arrhythmogenic cardiomyopathy (25.5%). Dilated cardiomyopathy was the most frequent cause of NSD (70%).

Only in three cases of SD had the MD been diagnosed during the patient's lifetime. Each of them had hypertrophic cardiomyopathy and was under cardiological treatment, and two of them were under pharmacological treatment (1 with verapamil and the other with amiodarone). Some cardiovascular symptoms and/or electrocardiographic abnormalities were recorded in ten people during their lifetime, but without the disease being diagnosed before death; the main diagnoses were arrhythmogenic cardiomyopathy ($n = 5$) and myocarditis ($n = 3$). In the other 17 cases, SD was the first manifestation of disease. Comorbid conditions were reported in six patients: two with

myocarditis who had received medical care for viral gastroenteritis and four who presented with morbid obesity. Six patients (20%) had prodromic symptoms, mainly syncope and chest pain.

In 25 patients cardiopulmonary resuscitation (CPR) maneuvers were carried out. In nine, the ECG obtained during CPR showed ventricular fibrillation; in eight, asystole; and in one, ventricular tachycardia that degenerated into ventricular fibrillation.

Arrhythmia-triggering factors were reported in 11 patients. In three young people, toxicological analysis detected the presence of ethanol. In seven, death occurred during the practicing of a sports activity (five during football, one while cycling, and one during basketball). In one patient, information was obtained regarding acute psychological stress in the instant prior to death. Of the arrhythmogenic cardiomyopathy cases, 71% of the patients died during a sports activity. SD related to a sports activity occurred in 23.3% of the cases of MD (7 out of 30) compared to 9.3% (13 out of 140) of the remaining causes of SD ($p = 0.05$).

In seven people, the death was not witnessed and occurred in the bed, probably while sleeping. Death occurred within 15 min (almost instantly) in 21 patients and within 15 and 60 min in two others. In 47% of cases death occurred outside a hospital, whereas 53% of the patients were admitted to the emergency ward in a state of cardiorespiratory arrest.

Discussion

The incidence of mortality due to MD in people between the ages of 1 and 35 years is low, and the risk of SD is significantly higher than that associated with NSD. Thus, it is important to include forensic case studies to avoid underestimation of the incidence of MD. In the present study, 75% of all the deaths due to MD were sudden.

Unlike in other MDs, in which death is mainly sudden and caused by an arrhythmic mechanism, in dilated myocardiopathy NSD predominates. This indicates that death occurs at a more advanced phase of the disease, due to congestive heart failure [3–7, 15].

Arrhythmogenic cardiomyopathy, hypertrophic cardiomyopathy, and idiopathic CLVH [8, 16–18] are well-known causes of SD during sports activities, with geographical variations among them: the second is especially frequent in North America [8], and the first in southern Europe [9–11, 18, 19]. Arrhythmogenic cardiomyopathy is a disease of unknown origin, although genetic and inflammatory causes have been proposed [12, 20]. In some patients, it could represent a form of myocarditis with scarring.

Idiopathic CLVH is a clinical condition in which the heart is morphologically very similar to an athlete's heart. Distinguishing between the two is fundamental in professional athletes but is not easy [8], as shown in the present series. A non-familial variant of hypertrophic cardiomyopathy or a form of hypertrophic cardiomyopathy without typical morphological expression has been suggested [17].

Preventing deaths due to MD in children and young adults is a difficult task, as a high percentage of these occur suddenly and without the subject having experienced previous cardiovascular symptoms [11]. One of the main findings in this study was the relatively high percentage of people with cardiovascular symptoms or electrocardiographic abnormalities before death, and in whom the disease had not been diagnosed during life, although all the patients had been examined by a physician. It may have been possible to prevent death in some of these cases, especially those involving arrhythmogenic cardiomyopathy and myocarditis. However, both diseases can be difficult to diagnose while the patient is alive. In contrast, half of the cases of hypertrophic cardiomyopathy had been diagnosed, which shows that SD risk stratification is not easy due to the clinical heterogeneity of the contributing diseases. Both arrhythmogenic and hypertrophic myocardiopathy are becoming an emerging indication for an implantable cardioverter defibrillator [20]. This could have been effective in two of our cases. Our results agree with the well-known greater risk of SD in people with morbid obesity [21]. The prevention and treatment of obesity could therefore be of interest regarding reducing mortality due to MD.

Certain triggering factors can precipitate lethal arrhythmias in a vulnerable myocardium; among these, vigorous physical activity is the most important in the context of MD, especially in arrhythmogenic cardiomyopathy [9, 10, 18]. Thus, in young men diagnosed with this disease, vigorous sports activities [12] should be strongly discouraged. In line with the protocol of the American Heart Association [22], at least three of our patients should have received this advice until a detailed cardiological examination had been done. One of the patients with myocarditis died during a cycling event, which supports the contraindication of sports activities during the acute phase of the disease [8]. Although hypertrophic cardiomyopathy has been pointed out as the leading cause of SD in young adult athletes [8], none of the subjects in the present series who were diagnosed with this disease died while engaged in sports activities.

Alcohol intake can induce malignant ventricular arrhythmias in susceptible myocardium [23]. Ventricular fibrillation is the rhythm most frequently leading to SD [12], which we also observed. Thus, efforts should be made to

achieve early defibrillation in cases of out-of-hospital cardiac arrest, especially in sports centers.

We should mention some limitations of the present study. Although the clinical histories of the cases for which medical death certificates had been issued were not available, we assumed that they did not fulfill the criteria for SD, since they involved in-hospital or out-of-hospital deaths but the patients had undergone forensic examination. As pointed out in other SD studies in Europe [7, 13, 24, 25], it is highly unlikely that a medical-forensic investigation would not be carried out in the case of an out-of-hospital SD in a child or young adult. However, the different distributions of MD in the SD and NSD groups provide additional support for the reliability of the present results. In all cases of SD in children and young adults, a forensic autopsy should be carried out for two fundamental reasons: (1) it offers useful and reliable information for epidemiological and preventive studies, and (2) since some MDs are hereditary, a precise diagnosis may prevent death in family members. Thus, it is desirable that genetic studies eventually be included in the autopsy protocol. Nevertheless, death may have been prevented in some cases through early diagnosis of the disease, and by identifying and modifying the risk factors of the disease as well as factors triggering SD. Finally, it would be useful to implement effective resuscitation programs (basic life-support defibrillator) for victims of cardiac arrest.

Acknowledgments
We express our gratitude to Dr. Gennaro Galasso and to Gianluigi Galizia for their editorial support.

References

1. Nugent AW, Daubeney PE, Chondros P, Carlin JB, Cheung M, Wilkinson LC et al (2003) The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med 348:1639–1646
2. Lipshultz SE, Sleeper LA, Towbin JA et al (2003) The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 348:1647–1653
3. Neuspiel DR, Kuller LH (1985) Sudden and unexpected natural death in childhood and adolescence. JAMA 254:1321–1325
4. Corrado D, Basso C, Poletti A et al (1994) Sudden death in the young. Is acute coronary thrombosis the major precipitating factor? Circulation 90:2315–2323
5. Shen W, Edwards WD, Hammill SC et al (1995) Sudden unexpected nontraumatic death in 54 young adults: a 30-year population-based study. Am J Cardiol 76: 148–152
6. Morentin B, Suárez-Mier MP, Audicana C et al (2001) Incidencia y causas de muerte súbita en menores de 36 años. Med Clin (Barc) 116:281–285

7. Wisten A, Forsberg H, Krantz P, Messner T (2002) Sudden cardiac death in 15-35-year olds in Sweden during 1992–99. J Intern Med 252:529–536
8. Maron BJ (2003) Sudden death in young athletes. N Engl J Med 349:1064–1075
9. Corrado D, Basso C, Rizzoli G et al (2003) Does sports activity enhance the risk of sudden death in adolescents and young adults? J Am Coll Cardiol 42:1959–1963
10. Aguilera B, Suárez-Mier MP, Morentin B (1999) Miocardiopatía arritmogénica como causa de muerte súbita en España. Presentación de 21 casos. Res Esp Cardiol 52:656–662
11. Liberthson RR (1996) Sudden death from cardiac causes in children and young adults. N Engl J Med 334:1039–1044
12. Huikuri HV, Castellanos A, Myerburg RJ (2001) Sudden death due to cardiac arrhythmias. N Engl J Med 345:1473–1482
13. Morentin B, Aguilera B, Garamendi PM, Suárez-Mier MP (2000) Sudden unexpected non-violent death between 1 and 19 years in north Spain. Arch Dis Child 82:456–461
14. Suárez-Mier MP, Gamallo C (1998) AV node fetal dispersion and His bundle fragmentation of the cardiac conduction system in sudden cardiac death. J Am Coll Cardiol 32:1885–1890
15. Dec GW, Fuster V (1994) Idiopathic dilated cardiomyopathy. N Engl J Med 331:1564–1575
16. Virmani R, Burke AP, Farb A, Kark JA (1997) Causes of sudden death in young and middle-aged competitive athletes. Cardiol Clin 15:439–466
17. Virmani R, Burke A, Farb A, Atkinson JB (2001) Sudden cardiac death. In: Virmani R, Burke A, Farb A, Atkinson JB (eds) Cardiovascular pathology, 2nd edn. Saunders, Philadelphia, pp 340–385
18. Suárez-Mier MP, Aguilera B (2002) Causes of sudden death during sports activities in Spain. Rev Esp Cardiol 55:347–358
19. Kishimoto C, Ochiai H, Sasayama S (1992) Intracardiac thrombus in murine Coxsackievirus B3 myocarditis. Heart Vessels 7:76–781
20. Tomé MT, García-Pinilla JM, McKenna WJ (2004) Actualización en miocardiopatía arritmogénica del ventrículo derecho: genética, diagnóstico, manifestaciones clínicas y estratificación de riesgo. Rev Esp Cardiol 57:757–767
21. Duflou J, Virmani R, Rabin I et al (1995) Sudden death as a result of heart disease in morbid obesity. Am Heart J 130:306–313
22. Maron BJ, Thompson PD, Puffer JC et al (1996) Cardiovascular preparticipation screening of competitive athletes. A statement for health professionals from the Sudden Death Committee (clinical cardiology) and Congenital Cardiac Defects Committee (cardiovascular disease in the young) American Heart Association. Circulation 94:850–856
23. Panos RJ, Sutton FJ, Young-Hyman P, Peters R (1998) Sudden death associated with alcohol consumption. Pacing Clin Electrophysiol 11:423–424
24. Bowker TJ, Wood DA, Davies MJ et al (2003) Sudden, unexpected cardiac or unexplained death in England: a national survey. Q J Med 96:269–279
25. Felicani C, Moccia E, Naccarella F et al (2007) La morte improvvisa da sport. Due database prospettici: 1990–2004 e 2005–2016: aspetti epidemiologici, preventivi, assistenziali. Giornale Italiano di Aritmologia e Cardiostimolazione (in press)

The Prevention of Sudden Death: New Perspectives

Savina Nodari, Marco Metra, Alessandra Manerba, Silvia Frattini, Giuseppe Seresini, Livio Dei Cas

Epidemiology and Etiology

Sudden cardiac death (SCD) is unexpected natural death due to cardiac causes, and includes the abrupt loss of consciousness within 1 h from the onset of acute symptoms, with or without preexisting heart disease. It is very difficult to evaluate the exact incidence of SCD because the concept of "sudden events" has not been precisely defined [1].

Estimates for the US show a mean incidence of 300,000 SCDs per year, 0.1–0.2% of the entire population [1]. In Italy, the number of events per year is around 50,000 (about 1/1,000 subjects/year) [2]. These estimates are related to the whole population, thus including SCDs as a primary cardiac event in healthy subjects and those occurring in high-risk patients. Despite the high number of events per year in the population, the percentage remains very low although it has increased progressively in high-risk subgroups. For example, in post-myocardial infarction (MI) patients and in subjects with prior malignant ventricular tachyarrhythmias the incidence of SCD is 35% [1]. In a Framingham Study re-analysis, risk factors for coronary artery disease were shown to be statistically related to SCD. The incidence in patients with several risk factors is 60 times higher than in those with only one [3]. Therefore, considering that the 80% of SCD is due to ischemic events, primary and secondary coronary artery disease prevention is of major importance. According to international guidelines and evidence-based medicine, the control of risk factors and of pharmacological treatment is very important.

Department of Cardiology, Spedali Civili, University of Brescia, Brescia, Italy

In the last 30 years, pharmacological and nonpharmacological approaches have improved the prognosis of post-acute-MI patients. The use of β-blockers and cardiac defibrillation in intensive care units has significantly reduced early mortality, from 30–35% to 15–18%. In acute MI (AMI) patients, thrombolysis and primary percutaneous transluminal coronary angioplasty (PTCA) have additionally reduced the mortality to 6–8%. Ventricular fibrillation, the most frequent of early complications, is now almost totally controlled in protected areas, even if 40–50% of patients with AMI still die from arrhythmias occurring before hospitalization. Malignant arrhythmias remain the most important cause of late mortality, thus underlining the importance of secondary prevention, too.

New interventional strategies and pharmacological approaches have reduced early mortality but increased the incidence of late complications, such as ischemic cardiomyopathies and heart failure. Chronic ischemia and post-AMI heart failure are associated with ventricular hyperkinetic arrhythmias such as ventricular sustained tachycardia, ventricular flutter, torsades de pointes, all of which often degenerate into ventricular fibrillation (VF) and cardiac arrest. It is well-understood that ~80% of SCDs in adults are caused by recognized or unrecognized coronary artery disease and that the percentage of mortality in patients with AMI is about 50% in the so-called door to needle time. In 25% of patients, SCD is the first event of acute ischemia. More often, it is a late complication of AMI or post-infarction cardiomyopathy, which account for 75% of deaths in patients with a previous MI. Fibrosis and hypoperfusion in perinecrotic areas induce electrophysiological changes, promoting reentrant arrhythmias and increasing automaticity [1].

Sudden death is the final event in 50% of patients with heart failure. Mortality is positively related to clinical severity (12% in NYHA class II, 24% in class III, and 36% in class IV), while SCD is the most frequent cause of mortality in NYHA class II (64%) and class III (59%) patients [4].

Arrhythmogenic mechanisms depend on the underlying pathologies (scar-tissue infarction, acute ischemia, ventricular hypertrophy, ventricular enlargement). Transient modulating factors, such as acute myocardial ischemia, adrenergic stimulation, and hypokalemia, play an important role as well, particularly in patients with severe left ventricular dysfunction. Additional important causes of arrhythmia are plaque rupture, intracoronary thrombosis, platelet emboli, coronary spasm induced by flow reduction, post-ischemic reperfusion damage, changes in membrane ionic currents, and adrenergic hyperstimulation [1].

Adrenergic hyperactivation increases automatism and reentrant arrhythmias. Acute myocardial ischemia alters the biochemical and biophysical features of myocytes, thus interfering with transmembrane ionic currents and electrophysiological status. As a consequence, the likelihood of automatism and reentrant-triggered arrhythmias may increase, such that prolonged acute ischemia may be associated with sustained ventricular tachycardia and VF.

Prevention of Sudden Death

The administration of β-blockers prevents SCD by reducing myocardial oxygen consumption and counteracting ventricular remodeling and neuroendocrine activation. Thus, β-blocker- and amiodarone-based therapies are fundamental components of the guidelines for SCD prevention [5]. Angiotensin-converting-enzyme inhibitors and aldosterone-receptor blockers are important in preventing ventricular remodeling, interstitial myocardial fibrosis, and arrhythmias [6].

A new pharmacological option in the prevention of SCD is the n-3 polyunsaturated fatty acids (n-3 PUFAs). These compounds act by opposing cellular remodeling and counteracting membrane structural changes as well as cellular electric instability. They also influence sympathovagal balance and have anti-ischemic properties [7–9].

A possible explanation for the anti-arrhythmogenic effects of n-3 PUFAs is their modulation of sympathovagal balance. n-3 PUFAs increase heart rate variability in healthy subjects and in patients at high risk for arrhythmia (post-AMI patients with left ventricular dysfunction, patients with chronic renal failure who undergo dialysis, and those with diabetes mellitus). The effect has been shown to be due to a higher membrane concentration of these compounds [10, 11].

Many studies have shown a decrease in HRV after AMI, as an expression of increased sympathetic influence on cardiac activity that is related to increased arrhythmic risk and mortality. The anti-arrhythmogenic effect of n-3 PUFAs has been demonstrated in isolated myocytes and in experimental studies, and is caused by a change in the concentration of cell-membrane phospholipids. Higher concentrations of n-3 PUFAs (eicosapentaenoic and docosahexaenoic acids) induce the production of thromboxane (TX)A3 and leukotriene (LT)B5 during ischemia. In addition, they have fewer vasoconstrictive and inflammatory effects than TXA2 and LTB4, which are derived

from n-6 PUFAs. The release of TXA3 and LTB5 leads to a reduction in both infarct size and the production of superoxide radicals, which reduce electric instability in peri-infarction areas [7–9].

By modulating the fluidity of lipid bilayers, n-3 PUFAs influence the conductance of membrane ion channels and increase the opening threshold in Na+ ion channels [12]. Besides cell membrane hyperpolarization, n-3 PUFAs induce a lengthening of the cardiac cycle refractory period. In Ca2+ ion channels, n-3 PUFAs inhibit L-type voltage-dependent currents, thus reducing the high Ca2+ cytosolic concentration responsible for partial membrane depolarization, arrhythmogenic post-potentials, and arrhythmias [13]. In ischemic or dysfunctional myocardium there is cytosolic-calcium overload because of sarco/endoplasmic reticulum Ca2+ (SERCA) dysfunction and diminished ryanodine receptor sensibility towards cytosolic calcium storage. Consequently, there is a reduction in calcium uptake in the sarcoplasmic reticulum and a nonmodulated outward current of this ion from the reticulum itself. Additionally, the NA+ inward current in exchange with Ca2+ ions increases, which also enhances arrhythmogenic triggers. Experimental studies on isolated ventricular myocytes showed the inhibitory effect of n-3 PUFAs on type L Ca2+ channels currents and SERCA activity. Microsomal Ca2+/Mg2+-ATPase stimulation, with a reduction in cytosolic Ca2+ concentration and fluctuations, was also observed and may contribute to the antiarrhythmogenic effects of n-3 PUFAs. The possibility that these drugs reduce the risk for SCD is actually based on evidence from a prospective cohort study, a case-control study, and prospective dietary intervention trials.

Results from Secondary-Prevention Clinical Trials

Following several observational prospective studies that confirmed an inverse correlation between n-3 PUFA intake from fish and cardiovascular mortality, randomized clinical trials for secondary prevention of CHD were established. DART was the first such trial to evaluate the effects of n-3 PUFAs on post-infarction survival [14]. After a 2-year follow-up, the results showed that intake of n-3 PUFAs (by diet or pharmacological therapy) induced a significant reduction in total mortality (-29%) and in fatal ischemic events (-32%); this benefit was observed as early as after 3 months. This result and the significant reduction in coronary death but not in non-fatal ischemic events indicated that n-3 PUFAs have a protective effect on arrhythmia-related death during ischemia.

The anti-arrhythmogenic effect of n-3 PUFAs was also confirmed by the GISSI Prevenzione trial [15], which showed a significant reduction in the primary end-point (15% in total mortality, non-fatal AMI, non-fatal stroke; 20% in cardiovascular mortality, non-fatal AMI and non-fatal stroke) only in the n-3 PUFAs group; in particular, a significant reduction in total mortality (20%), cardiovascular mortality (30%), and sudden death (45%) was documented (Fig.1). The early favorable effect on prognosis shown by the study supports a direct protective anti-arrhythmogenic effect of n-3 PUFAs on myocardium, independent from their anti-thrombotic and anti-atherogenic effects. A meta-analysis of n-3 PUFA secondary prevention trials, including about 15,700 patients, validated the GISSI Prevenzione trial results [16].

Primary Prevention

A recent re-analysis of the results of the US Physicians' Health Study confirmed the potential role of n-3 PUFAs in the primary prevention of sudden death [17]. In that study, a blood sample was taken at baseline in 22,071

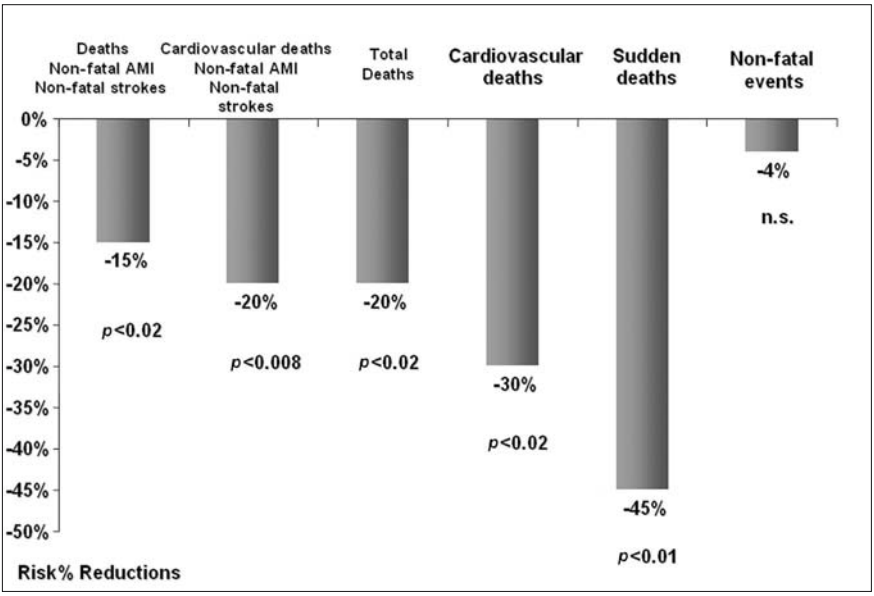


Fig. 1. The GISSI prevention study showed that treatment with n-3PUFAs significantly reduces cardiovascular events; in particular, sudden death decreased by 45%. *AMI*, Acute myocardial infarction

healthy American physicians. In a 17-year follow-up, 94 subjects died from SCD. Analysis of red-cell membrane fatty acids in these patients and in a control group of 184 patients with a similar cardiovascular risk profile demonstrated that only long-chain n-3 PUFA plasma concentrations were significantly lower in the group of patients who died suddenly. No statistically significant difference was found in the two groups with respect to saturated, mono-unsaturated, or n-6 PUFAs, or short-chain n-3 PUFAs (α-linolenic acid). In the same study, multivariate analysis confirmed the prognostic value of low-level n-3 PUFAs in sudden death, proving a strong inverse relationship between plasma concentrations of long-chain n-3 PUFAs and the risk of sudden death. The authors also found an 81% risk reduction in the quartile with higher n-3 PUFAs. These results were confirmed after statistical correction for age and smoking habit (Fig. 2).

Considering the high prevalence (50%) of sudden death in subjects without previous cardiovascular events, the usefulness of supplementary PUFA n-3 intake in primary prevention was emphasized.

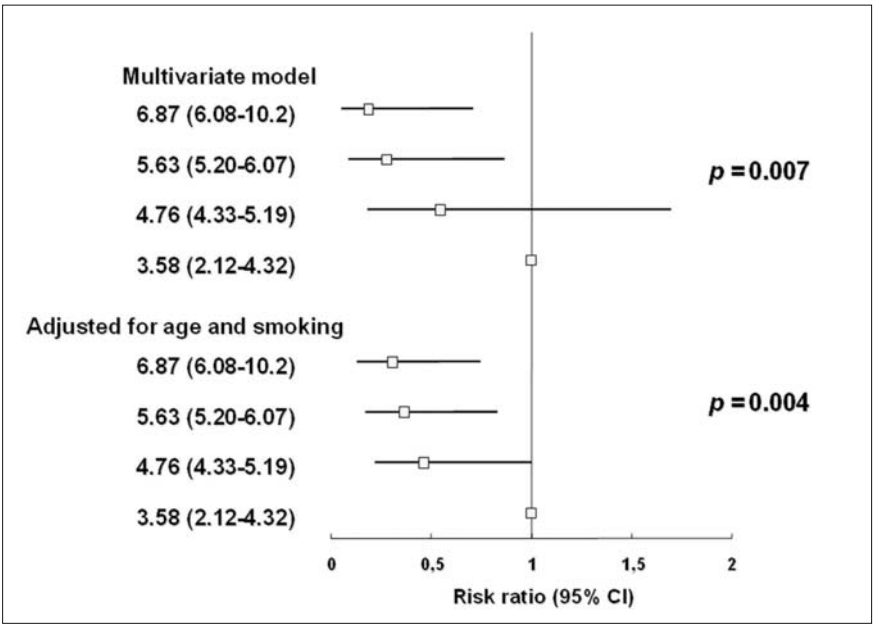


Fig. 2. Correlation between n-3 polyunsaturated fatty acid (n-3 PUFA) levels and the relative risk of sudden death. Patients with a higher blood concentration of long-chain n-3 PUFAs are at lower risk, even when the values are adjusted to take into account other risk factors. Adapted from [17]

Conclusions

The epidemiological observations, experimental study results, but most of all the secondary prevention clinical trial evidence together justify the use of n-3 PUFAs in the prevention of post-AMI sudden death. Moreover, while further confirmation is required, it appears that n-3 PUFAs also benefit patients at high risk for sudden death. The new AHA guidelines recommend the alimentary/pharmacological intake of n-3 PUFAs not only in CHD secondary prevention, but also in primary prevention and in patients with hypertriglyceridemia [18] (Table 1).

The recent report of the ESC Task Force for risk stratification and sudden death prevention [19] recommends n-3 PUFA treatment for primary prevention of SCD, with a type B evidence level (a single randomized trial).

Table 1. Recommendations of the AHA/ACC for n-3 PUFA intake in primary and secondary prevention. Adapted from [18]

Population	Recommendations
Patients without demonstrated CHD	Oily fish intake twice a week. Include oils and foods with α-linoleic acid (linseed oil, soybean oil, peanut oil, etc.)
Patients with demonstrated CHD	Intake ~1 g of EPA + DHA per die from oily fish. Possible EPA +DHA supplements
Patients with hypertriglyceridemia	2–4 g of EPA + DHA per die, capsules prescribed by the doctor

CHD, Chronic heart disease; *EPA*, Eicosapentaenoic acid; *DHA*, docosahexaenoic acid

References

1. Zipes DP, Camm AJ, Borggrefe M et al; European Heart Rhythm Association; Heart Rhythm Society; American College of Cardiology; American Heart Association Task Force; European Society of Cardiology Committee for Practice Guidelines (2006) ACC/AHA/ESC 2006 Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death. A Report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death). J Am Coll Cardiol 48:e247-e346

2. Tunstall-Pedoe H, Vanuzzo D, Hobbs M et al (2000) Estimation of contribution of changes in coronary care to improving survival, event rates, and coronary heart disease mortality across the WHO MONICA project populations. Lancet 355:688–700
3. Kannel WB, Schatzkin A (1985) Sudden death: lessons from subsets in population studies. J Am Coll Cardiol 5(6 Suppl):141B-149B
4. Anonymous (1999) Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/X1L Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet 353:2001–2007
5. Anonymous (1997) Effect of prophylactic amiodarone on mortality after acute myocardial infarction and in congestive heart failure: meta-analysis of individual data from 6500 patients in randomized trials. Amiodarone Trials Meta-Analysis Investigators. Lancet 350:1417–1424
6. Domanski MJ, Exner DV, Borkowf CB et al (1999) Effect of angiotensin converting enzyme inhibition on sudden cardiac death in patients following acute myocardial infarction. A meta-analysis of randomized clinical trials. J Am Coll Cardiol 33:598–604
7. Kim D, Duff RA (1990) Regulation of K+ channels in cardiac myocytes by free fatty acids. Circ Res 67:1040–1046
8. Leaf A (2001) Electrophysiologic basis for the antiarrhythmic and anticonvulsant effects of omega 3 polyunsatured fatty acids. World Rev Nutr Diet 88:72–78
9. Lundmark K, Abelnoor M, Urdal P et al (1998) Use of fish oils appears to reduce infarct size as estimated from peak creatinine kinase and locate dehydrogenase activities. Cardiology 89:94–102
10. Christensen JH, Kroup E, Aaroe J et al (1997) Fish consumption, n-3 fatty acids in cell membranes, and heart rate variability in survivors of myocardial infarction with left ventricular dysfunction. Am J Cardiol 79:1670–1673
11. Christensen HJ, Skou HA, Fog L et al (2001) Marine n-3 fatty acids, wine intake, and heart rate variability in patients referred for coronary angiography. Circulation 103:651–657
12. Xiao YF, Wright SN, Wang JK et al (2000) Coexpression with beta(1) subunit modifies the kinetics and fatty acid block of hH1(alpha) Na+ channels. Am J Physiol Heart Circ Physiol 279:H 35-H46
13. Pepe S, Bogdanov K, Hallaq H et al (1994) Omega 3 polyunsatured fatty acids modulates dihydropiridine effects on L-type Ca2+ channels, cytosolic Ca2+ and contraction in adult rat cardiac myocytes. Proc Natl Acad Sci USA 91:8832–8836
14. Burt ML, Fehily AM, Gilbert JF et al (1989) Effects of changes in fat, fish and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 2:757–761
15. Marchioli R, Barzi F, Bomba E et al (2002) Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction: time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. Circulation 105:1897–1903
16. Bucher HC, Hengstler P, Schindler C, Mayer G (2002) N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. Am J Med 112:298–308
17. Albert CM, Campos H, Stampfer MJ et al (2002) Blood levels of long-chain n-3 fatty acids and the risk of sudden death. N Engl J Med 346:1113–1118

18. Penny M, Kris-Eherton, William S et al (2002) Appeal for Nutrition Committee. Fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 106:2747–2757
19. Priori SG, Aliot E, Blomstrom-Lundqvist C et al (2002) Task Force on Sudden Cardiac Death, European Society of Cardiology. Europace 4:3–18

Which Patient and when Should Receive an ICD? Evolving New Indications on the Horizon

Roberto Verlato, Maria Stella Baccillieri, Pietro Turrini

Introduction

Internal cardioverter defibrillator (ICD) therapy has come a long way since its introduction in the 1980s as the first-line treatment for the few fortunate survivors of recurrent sudden cardiac arrest (SCA). Secondary- and primary-prevention trials enrolling patients with either ischemic or nonischemic cardiomyopathy with depressed left ventricular ejection fraction (LVEF) and NYHA II–IV (AVID, CIDS, CASH, MADIT, MUSTT, MADIT II, DEFINITE) have overwhelmingly demonstrated that ICD therapy reduces total mortality compared with anti-arrhythmic drug therapy and/or optimal medical therapy [1–7]. The most recent trials (COMPANION and SCD-HeFT) [8, 9] focused on patients with NYHA class II–IV heart-failure (HF) symptoms and depressed LVEF: ICD alone or combined with a left ventricular lead for cardiac resynchronization significantly reduced total mortality as compared with optimal medical therapy (ACE inhibitors/ARB blockers, beta-blockers, canrenoate, diuretics) and amiodarone.

In recent years, based on the results of clinical studies and trials, several guidelines have been published and revised on the optimal prevention of SCD and the indication for ICD therapy in patients with or at risk of ventricular tachyarrhythmias and in patients with HF. Guidelines from the European Society of Cardiology, the American College of Cardiology/American Heart Association [10], and the Associazione Italiana di Aritmologia e Cardiostimolazione (AIAC) [11] are available. Small differences exist between them regarding class IA indications for ICD. In particular, there is general agreement that an ICD is always indicated for secondary

Interventional Electrophysiology Unit, Department of Cardiology, Camposampiero Hospital, Padua, Italy

prevention of SCA not due to reversible causes, independent of the underlying cardiac pathology and the individual patient's electrophysiology. When ICDs are used in primary prevention, most recent recommendations underline the importance of chronic optimal medical therapy as well as the patient's overall clinical status and co-morbidities: only patients who have a reasonable expectation of survival with a good functional status for more than 1 year are candidates to receive an ICD.

A brief summary of current recommendations for ICDs implantation in patients with different types of heart disease, and of the differences among the guidelines is provided in the following.

Patients with Coronary Artery Disease

Patients with left ventricular dysfunction due to prior myocardial infarction (MI), on chronic optimal medical therapy, and not candidates to further coronary revascularization should receive an ICD if they survived ventricular fibrillation (VF) or have hemodynamically unstable ventricular tachycardia (VT) (class I, level of evidence A). ICD is also recommended for primary prevention to reduce total mortality by a reduction in SCA in patients who are at least 40 days post-MI, have an LVEF ≤ 30–40%, and are in NYHA functional class II–III (class I, level of evidence A). For patients with characteristics similar to the previous ones but in NYHA class I, the implantation of an ICD is reasonable, but this is a class IIa, level of evidence B indication. A class IIa indication for an ICD in post-MI patients is also the treatment of recurrent sustained VT in those subjects with normal o near normal left ventricular function.

Unlike the ESC and ACC/AHA, the AIAC committee adopted more restrictive criteria for primary prevention of SCA in post-MI patients: ICD is a class I indication only for patients with a LVEF ≤ 30%, whereas in patients with LVEF between 31 and 35%, an ICD is a class II indication.

Some of the most important innovations of the most recent ACC/ESC guidelines on the prevention of SCA are the recommendations regarding patients with nonischemic dilated cardiomyopathy (DCM). Besides the obvious class Ia indication for patients with documented sustained ventricular arrhythmias, the implant of an ICD is now a class I indication also in primary prevention for patients with DCM who are receiving chronic optimal medical therapy, who have a reasonable expectation of survival in a good functional status for more than 1 year, have a LVEF ≤ 30–35%, and who are NYHA functional class II or III (class I, level of evidence B). Moreover, in this category of patients, ICD therapy can also be beneficial for those with unex-

plained syncope (class IIa, level of evidence C) and it can be effective for termination of sustained VT in patients with normal or near normal ventricular function (class IIa, level of evidence C).

In these new guidelines, great importance is given to the NYHA functional class. For patients in NYHA I, all the class IIa indications become class IIb, level of evidence C. In clinical practice, the placement of an ICD in a NYHA class I DCM patient is therefore not recommended for primary prevention. As for ischemic cardimyopathy, the AIAC committee adopted more restrictive criteria for primary prevention of SCA also for patients with non-ischemic DCM: the LVEF cutoff for a class I indication for primary prevention is considered to be 30%; in patients with LVEF between 30 and 35% ICD is a class II indication.

An expanding indication for ICD treatment is the vast assortment of arrhythmogenic cardiomyopathies, including hypertrophic cardiomyopathy (HCM) and the so-called channelopathies, or membrane ion-channel disease, all of which are associated with an increased risk of sudden cardiac death (SCD). Sodium-channel disease (arrhythmogenic right ventricular cardiomyopathy, Brugada syndrome, and long QT syndrome type 3), potassium channel disease causing either different types of long QT syndromes or short QT syndrome in case of gain of function, L-type calcium channel loss of function also associated with short QT syndrome, and catecholaminergic ventricular tachycardia are common causes of SCD, mainly in young people, and sudden death may be the first symptom in such patients. For this reason, besides the accepted class I indication for secondary prevention, in all the above-mentioned situations ICD is gaining increasing popularity for primary prevention as well. However, the implant of an ICD for primary prevention in patients with an ion-channel disease is considered a class IIa indication, due to the lack of any prospective randomized trials in this specific patient population. Therefore, for primary prevention, ICD is class IIa, level of evidence C in hypertrophic cardiomyopathy patients who have one or more major risk factors for SCA. It is class IIa, level of evidence C for patients with arrhythmogenic right ventricular dysplasia (ARVD) without sustained VT if they have an extensive disease, including left ventricular involvement, have one or more affected family member with SCA, or undiagnosed syncope when VT/VF cannot be excluded as the cause of syncope. ICD is recommended as a class IIa level of evidence B also for patients with long QT syndrome who experience syncope and/or VT while receiving beta-blockers, and for Brugada syndrome patients with a spontaneous pattern of ST segment elevation coved type and syncope. The role of ICD as primary prevention in short QT syndromes is not well-defined. ICD implantation can

be also effective therapy for the termination of idiopathic sustained VT in patients with normal or near normal ventricular function (class IIa, level of evidence C).

The ICD as an adjunctive treatment to optimized medical therapy is the newest treatment for HF patients, considered in the most recent guidelines of either prevention of SCD or treatment of heart failure. SCD is the primary cause of death in NYHA functional class II–III congestive HF patients. Over 60% of these deaths are attributable to malignant ventricular arrhythmias. The recommendation to implant an ICD for secondary prevention in patients who survived a VF or hemodynamically unstable VT episode is today a class Ia indication. After the Companion and the SCDeHFT studies, a class I, level of evidence B indication is an ICD implant for primary prevention in HF patients who have a LVEF ≤ 30–40%, who are in NYHA functional class II or III, who are receiving chronic optimal medical therapy, who have a reasonable expectation of survival with a good functional status for more than one year, whose LV dysfunction is due to prior MI, and who are at least 40 days post-MI. Also assessed as class I with a level of evidence B, ICD therapy is recommended for primary prevention to reduce total mortality by a reduction in SCD in patients with nonischemic heart disease who have an LVEF ≤ 30–35%, and are NYHA functional class II or III. A class IIa, level of evidence B indication is ICD therapy combined with biventricular pacing in patients with NYHA functional class III or IV, in sinus rhythm with a QRS complex of at least 120 ms, and receiving optimal medical treatment.

Clinical guidelines certainly constitute the most important reference and they should guide our daily clinical practice. However when and in whom to implant an ICD is always a clinical decision that has to be carefully evaluated for each patient. Age, associated morbidities, risk of malfunction and infections, and psychological aspect also have to be considered. Further subgroup stratification to identify patients subgroups at particularly high risk of SCA is necessary, but unfortunately is still lacking today, to avoid an excessive increase in health-care costs due to both the high initial price of the device, the increased care necessary to treat device-related morbidities (recall, system malfunction, and infections), and the expanding indications. However, when patients are carefully selected within the criteria of the guidelines, ICD therapy is cost-effective.

Finally, guidelines are composed on the basis of the best available medical science, but their application will likely be impacted by the financial, cultural, and societal differences among individual countries.

References

1. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators (1997) A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 337:1576–1583
2. Connolly SJ, Gent M, Roberts RS et al (2000) Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 101:1297–1302
3. Kuck KH, Cappato R, Siebels J, Ruppel R (2000) Randomized comparison of antiarrhythimic drug therapy with implantable defibrillators in patients resuscitated from cardiac arrest: the Cardiac Arrest Study Hamburg (CASH). Circulation 102:748–754
4. Moss AJ, Hall WJ, Cannom DS et al (1996) Improved survival with an implantable defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. N Engl J Med 335:1933–1940
5. Ellison KE, Hafley GE, Hickey K et al (2002) Multicenter UnStained Tachycardia Trial Investigators. Effect of beta-blocking therapy on outcome in the Multicenter UnStained Tachycardia Trial (MUSTT). Circulation 106:2694–2699
6. Moss AJ, Zareba W, Hall J et al (2002) Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 346:877–883
7. Kadish A, Dyer A, Daubert J et al; Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators (2004) Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 350:2151–2158
8. Bristow MR, Saxon LA, Boehmer J et al; Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) investigators (2004) Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 350:2140–2150
9. Bardy GH, Lee KL, Mark DB et al; Sudden Death in Heart Failure Trial (SCD-HeFT) Investigators (2005) Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 352:225–237
10. Zipes DP, Camm AJ, Borggrefe M et al (2006) ACC/AHA/ESC 2006 Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (writing committee to develop Guidelines for Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. Circulation 114:1088–1132
11. Lunati M, Bongiorni MG, Boriani G et al (2005) Linee Guida AIAC 2006 all'impianto di pacemaker, dispositivi per la resincronizzazione cardiaca (CRT) e defibrillatori automatici impiantabili (ICD). Giornale Italiano di Aritmologia e Cardiostimolazione 8(4)

Implantable Cardiac Defibrillators: Is Defibrillation Threshold Testing Still Necessary in all Patients?

Franco Naccarella[1], Fabio Iachetti[1,2], Angela Wang[3], Cristina Felicani[4], Giovannina Lepera[1], Elvira Moccia[5], Leilei Sun[1,2], Luca Casari[6], Giorgio Morselli[1], Patrizia Capogreco[1], Gerald Naccarelli[7]

Defibrillation Threshold at Implantation

The defibrillation threshold (DFT) is the minimum amount of energy required to reliably defibrillate the heart during potentially life-threatening ventricular arrhythmia. Knowledge of the patient's DFT allows the physician and other clinicians to be sure that the ICD is programmed to deliver sufficiently high-energy shocks to defibrillate the heart.

Unlike the pacing threshold, however, the DFT is not an absolute value above which defibrillation will always be successful and below which it will always fail. The goal of defibrillation testing is to ensure that the maximal energy output of the device has an extremely high (> 99%) probability of terminating ventricular fibrillation in a given patient. Figure 1 shows a sigmoidal-shaped curve for two different patients. The second patient requires either revision of the lead system to reduce the DFTs or the implantation of a high-output device with at least 37 J output.

There are many testing algorithms to assess defibrillation efficacy, but two predominate: the single energy success and step-down protocols [1–3]. Other algorithms that can be used to determine DFT are the binary search method and the Bayesian search method [4–6].

There is increasing interest in minimizing defibrillation testing. Consequently, the practice of testing only one episode of VF and then programming devices, to achieve maximum output, is gaining in popularity. This strategy probably works because of the very high efficacy of modern lead systems and due to shock waveforms. There is even a growing practice

[1]Cardiology Department, Azienda USL of Bologna; [2]TELBIOS, Scienfic Park S. Raffaele Hospital, Milan, Italy; [3]University of Beijing, China; [4]Internal Medicine Department Policlinico Sant' Orsola, Bologna; [5]Institute of Forensic Medicine Gemelli University Hospital Rome; [6]TECHNOCHIM ROCHE Milan, Modena, Italy; [7]Penn State University, Hershey, PA, USA

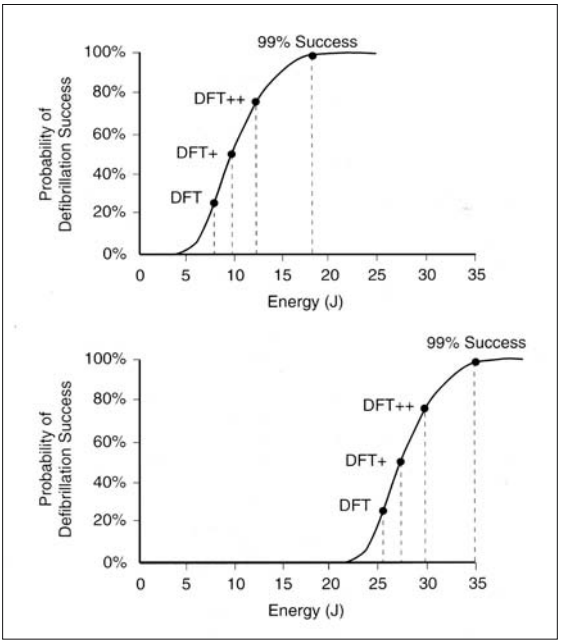


Fig. 1. Sigmoidal-shaped curve for two different patients. (Modified from [3])

of omitting defibrillation testing at the time of implantation, although the prospective data to support this strategy are lacking [2, 3, 7, 8].

Alternatively, determination of the upper limit of vulnerability (ULV) has been used to estimate the DFT, while minimizing or even eliminating the need to induce ventricular fibrillation. The lowest energy value that does not induce fibrillation is the ULV. The ULV is as probabilistic as the actuarial DFT [9].

In some cases, the implanting physician may opt to forego DFT testing, because it is painful, time-consuming, and consumes battery energy. If the implanting physician intends to program the device to maximum output anyway, DFT testing (which would involve programming at less than maximum output values) may not be worth the effort. Furthermore, many patients are likely to be shocked only rarely and only for serious situations. For such patients, programming maximum energy therapy is appropriate, and DFT testing is not necessary [1]. This approach has been criticized by many internationally recognized clinical investigators [2, 6, 10].

Increasingly, DFT testing is omitted at implant. However, when performed, it can help physicians optimize the output settings of the device. Furthermore, the intracardiac electrogram should be monitored to verify

that: (1) there was appropriate sensing during the episode; (2) there was appropriate detection of the episode; (3) the arrhythmia was converted; (4) the delivered energy is known; (5) shocking impedance values are within the acceptable range; (6) the charge time is acceptable.

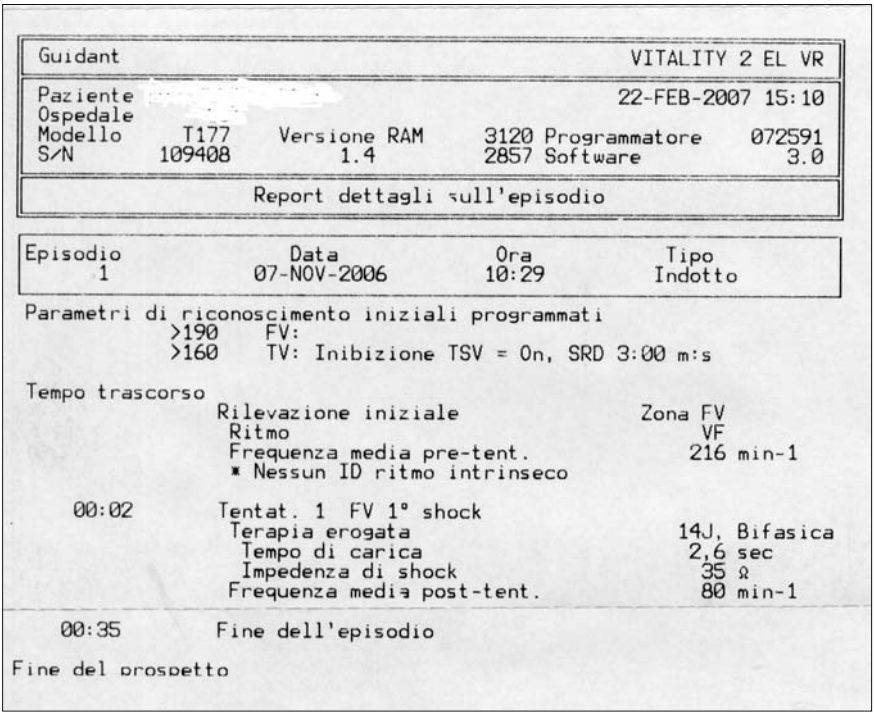
At least 2 min, but more typically 3–5 min, should be allowed between defibrillation episodes to ensure full hemodynamic recovery and to minimize any cumulative effects of multiple shocks. The appropriate sensing of each episode of induced arrhythmia should be confirmed after each induction. The sensitivity is typically decreased at implant testing (e.g., from 0.3 to 1.2 mV) for adequate sensing of spontaneous ventricular arrhythmias. The accurate postoperative management of patient, including monitoring of vital signs and heart rhythm during recovery from anesthesia or conscious sedation, is mandatory (Figs. 2-6) [3].

Biphasic waveforms have become the standard for all ICD pulse generators. Another factor that can affect DFTs is the polarity of the defibrillation shock. Reverse polarity, or anodal shocks, result in significantly lower DFTs. Shock polarity has much less effect on biphasic defibrillation thresholds than on monophasic thresholds [3, 11–18].

Capacitance is another factor that may affect defibrillation efficacy. Decreasing the capacitance to 60 to 90 μf modestly reduced DFT in some studies, but had no effect on stored energy requirements and increased peak voltage in others. The defibrillation safety margin is reduced with lower capacitance, because of the higher peak voltages required. As a result, the strategy of marked reductions of pulse generator capacitance is unlikely to be pursued in the future.

Some investigators showed that, with active pulse generators, or "hot cans", adequate DFTs (< 20 J) could be achieved in approximately 90% of patients, with this simple single coil lead system [2, 3].

DFT is relatively insensitive to pulse generator size, indicating that defibrillation efficacy will not be affected adversely as the pulse generator becomes progressively smaller. The effect of combining an active pectoral pulse generator with a dual-coil lead (the "triad" configuration) includes three shocking electrodes, the active can, and two transvenous coils. In the initial study of this lead system, it was shown that mean DFT decreased to 36% compared with a dual-coil shocking vector. In that study, 98% of the patients had a threshold less than 15 J. Of particular clinical relevance is a reduction of the number of patients with high DFTs, because such patients have an inadequate safety margin and often require complicated implantation procedures to test multiple lead positions or shocking vectors [13–18].



Guidant VITALITY 2 EL VR

Paziente [redacted] 22-FEB-2007 15:10
Ospedale
Modello T177 Versione RAM 3120 Programmatore 072591
S/N 109408 1.4 2857 Software 3.0

Report dettagli sull'episodio

Episodio	Data	Ora	Tipo
1	07-NOV-2006	10:29	Indotto

Parametri di riconoscimento iniziali programmati
>190 FV:
>160 TV: Inibizione TSV = On, SRD 3:00 m:s

Tempo trascorso

	Rilevazione iniziale	Zona FV
	Ritmo	VF
	Frequenza media pre-tent.	216 min-1
	* Nessun ID ritmo intrinseco	
00:02	Tentat. 1 FV 1° shock	
	Terapia erogata	14J, Bifasica
	Tempo di carica	2,6 sec
	Impedenza di shock	35 Ω
	Frequenza media post-tent.	80 min-1
00:35	Fine dell'episodio	

Fine del prospetto

Fig. 2. DFT programming with Guidant VITALITY 2 EL VR

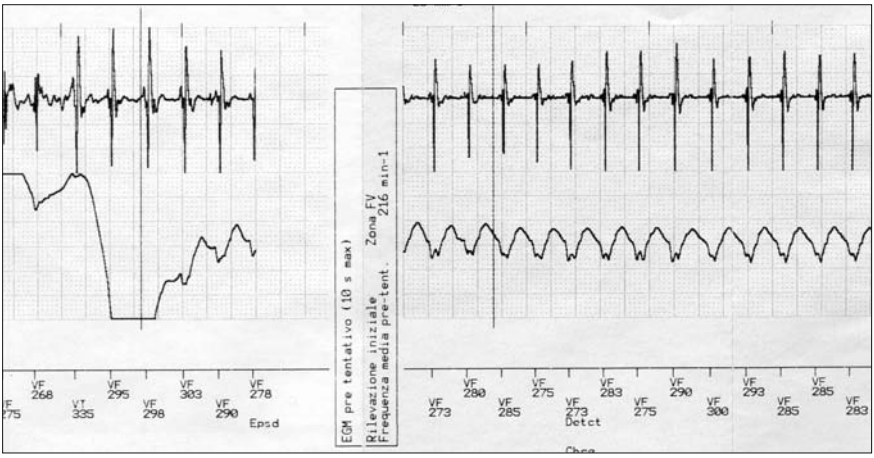


Fig. 3. Induction of ventricular tachycardia at implant

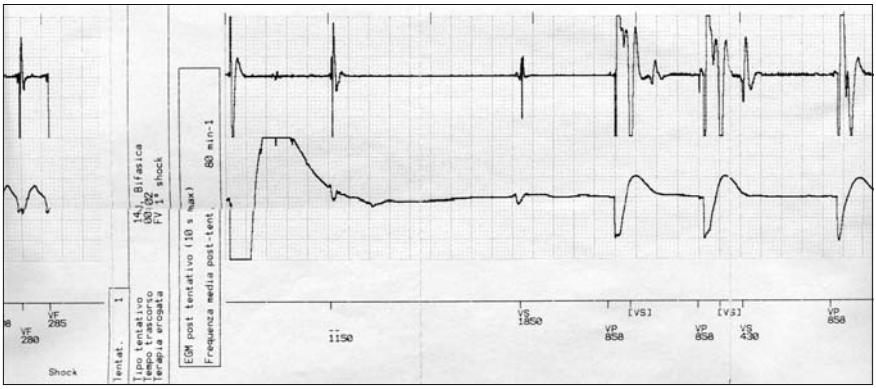


Fig. 4. Termination of ventricular tachycardia and identification of the defibrillation threshold (DFT) at implant 14 J

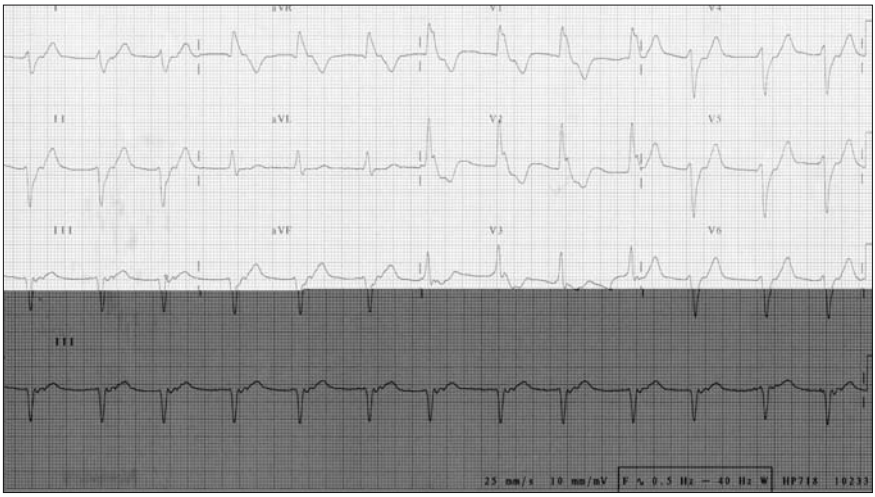


Fig. 5. ECG of a patient with post-acute myocardial infarction severe dilated cardiomyopathy and high threshold at implant even with biphasic inverted shock. At follow-up, a new electrode position and configuration had to be found for increasing ventricular defibrillation and defibrillation failure episodes during hospitalization

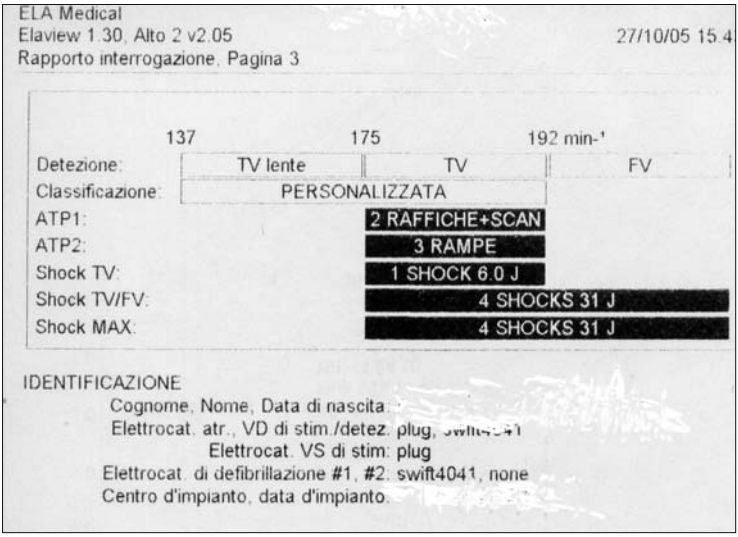


Fig 6. ELA Medical Programming of implantable cardiac defibrillator therapies after DFT documentation at implant. A DFT of 18 J, and the maximum highest values were set up at follow-up

DFT at Follow-up

Traditionally ICD patients are evaluated with device interrogation and threshold testing every 3 months. However, given the reliability of modern pulse generators and leads, follow-up every 6 months among clinically stable patients is rapidly becoming the norm. Trans-telephonic monitoring of ICD is growing in popularity, and this approach can further reduce the frequency of office visits, as reported by Iachetti et al. [19]. Nonetheless, the FDA does not advocate remote monitoring of critically ill patients with and without implanted devices and does not recommend the new implanted devices offered by Medtronic. Many expert-panel members have encouraged the company to continue studying the device. The problem of DFT monitoring or reprogramming during follow-up cannot be reasonably addressed by remote monitoring [3, 19].

Causes and Correction for High DFT at Implant or Follow-up

Despite the marked reduction of DFT with active pectoral pulse generators, there are still some patients with unacceptably high thresholds. Unfortunately, identifying these patients prospectively is difficult. Raitt [20]

showed that there are some clinical predictors of defibrillation efficacy. The only independent predictors of biphasic DFT were left ventricular mass and resting heart rate, but not the underlying heart disease, dilated cardiomyopathy, or QRS width [20, 21].

Many causes of elevated DFT have been identified, including poor lead position, increased high-voltage impedance, pneumothorax, hypoxia, ischemia, multiple defibrillations, anti-arrhythmic drugs or anesthetics, poor current distributions, shunting current through guidewires or retained leads, suboptimal waveform tilt, poor myocardial substrate.

Pacifico [2] reported all the suggested ICD implant values for a 30 J maximum output ICD. Furthermore, he found that the most commonly used and conceptually simple algorithm is a step-down determination of DFT. Clinically, adequate approximation of the DFT can usually be achieved with 1–3 inductions of ventricular fibrillation. For example, successful defibrillation with 10 J using a device with a maximum output of 30 J is generally adequate to establish an accurate safety margin [2].

Furthermore, based on his own experience and that reported in the literature, Pacifico described the factors influencing DFT [2]: (1) instrumentation-dependent factors (active can, shock waveform, lead system, electrode surface area); (2) recipient-dependent factors (LV mass, LV dilation, body size, body position, right- vs left-sided implantation, underlying heart disease including heart failure, ischemia, cardiomyopathy, and an associated pneumothorax); (3) drug-dependent factors, (anti-arrhythmic drugs, anesthetic agents); and (4) ventricular-fibrillation-dependent factors (duration, spontaneous vs induced ventricular tachyarrhythmia). Pacifico also noted the problem of routine late (> 1 year) DFT retesting of non-thoracotomy systems.

Tokano [22] found no significant changes in the mean DFT in the follow-up of a series of patients; however, the DFT increased by 10 J or more after 2 years of follow-up in 15% of the patients [22].

Since a 25% increase in DFT over time may be expected for many systems, even in the absence of anti-arrhythmic therapy or apparent change in cardiac status, a safety margin of 10 J at implantation may not be sufficient. Typically, the goal is a safety margin of 15 J, whenever feasible. This may be even more important for patients who are likely to receive anti-arrhythmic drug therapy. Other clinical implications of DFT stability have been reported. Chronic DFT testing is warranted in patients who receive anti-arrhythmic drug therapy. Most investigators would agree that follow-up testing is indicated, also in patients with a change in cardiac status, such as those with recent infarction or worsening left ventricular function, or the occurrence of ineffective or unexplained defibrillator shocks, marginal DFT at implant,

patients who would have not received an ICD shock or when adequate testing could not be performed at the time of initial implantation [15–18, 20–22].

In addition, Pacifico routinely carried out follow-up DFT testing after adding any new anti-arrhythmic drug [2]. He stressed the importance of follow-up chest X-ray to asses the position and proper function of the implanted electrodes, because migration and dislodgment can affect DFT. There have been many advisories and recalls of defibrillators and leads. It is therefore recommended that all patients, returning for an ICD evaluation with NIPS should be tested in the electrophysiology laboratory to confirm stability of the DFT [2].

DFT in the Pediatric Patient

In pediatric patients, the initial shock is programmed to deliver 20 J and the second is programmed to deliver the maximum output. If 20 J is successful in terminating the arrhythmia, the permanent settings used are set for 30–35 J. If 20 J does not successfully terminate the arrhythmia, the polarity is reversed and DFTs are performed again. If the DFT continues to be > 20 J, the lead is repositioned. If high DFTs persist, a second coil or subcutaneous patch is added. The first choice of coil placement is the innominate vein in most patients, the superior vena cava in larger patients, and the inferior vena cava in patients with transposition of the great arteries. A subcutaneous patch is also used if the veins are too small, stenosed, or thrombosed [7].

Conclusions

The defibrillation threshold should be always tested at implantation. We and others [2, 6, 10] do not agree with the reasoning that, because many patients are likely to be shocked only rarely and then for serious situations, programming maximum energy therapy is appropriate for such patients and DFT testing is not necessary [1].

Traditionally, an implantation safety margin of at least 10 J between the measured DFTs and the maximal output of the pulse generator is considered adequate. Since these safety margins are associated with very low rates of death, due to arrhythmia, in patients with first-generation devices, programming shock strengths to at least 10 J greater than the defibrillation thresholds measured at implantation has become common practice. Results from the *Low Energy Safety Study* (LESS) suggested that a safety margin of

approximately 5 J is adequate with modern ICD systems, employing biphasic waveforms, transvenous lead, and active pectoral pulse generators, when rigorous DFT testing (DFT++) is used.

Thus, traditionally, DFTs are measured only at implantation. This strategy is supported by studies that showed no significant long-term changes of DFT with epicardial lead systems and transvenous lead and biphasic waveforms. However, a minority of patients may show an increase of DFT over time [20-22].

Routine revaluation of DFT is no longer commonly performed [1–3, 15–18, 20–22]. Nonetheless, such testing is still necessary among patients treated with anti-arrhythmic drugs, particularly amiodarone, patients with marginal defibrillation efficacy, at implantation, and patients in whom the initial shock failed to terminate a spontaneous episode of ventricular tachycardia or fibrillation [2, 3], or at ICD substitution [3, 19].

Most investigators would agree that follow-up testing is also indicated in patients with a change in cardiac status, such as recent infarction or worsening LV function, the occurrence of ineffective or unexplained defibrillator shocks, marginal DFT at implant, patients who did not receive an ICD shock or in whom, despite adequate testing, a threshold could not be established at the time of initial implantation [1–3, 15–18, 20–22].

Acknowledgements

We thank Leilei Sun for preparing the manuscript. We thank Elena Cuomo and Elena Seragnoli of the Knowledge Management department of the Maggiore Hospital library of the Azienda of USL di Bologna, Bologna, Italy.

References

1. Kenny T (2006) The nuts and bolts of ICD therapy. Blackwell Futura, Oxford, pp 26–36
2. Pacifico A et al (2002) Implantable defibrillator therapy: a clinical guide. Kluwer, The Netherlands, pp 113–145
3. Ellenbogen KA, Wood MA (2005) Cardiac pacing and ICD, 4th edn. Blackwell, Oxford, pp 387–394
4. Singer I, Lang D (1996) The defibrillation threshold. In: Knoll MW, Lehmann MH (eds) Implantable cardioverter defibrillator therapy. The engineering clinical interface Norwell. Kluwer Academic, The Netherlands, pp 89–129
5. Shorofsky SR, Peters RW, Rashba EJ, Gold MR (2004) Comparison of step-down and binary search algorithms for determination of defibrillation threshold in humans. Pacing Clin Electrophysiol 27:218–220
6. Malkin RA, Herre JM, McGowen L et al (1999) A four-shock Bayesian up-down estimator of the 80% effective defibrillation dose. J Cardiovasc Electrophysiol 10:973–980

7. Zeigler VL et al (2001) Implantable cardioverter defibrillators. In: Zeigler VL, Gillette PC (eds) Practical management of pediatric cardiac arrhythmias. Futura, Armonk, NY, pp 350, 359, 409
8. Swerdlow CD (2001) Implantation of cardioverter defibrillators without induction of ventricular fibrillation. Circulation 103:2159–2164
9. Feder (2007) FDA panel unimpressed by heart device. The New York Times 3/2–2007 (also see Corbett–Dooren The Wall Street Journal 3/2–2007)
10. Guo JH (2006) Critical comments on: Kenny T (2006) The nuts and bolts of ICD therapy. Blackwell Futura, Armonk, NY, pp 26–27
11. Shorofsky SR, Gold MR (1996) Effects of waveform and polarity on defibrillation thresholds in humans, using a transveous lead system. Am J Cardiol 78:313–316
12. Olsovsky MR, Shorofsky SR, Gold MR (1998) Effect of shock polarity on biphasic defibrillation thresholds using an active pectoral lead system. J Cardiovasc Electrophysiol 9:350–354
13. Bardy GH, Johnson G, Poole JE et al (1993) A simplified, single-lead unipolar transvenous cardioversion-defibrillation system. Circulation 88:543–547
14. Gold MR, Foster AH, Shorofsky SR (1996) Effects of an active pectoral-pulse generator shell of defibrillation efficacy with a transvenous lead system. Am J Cardiol 78:540–543
15. Gold MR, Olsovsky MR, Pelini MA et al (1998) Comparison of single- and dual-coil active pectoral defibrillation lead systems. J Am Coll Cardiol 31:1391–1394
16. Higgins SL, Alexander DC, Kuypers CJ, Brewster SA (1995) The subcutaneous array: a new lead adjunct for the transvenous ICD to lower defibrillation thresholds. Pacing Clin Electrophysiol 18:1540–1548
17. Epstein AE, Ellenbogen KA, Kirk KA et al (1992) Clinical characteristics and out come of patients with high defibrillation thresholds: a multicenter study. Circulation 86:1206–1216
18. Gold MR, Higgins S, Klein R et al (2002) Efficacy and temporal stability of reduced safety margins for ventricular defibrillation. Primary results from the Low Energy Safety Study (LESS) Circulation 105:2043–2048
19. Iachetti F, Naccarella F, Naccarelli G et al (2007) Remote monitoring systems of implanted devices: critical evaluation in US, Europe and Italy. MESPE Journal (in press)
20. Raitt MH, Johnson G, Dolack GL et al (1995) Clinical predictors of the defibrillation threshold with unipolar implantable defibrillation system. J Am Coll Cardiol 25:1576–1583
21. Hodgson DM, Olsovsky MR, Shorofsky SR et al (2002) Clinical predictors of the defibrillation thresholds with an active pectoral pulse generator lead system. Pacing Clin Electrophysiol 25:408–413
22. Tokano T, Pelosi F, Flemming M et al (1998) Long-term evaluation of the ventricular defibrillation energy requirement. J Cardiovasc Electrophysiol 9:916–920

Current Practice in Italy of VF Testing at Implant: What Do We Know and Where Do We Go From Here?

Michele Brignole[1], Giovanni Raciti[2], Maria Grazia Bongiorni[3], Giuseppe De Martino[4], Stefano Favale[5], Maurizio Gasparini[6], Raffaele Luise[7], Eraldo Occhetta[8], Alessandro Proclemer[9]

What Do We Know?

The standardized requirements for cardioverter defibrillator (ICD) implantation, with or without cardiac resynchronization therapy (CRT), include defibrillation testing (DT), which consists of the induction and termination of ventricular fibrillation (VF). This procedure has been followed from the early days of ICD therapy in order to assess the reliability of an implanted ICD device and to measure the defibrillation threshold. Effective DT is considered mandatory in accordance with the rules of good clinical practice.

Nowadays, since the implantation procedure for ICDs has become markedly simplified and the surgical risk is very low, DT can be considered to be the most critical part of the implantation procedure itself. Although the risk associated with DT is usually low, serious complications may nonetheless occur as a consequence of this practice. Complications include transient ischemic attack or stroke, cardiopulmonary arrest due to refractory VF or pulseless electrical activity, cardiogenic shock, embolic events, and death. This knowledge comes from small single-center retrospective surveys [1] and from anecdotal experience. However, in the absence of data from large populations enrolled in multi-center registries, the real magnitude of intra-operative complications related to DT is still largely unknown.

Although the standardized approach to ICD implantation still includes a VF induction test, data coming from real-world experience suggest that an increasing number of first-implantation procedures are performed without

[1]Department of Cardiology, Ospedali del Tigullio, Lavagna (GE); [2]Boston Scientific Italy, Milan; [3]Ospedale Cisanello, Pisa; [4]Casa di Cura Santa Maria, Bari; [5]Ospedale Consorziale Policlinico, Bari; [6]Istituto Clinico Humanitas, Rozzano(MI); [7]Casa di Cura Villa Pini d'Abruzzo, Chieti; [8]Ospedale Maggiore della Carità, Novara; [9]Azienda Ospedaliero-Universitaria, Fondazione IRCAB, Udine, Italy

any induction test. It seems that some physicians are concerned about practicing DT in patients considered to be at very high clinical risk. For example, in two single-center populations, Russo et al. [2] reported a lack of induction testing in 4.7% and Pires et al. [3] in 24% of patients. The reasons for omitting induction testing included intraoperative hypotension or hemodynamic instability, known cavity thrombus or previous inadequate anticoagulation therapy, recent cardiovascular accident, severe comorbidities, and the absence of anesthesia support.

The *Associazione Italiana di Aritmologia e Cardiostimolazione* (AIAC) recently conducted a systematic nation-wide retrospective survey to determine how often and for what reason intra-operative DT was or was not performed, and the complication rate related to induction testing.

An ad-hoc questionnaire was sent to 343 centers implanting ICDs (listed in the database of the Italian ICD Registry of the AIAC), which essentially represents all of Italy's implanting centers. The ICD implantation data collected by the Italian ICD Registry of the AIAC is formatted according to the recommendations of the European ICD Registry (EURID).

The survey was limited to patients undergoing initial ICD implantation during the year 2005. Questionnaire and data collection were carried out through the World Wide Web from June to October 2006. Participating centers were asked to communicate their data regarding the total number of ICDs (including those with CRT features), number of implantations in which DT was performed intraoperatively or before discharge, and number and type of DT-related complications. DT was defined as at least one induction of VF. DT-related complications were considered those life-threatening events occurring immediately after VF induction.

Of the 8,820 first ICD/CRTs implanted in Italy during 2005, data on 7,857 (89%) implantations (38% of whom CRT) performed in the 229 centers that participated in the survey were analyzed. Of these, 2,356 (30%) implantations did not include an induction test (Table 1). In 35 (15%) centers, an induction test was administered in < 25% of the patients, while in 136 (59%) centers it was done in > 75% of the patients. In a multivariable analysis of a subset of 1,206 patients from 107 centers, CRT device (OR 1.82) and primary prevention (OR 1.47) were independent predictors of the decision to not administer DT. However, all together, clinical variables accounted only for 35% of the total variance, and the remaining 65% was probably unrelated to clinical factors (Table 2). Life-threatening complications as a consequence of the induction test were reported in 22 (0.4%) patients: four deaths (0.07%), eight cardiopulmonary arrests requiring resuscitation maneuvers (0.15%), six cases of cardiogenic shock (0.11%), three strokes (0.05%), and one pul-

Table 1. Principal findings

Centers invited to participate	343 (%)
Centers that participated	229 (67)
Total number of first-implant procedures	7,857
With intraoperative defibrillation test	5,501 (70)
Without intraoperative defibrillation test	2,356 (30)
Total number of complications related to defibrillation test	22 (0.4)
Death	4 (0.07)
Cardiopulmonary arrest requiring resuscitation	8 (0.15)
Cardiogenic shock	6 (0.11)
Stroke	3 (0.05)
Pulmonary embolism	1 (0.02)

Table 2. Univariable and multivariable predictors of the decision to not perform the induction test in a subset of 1,206 patients

Factors	**Percent**	**Univariable Odds ratio (95% CI)**	***p***	**Multivariable Odds ratio (95% CI)**	***p***
Age (70	43	1. 31(1.03–0.67)	0.03	1.29 (0.99–1.67)	0.06
Male gender	87	1.22 (0.86–1.72)	0.25	–[a]	–
CRT device	19	2.01 (1.50–2.68)	< 0.001	1.81 (1.30–2.53)	< 0.001
Primary prevention	45	1.65 (1.30–2.09)	< 0.001	1.50 (1.14–1.97)	0.003
Ejection fraction (30%	51	1.68 (1.30–2.16)	< 0.001	1.30 (0.97–1.72)	0.07
Dilated vs ischemic	47	1.42 (1.12–1.80)	0.004	–[b]	–
NYHA class > 2	23	1. 96 (1.46–2.63)	< 0.001	–[b]	–

[a]Male gender was not analyzed in the multivariate model because it was not significant in the univariable analysis
[b]Dilated vs ischemic and NYHA class were not inserted in the multivariable model as these resulted were covered by the parameter CRT device
CRT, Cardiac resynchronization therapy; *NYHA*, New York Heart Association

monary embolism (0.02%). Failure of an ICD defibrillation test, and thus the need for a backup external defibrillator, was 2.7%, which determined a system revision (i.e., additional lead insertion, etc.) in 2.3% of patients.

This nation-wide survey was the largest ever performed and covered 89% of the overall first-implantations in Italy during 2005. The main finding was that, in real-world clinical practice, DT was not administered in 30% of

patients, and in most of these cases there was no legitimate reason for the omission. Nonetheless, DT is still considered part of the standard procedure of ICD implantation. There was wide heterogeneity between centers and more than a quarter of Italian centers did not administer DT in ≥ 50% of their patients. These figures, which were much higher than those expected from the literature [2, 4], not only reflect the spontaneous non-conformist opinions of several physicians they also go beyond the current recommendations of ICD manufacturers. Given the large number of physicians who do not include DT during ICD implantation, the decision requires explanation and merits specific actions in response.

One explanation for the limited use of DT is the increasing role of primary prevention strategies [5, 6], which address patients with very low ejection fraction and advanced NYHA class [7]. The selection of sick patients due to expanded ICD indications was recently confirmed in a comparison of USA and Italian practices [8]. However, all together, the clinical variables accounted only for 35% of the total variance whereas the remaining 65% was probably unrelated to clinical factors. Therefore, the main reasons for the violation of current standards in so many patients seem to be, on the one hand, the concern for severe complications related to intraoperative DT and, on the other, the conviction of a small risk of death due to failure of the ICD to interrupt VF during long-term follow-up.

In the Italian survey study, the DT-related life-threatening complication rate was not negligible, accounting for 0.40% of cases, considering that DT in the analyzed cohort of patients was preferably administered to less sick patients (Table 2). The complication rate might have been even higher if the patients with severe heart failure and very low ejection fraction were not preventively excluded from undergoing DT. In the literature, there are a few reports based on small studies concerning intraoperative complications. A report [1] on 440 consecutive single-center ICD implantations showed 0.2% perioperative deaths, 0.5% difficulty in defibrillation with requirements for more than three external shocks, and 0.7% perioperative ischemic attack. In another single-center study [2], consisting of 835 ICD implantations, there were three (0.35%) perioperative deaths (within 30 days of implant). It has been reported that shocks during DT may cause hemodynamic compromise [9], especially in patients with severe heart failure, as are candidates for CRT. Moreover, anesthesia has a cardiac-depressive effect in the presence of VF induction [10]. The clinical conditions of patients undergoing implantation may be worse but might improve later with CRT, thus decreasing the risk of complications related to DT. For example, a DT delayed up to 2 months after

CRT device implant, when the patient's clinical condition has improved due to CRT, showed effectiveness without compromising safety [11].

Few data are available on the risk of death due to the failure of the ICD to interrupt a VF during long-term follow-up. Sudden death in patients with ICD is reported to range from 1.8 to 2.6% during 1–3 years of follow-up [12–14]. Analysis of the mechanisms of sudden death, with data retrieved from ICD diagnostic memory, showed that only a quarter of the above-mentioned cases could be attributed to shock failure during VF [13]. Therefore, it can be assumed that the sudden death rate potentially attributable to shock failure ranged from 0.45 to 0.65% during 1–3 years of follow up. This percentage is very similar to the percentage of intra-operative deaths following VF induction during implantation. There are no data that specifically demonstrate increased mortality among patients with high DT thresholds at implant. In a recent study [3], both the success of ICD therapy and sudden-death-free survival were similar in patients who had defibrillation threshold measurement, safety margin testing, or no testing.

Where Do We Go from Here?

Is it time to change the current standard of performing DT at the time of ICD implantation? The question has been previously raised by several experienced clinicians [2–4, 14, 15]. However, there is no evidence-based answer yet. The reasons for and against DT are summarized in Table 3. The clinical impact of DT vs. no DT will remain unclear until the not-negligible intraoperative complication rate is weighted against the long-term potential benefit of DT. Long-term follow-up data regarding the safety and efficacy of ICD implantation in large groups of patients in whom DT is not performed are needed. Until this information becomes available, DT should be considered as a standard practice. Data from the literature and from the present study support the need to carry out large multicenter studies and emphasize the urgent need for precise recommendations from the relevant clinical specialties.

Acknowledgements
The study was officially approved by the National Board (M. Brignole, N. Bottoni, A. Campana, A. Curnis, M. Di Biase, E. Feraco, M. Gulizia, R. Pedretti, M. Santini, M. Tritto, R. Verlato), endorsed by the AIAC (Associazione Italiana di Aritmologia e Cardiostimolazione), and supported by a grant from Guidant-Boston Scientific Corporation.

Table 3. Advantages and disadvantages of performing DT at the time of implant

Reasons in favor of induction	Reasons in favor of noninduction
• Standard practice for ICD implant • Most device safety studies required DT at implant • DT allows the choice of corrective measures at implant in case of high threshold • DT ensures that the system provides appropriate sensing of VF • DT may include the defibrillation threshold evaluation for better ICD programming	• No data specifically demonstrate increased mortality among patients with high DT thresholds • A quite small probability of a high threshold and a failed implant with current technology • The nature of the defibrillation threshold is probabilistic and repeated shocks below threshold can be effective • The shocks may cause hemodynamic compromise • The cardiac depressive effect of anesthesia in addition to VF induction • In the great majority of patients receiving an ICD, the initial spontaneous life-threatening arrhythmia is VT and not VF; thus, a DT at implant imposes an additional risk that most patients would not otherwise have in their lives • Patients at implant may have worse clinical conditions that could improve later with CRT, thus decreasing the risk of complications related to DT • In one retrospective analysis, success of ICD therapies and sudden-death-free survival were similar in patients who had defibrillation threshold testing, safety margin testing, and no testing

ICD, Cardioverter defibrillator; *DT*, defibrillation testing; *VT*, ventricular tachycardia; *VF*, ventricular fibrillation; *CRT*, cardiac resynchronization therapy

References

1. Alter P, Waldhans S, Plachta E et al (2005) Complications of implantable cardioverter defibrillator therapy in 440 consecutive patients. Pacing Clin Electrophysiol 28:926–932
2. Russo AM, Sauer W, Gerstenfeld EP et al (2005) Defibrillation threshold testing: is it really necessary at the time of implantable cardioverter-defibrillator insertion? Heart Rhythm 2:456–461
3. Pires LA, Johnson KM (2006) Intraoperative testing of the implantable cardioverter-defibrillator: how much is enough? J Cardiovasc Electrophysiol 17:140–145
4. Strickberger SA, Klein GJ (2004) Is defibrillation testing required for defibrillator implantation? J Am Coll Cardiol 44:88–91

5. Ezekowitz JA, Armstrong PW, McAlister FA (2003) Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials. Ann Intern Med 138:445–452
6. Sweeney MO, Schoenfeld MH, Cannom DS (2005) Rules of evidence: CMS and primary prevention of sudden cardiac death in systolic heart failure. Pacing Clin Electrophysiol 28:81–88
7. Proclemer A, Ghidina M, Cicuttini G et al (2006) Impact of the main implantable cardioverter-defibrillator trials for primary and secondary prevention in Italy. A survey of the national activity during the years 2001–2004. Pacing Clin Electrophysiol 29(Suppl 2):S20-S28
8. Greenberg SM, Epstein AE, Deering T et al (2007) Differences in international ICD implantation rates: comparison of US and Italian practice. Pacing Clin Electrophysiol (in press)
9. Tokano T, Bach D, Chang J et al (1998) Effect of ventricular shock strength on cardiac hemodynamics. J Cardiovasc Electrophysiol 9:791–797
10. Gilbert TB, Gold MR, Shorofsky SR et al (2002) Cardiovascular responses to repetitive defibrillation during implantable cardioverter-defibrillator testing. J Cardiothorac Vasc Anesth 16:180–185
11. Gasparini M, Galimberti P, Regoli F et al (2005) Delayed defibrillation testing in patients implanted with biventricular ICD (CRT-D): a reliable and safe approach. J Cardiovasc Electrophysiol 16:1279–1283
12. Fiek M, Zieg B, Matis T et al (2006) Analysis of the cause of death of ICD patients during long-term follow-up. Herzschrittmacherther Elektrophysiol 17:6–12
13. Mitchell LB, Pineda EA, Titus JL et al (2002) Sudden death in patients with implantable cardioverter defibrillators: the importance of post-shock electromechanical dissociation. J Am Coll Cardiol 39:1323–1328
14. Neuzner (2005) Is DFT testing still mandatory? Herz 30:601–606
15. Favale S (2005) Test di defibrillazione durante l'impianto di defibrillatore automatico: è ancora necessario? G Ital Aritmol Cardiostim 2:73–77

How To Choose Between Single-Chamber and Dual-Chamber ICD

Maurizio Del Greco, Lorena Gramegna, Massimiliano Marini, Marcello Disertori

Introduction

Patients in whom an implantable cardioverter defibrillator (ICD) is indicated and who have concomitant significant sinus-node disease or atrioventricular block may be candidates for a dual-chamber device. However, it is still a matter of debate whether the dual-chamber ICD is also advantageous for patients with preserved sinus and atrioventricular nodal function, as data from prospective randomized trials are limited. Overall, the number of implanted dual-chamber devices has been increasing and, according to the 2003 AIAC Registry data, accounted for one-third of all the defibrillators implanted in Italy, while single chamber devices made up 39%. The theoretical advantages of dual-chamber ICDs are: better supraventricular tachycardia (SVT) discrimination, optimal treatment of bradyarrhythmias (pre-existing or drug induced), and major hemodynamic benefits.

SVT Discrimination

The performance of the SVT discrimination algorithm performance in dual-chamber devices is still under debate. So-called third-generation algorithms, such as Sudden Onset, Stability, and QRS morphology, have increased the performance of single chamber ICDs [1, 2]. However, the weakness of these "advanced" algorithms is the risk of less sensitivity in detecting actual ventricular tachycardia when they are programmed to obtain a higher specificity [3].

Electrophysiology Laboratory, Cardiology Department, S. Chiara Hospital, Trento, Italy

The distinctive feature of dual-chamber devices is their capability of sensing and analyzing atrial rhythm and comparing it with ventricular rhythm during hearth high rates. Clinical trials demonstrated that dual-chamber devices had a specificity of 80–90% while maintaining 100% sensibility [4–6]. However dual-chamber algorithms can lead to inappropriate detections and therapies due to the fact that some arrhythmias are difficult to interpret. Overall, the most difficult rhythms to detect are the 1:1 atrial flutter and junctional arrhythmia. Since dual-chamber discrimination algorithms rely on information from the atrial lead, final placement of this lead is crucial. Clinical studies [7, 8] have not demonstrated significant differences between single- and dual-chamber devices when the number of inappropriate therapies was compared. A more detailed data analysis revealed that in patients with dual-chamber devices, 75% of the inappropriate therapies were due to atrial oversensing or undersensing. This again stresses the primary role of the atrial lead and the need to carefully position it in order to get both good atrial sensing and accurate ventricular far-field discrimination. The importance of the atrial lead position is greater in ICDs than in pacemakers since the filters used in defibrillators allow continuous and accurate monitoring only if blanking periods are short or even absent. This might lead to inappropriate detection, in particular when the amplitude of a sensed P-wave is very low, e.g., during atrial fibrillation (AF) or when ventricular far-field could not be correctly detected.

Recently, the rate of inappropriate detection of SVT was evaluated in the multicenter *Detect Supraventricular Tachycardia Study* [9], which enrolled patients with clinical indications for ICD. The study subjects were randomly assigned to receive either a single-chamber ICD or dual-chamber ICD ("last generation"). In this study, the odds of inappropriate detection decreased by almost half with use of dual-chamber detection enhancement. It is worth nothing that this result was also obtained when the device was programmed in order to minimize unnecessary ventricular pacing.

Hemodynamic Benefits

An emerging issue when choosing the best device to implant is often the latter's impact on the patient's hemodynamics parameters. It was shown that, in sinus-node-disease patients or in patients with AV conduction disease, sequential AV pacing with optimized AV delays could yield hemodynamic benefits and improve clinical outcome, especially in heart-failure patients [10, 11].

It was also demonstrated that asynchronous ventricular activation provoked by right ventricular apical pacing, may lead to a deterioration of

ventricular performance [12]. The DAVID [13] (*Dual Chamber and VVI Implantable Defibrillator*) study compared the efficacy of dual-chamber pacing with backup VVI pacing in patients indicated for ICD therapy, with no pacing indication and left ventricle ejection fraction < 40%. The study endpoint was a combined endpoint of death or first hospitalization due to heart failure. The study was prematurely discontinued because there were fewer events in the VVI arm (survival rate 83.9% vs 73.3% at 1 year, $p \leq 0.03$).

The deleterious effects of apical right ventricular pacing were conclusively shown in a recent long term follow-up study (53 months) in which 100 ICD patients were enrolled [14]. The results demonstrated that in ICD recipients without conventional indications for dual-chamber pacing, dual chamber had no advantage over single-chamber ICD with respect to mortality and arrhythmogenic morbidity in a long-term follow-up. However, a subgroup analysis in which 35% of ventricular-paced beats served as the cutoff value in the dual-chamber ICD group revealed a 42% mortality rate for patients with frequent ventricular pacing compared to 10% of patients with a low rate of ventricular pacing ($p = 0.05$, relative risk 4.21).

Furthermore, left ventricular ejection fraction was impaired to a greater extent in patients with dual-chamber ICD than in patients with single-chamber ICD [15].

In conclusion, prolonged right ventricular pacing, as a consequence of DDD stimulation, with subsequent impairment of left ventricular function highlights the positive effects of AV synchronization and negatively affects prognosis in the ICD patient population. Implementation of an algorithm that reduced unnecessary ventricular pacing (in patients with preserved AV conduction) could minimize these negative effects of DDD stimulation [16].

Atrial Fibrillation in ICD Patients

Dual-chamber defibrillators might provide a clinical benefit to patients with AF, when atrial prevention algorithms and early treatment of AF are considered. Patients who are indicated for ICDs have a higher incidence of AF, ranging from 5% to slightly less than 50% depending on the NYHA class [17]. AF could lead to inappropriate shocks [17], induce ventricular arrhythmias [18], worsen hemodynamic status, and be associated with a higher risk of embolism. AF in ICD patients is associated with a worse clinical outcome [19–21].

Anti-tachycardia features, such as overdrive pacing or atrial anti-tachycardia pacing therapies (ATPs), available in some of dual-chamber devices, were demonstrated to be effective in preventing and terminating atrial

arrhythmias and reduced the clinical impact of such arrhythmias [22, 23]. Atrial shock, either automatic or manually delivered (with an external activator), could be used in selected patients in whom the onset of atrial fibrillation causes rapid clinical worsening.

Conclusions

A dual-chamber ICD is indicated in patients with significant sinus-node disease or atrioventricular block. In patients with preserved sinus and atrioventricular nodal function, this approach should be considered only when a previous history of AF or a high risk of AF is present. However, accurate implantation of the atrial lead and programming of the device are necessary to reduce the inappropriate-therapy rate.

Finally, in patients with left ventricular dysfunction, the use of dual-chamber ICD should be associated with alternative pacing sites or biventricular pacing.

References

1. Barold HS, Newby KH, Tomassoni G et al (1998) Prospective evaluation of new and old criteria to discriminate between supraventricular and ventricular tachycardia in implantable defibrillators. Pacing Clin Electrophysiol 21:1347–1355
2. Swerdlow CD, Chen PS, Kass RM et al (1994) Discrimination of ventricular tachycardia from sinus tachycardia and atrial fibrillation in a tiered-therapy cardioverter defibrillator. J Am Coll Cardiol 23:1342–1355
3. Neuzner J, Pitschner HF, Schlepper (1995) Programmable VT detection enhancements in implantable cardioverter defibrillator therapy. Pacing Clin Electrophysiol 18:539–547
4. Sadoul N, Jung W, Jordaens L et al (2002) Diagnostic performance of a dual-chamber cardioverter defibrillator programmed with nominal settings: a European prospective study. J Cardiovasc Electrophysiol 13:25–32
5. Wilkoff BL, Kuhlkamp V, Volosin K et al (2001) Critical analysis of dual chamber implantable cardioverter defibrillator arrhythmia detection. Results and technical considerations. Circulation 103:381–386
6. Korte T, Jung W, Wolpert C et al (1998) A new classification algorithm for discrimination of ventricular from supraventricular tachycardia in a dual chamber implantable cardioverter defibrillator. J Cardiovasc Electrophysiol 9:70–73
7. Hintringer F, Schwarzacher S, Eibl G, Pachinger O (2001) Inappropriate detection of supraventricular arrhythmias by implantable dual chamber defibrillators: a comparison of four different algorithms. Pacing Clin Electrophysiol 24:835–841
8. Deisenhofer I, Kolb C, Ndrepepa G et al (2001 Do current dual chamber cardioverter defibrillators have advantages over conventional single chamber cardioverter defibrillator in reducing inappropriate therapies? A randomized, prospective study. J Cardiovasc Electrophysiol 12:134–142

9. Friedman PA, McClelland RL, Bamlet WR et al (2006) Dual-chamber versus single-chamber detection enhancements for implantable defibrillator rhythm diagnosis: the detect supraventricular tachycardia study. Circulation 113:2871–289
10. Hesselson AB, Parsonnet V, Bernstein AD, Bonavita GJ (1992) Deleterious effect of long-term single-chamber ventricular pacing in patients with sick sinus syndrome: the hidden benefits of dual-chamber pacing. J Am Coll Cardiol 19:1542–1549
11. Frielingsdorf J, Deseo T, Gerber AE, Bertel O (1996) A comparison of quality-of-life in patients with dual chamber pacemakers and individually programmed atrioventricular delays. Pacing Clin Electrophysiol 19:1147–1154
12. Harper GR, Pina IL, Kutalek SP (1991) Intrinsic conduction maximizes cardiopulmonary performance in patients with dual chamber pacemakers. Pacing Clin Electrophysiol 14:1787–1791
13. Wilkoff BL, Cook JR, Epstein AE et al (2002) The DAVID Trial Investigators: dual chamber pacing or ventricular backup pacing in patients with an implantable defibrillator. The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial. JAMA 288:3115–3123
14. Kolb C, Deisenhofer I, Schmieder S et al (2006) Long-term follow-up of patients supplied with single-chamber or dual-chamber cardioverter defibrillators. Pacing Clin Electrophysiol 29:946–952
15. Sukhija R, Aronow WS, Sorbera C et al (2005) Left ventricular ejection fraction and prevalence of new left ventricular wall motion abnormality at long-term follow-up in patients with automatic implantable cardioverter-defibrillators treated with dual-chamber rate-responsive pacing at a rate of 70/minute versus backup ventricular pacing at a rate of 40/minute. Am J Cardiol 96:412–413
16. Sweeney MO, Ellenbogen KA, Miller EH et al (2006) The Managed Ventricular pacing versus VVI 40 Pacing (MVP) Trial: clinical background, rationale, design, and implementation. J Cardiovasc Electrophysiol 17:1295–1298
17. Schmitt C, Montero M, Melichercik J (1998) Significance of supraventricular tachyarrhythmias in patients with implanted pacing cardioverter defibrillators. Pacing Clin Electrophysiol 17:295–302
18. Grimm W, Flores BF, Marchlinski FE (1992) Electrocardiographically documented unnecessary, spontaneous shocks in 241 patients with implantable cardioverter defibrillators. Pacing Clin Electrophysiol 15:1667–1673
19. Marchlinski FE, Callans DJ, Gottlieb CD et al (1995) Benefits and lessons learned from stored electrogram information in implantable defibrillators. J Cardiovasc Electrophysiol 6:832–851
20. Pinski SL, Yao Q, Epstein AE et al (2000 Determinants of outcome in patients with sustained ventricular tachyarrhythmias: the antiarrhythmic versus implantable defibrillators (AVID) study registry. Am Heart J 139:804–813
21. Wolf PA, Mitchell JB, Baker CS et al (1998) Impact of atrial fibrillation on mortality, stroke and medical costs. Arch Intern Med 158:229–234
22. Ricci R, Pignalberi C, Disertori M et al (2002) Efficacy of a dual chamber defibrillator with atrial antitachycardia functions in treating spontaneous atrial tachyarrhythmias in patients with life-threatening ventricular tachyarrhythmias. Eur Heart J 23:1471–1479
23. Friedman PA, Dijkman B, Warman EN et al for the Worldwide Jewel AF Investigators (2001) Atrial therapies reduce atrial arrhythmia burden in defibrillator patients. Circulation 104:1023–1028

Which Patients Should Receive Dual Defibrillators? Results of DATAS

Aurelio Quesada, Mónica Giménez, Victor Palanca, Javier Jiménez, Alfonso Valle, José Roda

Introduction

The dual-chamber (DC) implantable cardioverter defibrillator (ICD) was primarily introduced in the market to add atrial-based pacing for those patients simultaneously affecting by bradycardia and fatal ventricular arrhythmias. Following the successful introduction of the original VVED ICDs, device capabilities were rapidly expanded by the addition of AV discrimination and atrial anti-tachycardia therapies (DDED ICDs). It was suggested that these sophisticated devices would overcome the limitations of the single chamber (SC) devices and that their recommended use would be extended.

However, some cardiologists and institutions remained concerned whether the higher costs and complexity of DC ICD could be justified in terms of real improvement in clinical outcome, and preferred SC ICDs as the initial option for the majority of candidate patients. In truth, to prevent sudden cardiac death from ventricular tachyarrhythmias, which is the primary mission of a defibrillator, a SC ICD seems sufficient, and most trials focused on the use of ICDs have been conducted using these devices, including conservative studies that used shock-only ICDs (SCD-HeFT) [1–3].

However, physicians involved daily in ICD follow up are aware that a non-negligible number of patients with these devices frequently require atrial pacing and develop atrial tachyarrhythmias that can influence clinical outcome by inducing inappropriate shocks, requiring hospitalization due to heart failure and stroke, and even resulting in increased mortality. Moreover, the task of differentiating a supraventricular from ventricular origin of the

Cardiac Electrophysiology and Arrhythmias Section, Department of Cardiology, Hospital General Universitario de Valencia, Valencia, Spain

episodes in stored electrograms when only the ventricular channel is available can become very difficult if not impossible.

Nevertheless, these theoretical benefits of the widely-used DC ICDs have been questioned for several reasons, among them the higher cost and possible complications. Moreover, the possibility of deterioration in left ventricular systolic function, with an increase in hospitalizations and mortality, has become evident in the last several years. The DAVID study [4], which tried to assess the superiority of DC over SC ICDs, was prematurely interrupted after detecting a worsened outcome in the DC group. This was largely attributed to the unintended adverse effects on left ventricular structure and function of a high percentage of the right ventricular cumulative pacing, associated with non-controlled AV interval programming.

The *Dual Chamber & Atrial Tachyarrhythmias Adverse Events Study* (DATAS) was designed to study the ability of DC ICDs to better reduce clinically significant adverse event compared to SC ICD in a non-selected population with conventional indications for ICDs [5]. DC ICD was intended as a device able to offer atrial-based pacing, AV discrimination, and electrical therapies for both atrial and ventricular tachyarrhythmias (DDED in the NASPE/BPEG Defibrillation Code) [6]. In spite of the recommendation for atrial-based stimulation, special care was taken to prevent unnecessary ventricular pacing by prolonging AV interval programming.

How Does Dual-Chamber ICD Improve Outcome?

Obviously, atrial-based pacing for correction of bradycardias not present at the time of implant could constitute an important benefit, especially in the treatment of drug-induced disturbances. Except for ACE inhibitors or angiotensin II receptor blockers (ARBs), those treatments that demonstrate a reduction in mortality and improved symptoms and quality of life, i.e. beta-blockers and sotalol [7, 8], are able to deteriorate sinus and AV node functions, as can amiodarone. For example, 70% of the MADIT II patients were under beta-blocker therapy [9]. In clinical practice, beta-blocker therapy should be withdrawn in 15% of patients, even more in the case of those with bradycardia.

Atrial pacing can favorably impact such patients by acting synergistically with drugs, not only preventing pauses, but providing adequate exercise rate response. Melzer et al. reported a prevalence of chronotropic incompetence > 38% in 123 ICD patients. Chronic anti-arrhythmic therapy with beta-blockers and amiodarone, particularly a combination of the two, was associated with a higher occurrence of the condition [10].

Atrial tachyarrhythmias are very prevalent in ICD recipients, resulting in inappropriate therapies [11]. However, if atrial tachyarrhythmias are considered only as a source of inappropriate shocks, then this is probably an oversimplification of the case. Atrial tachyarrhythmias can induce or worsen heart failure or stroke, and AF is an independent factor of increased mortality. AF after myocardial infarction independently predicted death in the GUSTO-III trial [12]. Furthermore, a retrospective analysis of the Studies of Left Ventricular Dysfunction Prevention and Treatment trials [13] showed that patients with AF at baseline, compared to those in sinus rhythm, had greater and significant all-cause mortality (34 vs 23%), death attributed to pump failure (16.7 vs 9.4%), and were more likely to reach the composite end-point of death or hospitalization for heart failure (45 vs 33%); but there was no significant difference between the groups regarding arrhythmia-induced deaths. Also, the European GEM DR evaluation study detected a higher early mortality of patients with ICDs compared to patients with episodes of AF [14].

By definition, the DC ICD is a unique device with atrial electrical therapy capabilities, i.e., anti-tachycardia pacing, and atrial shocks. A high efficiency in the treatment of atrial tachyarrhythmias has been shown with either of the two components. The efficacy of atrial anti-tachycardia pacing ranges from 55 to 66% and the adjusted success rate of atrial shock for atrial fibrillation is > 60% [15, 16]. The administration of atrial electrical therapy decreases AF burden and the number of episodes [17, 18]. Significantly, at least in the group of patients with drug-refractory AF, the efficacy of atrial electrical therapy seems to have clinical repercussions, with a reduction in the number of hospitalizations and cardioversions [19].

Although the so-called additional criteria offered by SC devices can achieve acceptable results in certain patients, the difficulty in achieving a balance between sensitivity and specificity remains their most important limitation. For example, in SC ICDs the use of the sudden onset and stability alone may yield a specificity as high as 96% for rejecting sinus tachycardia and AF at ventricular rates < 180–190 bpm [20, 21]. At higher rates, because of regularization of ventricular activation, the specificity for AF using ventricular interval stability alone declines significantly. At higher rates, because of normalization of ventricular activation, the specificity for AF using ventricular interval stability alone declines significantly. Further improvements come at a high price, i.e., an unacceptable reduction in sensitivity for the detection of true ventricular arrhythmias (to 80–90%). The addition of an atrial signal can enhance detection performance. Although some studies have not found improved discrimination with such algorithm types [22], a specificity of 85.8%, sensitivity of 100%, and a positive predictive value of

95.2% with the second version of the PR Logic (Medtronic) were recently reported [23].

It must be stressed that recognition of dual tachycardias (a condition not rare in ICD recipients) is not possible without atrial electrograms [24] (Fig. 1). The distinction is meaningful because it has been suggested that dual tachycardia episodes in which ventricular therapy stops only the ventricular arrhythmia but not the AF promote earlier recurrences than when both tachycardias are therapeutically suppressed (AF begets VT/VF) [25]. In virtually all such episodes, information from the atrial chamber allows proper interpretation of detection and therapy outcome, avoiding speculative diagnoses of many of them. Significant changes in patient treatment and management could be introduced from this more accurate information.

The above-described benefits are assumed to be associated with a low rate of complications with respect to implant procedure, system performance

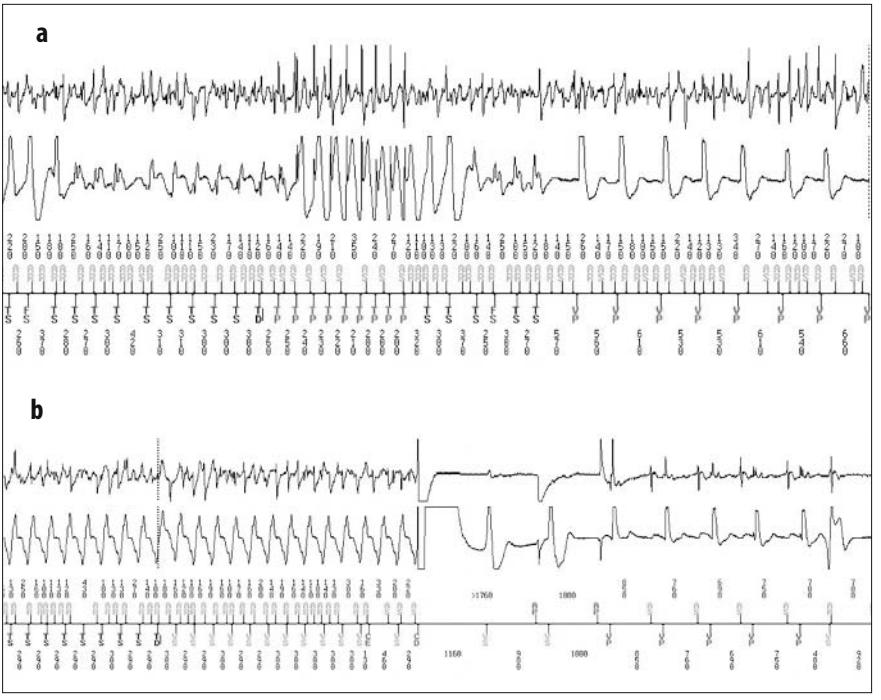


Fig. 1. Dual tachycardia. **a** Ventricular tachycardia during an episode of atrial fibrillation treated with unsuccessful antitachycardia pacing. **b** The shock administered for the ventricular tachycardia suppresses both arrhythmias and restore synus rhythm. The data are arranged as an atrial electrogram (A-tip to A-ring), HVA-RV coil electrogram, PP interval values, atrial and ventricle marker channel, and RR interval values (25 mm/s chart speed). The correct diagnosis is not possible without information from the atrial channels

during follow-up, and avoidance of the previously unsuspected deleterious effects of right ventricular pacing. Complications reported in the evaluation of DC devices are few and their rates are closed to those reported for SC ICDs; the actuarial estimates of 6-month complication-free survival and total survival were 88 and 94%, respectively [11]. Both the avoidance of complications and the ability to achieve high-quality system performance require adequate training and implant volume [26]. It has been suggested that the rate of complications, mainly lead dislodgements, is related to the learning curve, and improves with increasing team experience [27]. Current algorithms to minimize ventricular pacing or biventricular stimulation prevent previously unsuspected deleterious effects of right ventricular pacing, although high-quality training and volume are essential requirements for insertion of the left ventricular leads.

Thus, the different benefit mechanisms and complication sources indicate that DC ICD evaluation should be performed through randomized trials seeking improvements of global outcome, and avoiding investigation on only partial aspects. This was the subjacent rationale to the design of DATAS.

The DATAS Trial Design and Results

DATAS trial was a prospective, multicenter, randomized, open-label study with three arms (two of them cross-over and the third paralleling the other two) (Fig. 2) involving 36 centers in Spain, Germany, Italy, the UK, Portugal, and Israel.

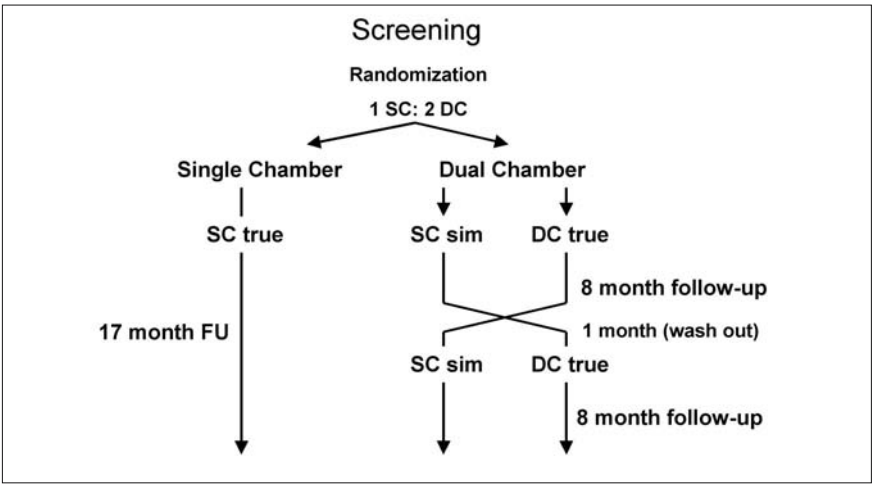


Fig. 2. DATAS trial design. SC, Single chamber ICD; *DC*, dual chamber ICD; *sim*, simulated; *FU,* follow-up

Inclusion criteria were standard class I criteria for a Sc ICD [28], with an amendment in November 2001 to include MUSTT patients, when such indications appeared in the European Society of Cardiology guidelines [29]. The main exclusion criteria were patients without structural heart disease, indication for biventricular pacing, previous ICD implanted, and accepted indications (symptomatic sinus node disease, all second-degree AV block, except asymptomatic Mobitz I, and all third-degree AV block) and contraindications (permanent atrial tachyarrhythmias) for DC pacing.

The 354 patients who fulfilled the study inclusion criteria were randomly assigned in a 1:1:1 proportion between SC ICD (SC true arm), DC ICD (DC true arm), and a DC ICD programmed as a SC device (SC-simulated). All patients were followed for 17 months. SC-simulated and DC true were crossed-over at 8 months of follow-up, with a 1 month wash-out period. All DC true devices were programmed with the PR Logic discrimination algorithm activated. For SC arms, stability criteria were used and other available SC algorithms for discrimination of supraventricular tachyarrhythmias were allowed (i.e., onset criteria and electrogram width).

Pacing mode was DDD 60–70 bpm with strong recommendation for long AV delays (minimum values of sensed AV interval 200 ms and paced AV interval 230 ms) to avoid unnecessary pacing in the DC arm, and mode switch was turned on. Pacing mode was VVI-40 or less in the true SC and SC-simulated arms.

Atrial detection was activated in both the DC and SC-simulated (atrial fibrillation 100–150 ms, atrial tachyarrythmias 100–320 ms) arms, but atrial therapies (i.e., burst, ramp, 50 Hz burst and defibrillation therapy) were only programmed in the DC arm.

The primary composite end-point included all-cause death, invasive intervention, hospitalization or prolongation of hospitalization of cardiac origin, inappropriate shocks (at least 2 episodes), and symptomatic sustained (more than 48 h) atrial tachyarrythmias. This composite endpoint was denominated *Clinically Significant Adverse Events* (CSAE). It was evaluated by defining a prespecified score corrected for the follow-up duration. Each component of the composite end-point counted as one point, except death, which as worst outcome was assigned the maximum number of adverse events reached plus one.

The complete analysis, which will be the primary publication objective, is still on-going, although preliminary results regarding the main comparison, DC vs SC have been obtained and were presented in the last Cardiostim Late Breaking Clinical Trial.

Among the 334 patients, 111 were randomly assigned to SC true ICD, 111 to SC-simulated and 112 to DC true and were followed during a mean follow up of 15.7 ± 3.4 months.

The patients were score-ranked according to CSAE criteria, death, and suitability of intervention by intention to treat. In the SC arm there were 193 CSAE, with a total follow-up of 1728 months, compared with 138 CSAEs and 1833 months for the DC true arm (rate of CSAEs 0.112 vs 0.075). Relative risk of CSAEs in patients treated with DC ICDs compared to SC true ICDs was 0.67 (CI95% 0.59–0.78), resulting in a clinically and statistical significant 33% reduction in the risk of suffering S-CSAE in DC ICDs recipients.

Thus, the conclusion from DATAS was that if ventricular pacing is minimized and the complications rate is low, then DC ICD can improve the outcome of non-selected patients with class I ICD indications, regardless of the absence of pacing indications.

The mean AV intervals programmed in the DC devices were 221.8 ± 51.2 ms (spontaneous atrial activity sensed) and 231.6 ± 45.0 ms (atrium paced). With these AV intervals, the median cumulative right ventricular pacing was 30.0% while median atrial pacing was 35%.

DATAS and Other Clinical Studies

So far, there has been no other study comparing DC ICDs with SC ICDs. The few trials available were conducted with DC devices without atrial therapies and were compared, on the one hand, with AV discrimination performance between DC algorithms vs other criteria and, on the other hand, with the prognosis to add or not atrial-based pacing

Although other, smaller studies did not encounter differences in AV discrimination with the use of DC ICDs, the Detect SVT study [30] did. The trial randomized 400 patients who received DC ICDs for conventional indications to single- or dual-chamber detection. The primary end-point was the proportion of expertly adjudicated SVT episodes that met ventricular rate detection criteria and were inappropriately classified as VT. The corrected inappropriate detection rates were 46.5 vs 32.3% for the single- versus dual-chamber groups, respectively. Thus, DC enhancements reduced overall inappropriate detections by nearly 50% compared with SC detection.

The DAVID trial [4] compared SC programming VVI-40 vs DDDR-70 (rate-responsive atrial pacing and AV discrimination) in patients very similar to those enrolled in the DATAS trial (class I) but with a ejection fraction ≤ 40%. The study was prematurely stopped after a low conditional power for

the original alternative was detected (DDDR-70 being better that VVI-40). Pacing settings, specifically with AV interval duration allowing high rates of right ventricle pacing, may have accounted for this trend to worst status in the VVED arm. Actually, the main comparison in the DAVID trial was patients with a high cumulative percentage of right ventricular pacing (up to 59% in the DDDR arm) vs patients hardly paced (3% in VVI-40 arm). Similarly, control of the AV interval in the DATAS trial seems crucial to explaining the improved outcome in patients assigned to the DC-ICD arm.

Recently, the INTRINSIC trial, a non-inferiority trial with a design very similar to that of the DAVID study, also reported a preserved (better) outcome in patients randomized to DC ICD (DDDR mode programmed but with an AV extension algorithm activated; AV search hysteresis, Boston Guidant) compared to patients programmed in VVI-40. The findings pointed out the importance of maintaining both AV and VV synchronies in this very sensitive group of patients [31].

Conclusions

Patients with conventional indications for ICD are predisposed to frequent atrial-related problems, with a significant clinical impact on quality of life, morbidity, and mortality. DC ICDs with both atrial pacing and anti-tachycardia therapies offer a rational approach to solving these problems. The DATAS trial results are thus far concordant with the data from several recent trials and support the role of DC ICDs in the general candidate population, in spite of the absence of atrial-based pacing indications at the time of implant.

References

1. The AVID investigators (1997) A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 337:1576–1583
2. Buxton AE, Lee KL, Fisher JD et al (1999) A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 341:1882–1890
3. Bardy GH, Lee KL, Mark DB et al; Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators (2005) Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 352:225–237
4. The DAVID Investigators (2002) The dual chamber and VVI implantable defibrillator (DAVID) trial. Dual chamber pacing or ventricular backup in patients with an implantable defibrillator. JAMA 288:3115–3123
5. Quesada A, Almendral J, Arribas F et al (2004) The DATAS rationale and design: a controlled, randomized trial to assess the clinical benefit of dual chamber (DDED) defibrillator. Europace 6:142–150

6. Bernstein AD, Camm AJ, Fletcher RD et al (1987) The NASPE/BPEG generic pacemaker code for antibradyarrhythmia and adaptive-rate pacing and antitachyarrhythmia devices. Pacing Clin Electrophysiol 10:794–799
7. Pacífico A, Hohnloser S, Williams J et al (1999) Prevention of implantable-defibrillator shocks by treatment with sotalol. N Engl J Med 340:1855–1862
8. Joglar JA, Acusta AP, Shusterman NH et al (2001) Effect of carvedilol on survival and hemodynamics in patients with atrial fibrillation and left ventricular dysfunction: retrospective analysis of the US Carvedilol Heart Failure Trials Program. Am Heart J 142:498–501
9. Moss AJ, Zareba W, Hall WJ et al (2002) Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 346:877–883
10. Melzer C, Ohm M, Bondke HJ et al (2005) Chronotropic incompetence in patients with an implantable cardioverter defibrillator: prevalence and predicting factors. Pacing Clin Electrophysiol 28:1025–1031
11. Wolpert C, Jung W, Spehl S et al (2003) Incidence and rate characteristics of atrial tachyarrhythmias in patients with a dual chamber defibrillator. Pacing Clin Electrophysiol 26:1691–1698
12. Wong CK, White HD, Wilcox RG et al (2000) New atrial fibrillation after acute myocardial infarction independently predicts death: the GUSTO III experience. Am Heart J 140:878–885
13. Dries DL, Exner DV, Gersh BJ et al (1998) Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol 32:695–703
14. Denekea T, Lawoa T, Gerritseb B, Lemkea B for the European GEM DR Investigators (2004) Mortality of patients with implanted cardioverter/defibrillators in relation to episodes of atrial fibrillation. Europace 6:151–158
15. Schoels W, Swerdlow CD, Jung W et al (2001) Worldwide clinical experience with a new dual-chamber implantable cardioverter defibrillator system. The Worldwide Jewel AF Investigators. J Cardiovasc Electrophysiol 12:521–528
16. Ricci R, Pignalberi C, Disertori M et al (2002) Efficacy of a dual chamber defibrillator with atrial antitachycardia functions in treating spontaneous atrial tachyarrhythmias in patients with life-threatening ventricular tachyarrhythmias. Eur Heart J 23:1471
17. Friedman PA, Dijkman B, Warman EN et al (2001) Atrial therapies reduce atrial arrhythmia burden in defibrillator patients. Circulation 104:1023–1028
18. Schwartzman D, Gold M, Quesada A et al for the Worldwide Jewel AF-Only Investigators (2005) Serial evaluation of atrial tachyarrhythmia burden and frequency after implantation of a dual-chamber cardioverter-defibrillator. J Cardiovasc Electrophysiol 16:708–713
19. Ricci R, Quesada A, Pignalberi C et al (2004) Dual defibrillator improves quality of life and decreases re-hospitalizations in patients with drug refractory atrial fibrillation. J Interventional Card Electrophysiol 10:85–92
20. Brugada J, Mont L, Figueiredo M et al (1998) Enhanced detection criteria in implantable defibrillators. J Cardiovasc Electrophysiol 9:261–268
21. Kettering K, Dornberger V, Lang R et al (2001) Enhanced detection criteria in implantable cardioverter defibrillators: sensitivity and specificity of the stability algorithm at different heart rates. Pacing Clin Electrophysiol 24:1325–1333

22. Deisenhofer I, Kolb Ch, Ndrepepa G et al (2001) Do current dual chamber cardioverter defibrillators have advantages over conventional single chamber cardioverter defibrillators in reducing inappropriate therapies? A randomized, prospective study. J Cardiovasc Electrophysiol 12:134–142
23. Wilkoff B, Gillberg J, De Souza C (2001) The enhanced PR logic dua chamger tachyarrhythmia detection algorithm: retrospective analysis of supraventricular tachycardia with long PR intervals. J Am Coll Cardiol 37(Suppl 2):131A (abs)
24. Dijkman B, Wellens HJ (2000) Importance of the atrial channel for ventricular arrhythmia therapy in the dual chamber implantable cardioverter defibrillator. J Cardiovasc Electrophysiol 11:1309–1319
25. Stein KM, Euler DE, Mehra R et al (2002) Do atrial tachyarrhythmias beget ventricular tachyarrhythmias in defibrillator recipients? Jewel AF Worldwide Investigators. J Am Coll Cardiol 40:335–340
26. Al-Khatib S, Lucas F, Jollis J et al (2005) The relation between patients' outcomes and the volume of cardioverter-defibrillator implantation procedures performed by physicians treating Medicare beneficiaries. J Am Coll Cardiol 46 1536–1540
27. Eberhardt F, Bode F, Bonnemeier H et al (2005) Long term complications in single and dual chamber pacing are influenced by surgical experience and patient morbidity. Heart 91:500–506
28. Gregoratos G, Cheitlin MD, Conill A et al (1998) ACC/AHA Guidelines for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices: Executive Summary – a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Pacemaker Implantation). Circulation 97:1325–1335
29. Priori S, Aliot E, Blomstrom-Lundqvist C et al (2001) Task Force on Sudden Cardiac Death of the European Society of Cardiology. Eur Heart J 22:1374–1450
30. Friedman PA, McClelland RL, Bamlet WR et al (2006) Dual-chamber versus single-chamber detection enhancements for implantable defibrillator rhythm diagnosis: the Detect Supraventricular Tachycardia Study. Circulation 113:2871–2879
31. Olshansky B, Day JD, Moore S et al (2007) Is dual-chamber programming inferior to single-chamber programming in an implantable cardioverter-defibrillator? Results of the INTRINSIC RV (Inhibition of Unnecessary RV Pacing With AVSH in ICDs) study. Circulation 115:9–16

Prevention of Sudden Death in Patients with Genetic Arrhythmias

Pietro Delise

Introduction

In recent years a number of genetic heart diseases have been recognized that can be complicated by malignant arrhythmias leading to sudden death [1]. These genetic diseases can be divided into two groups: (1) channelopathies (congenital dysfunction of cellular ion-channels without macroscopic heart disease) and (2) genetic cardiomyopathies.

Channelopathies

Table 1 summarizes the main channelopathies. Long QT syndrome (LQTS), short QT syndrome (SQTS), Brugada syndrome (BS), and catecholaminergic polymorphic ventricular tachycardia (CPVT) can lead to sudden death due to malignant ventricular arrhythmias.

Long QT Syndrome

In LQTS [2–9] there is either a loss of function of K channels, including IKr, IKs, and IK1, or a gain of function of the Na+ channel. In about 70% of cases the responsible gene can be identified, and many different genes may be involved (KCNQ1/KvLQT1, KCNH/HERG, SCN5A, etc.). Currently, eight forms of LQTS have been identified (LQT1–LQT8), the most common being LQT1, LQT2, and LQT3 (globally 90% of genotyped patients). The respective prevalence of LQT1, LQT2, and LQT3 is about 60, 32, and 8%. LQTS can also

Cardiology Operative Unit, Conegliano Hospital, Conegliano (TV), Italy

Table 1. List of main channelopathies

Defect	Clinical syndrome	Inheritance	Gene involved	Channel function	Phenotype
Channel Iks	LQT1	AD	KCNQ1/KvLQT1	Loss	Long QT, AF
	SQTS2	AD	KCNQ1/KvLQT1	Gain	Short QT, AF
	JLNS 1	AR	KCNQ1	Loss	Long QT, deafness
	Familial AF	AD	KCNQ1	Gain	AF
	LQT5	AD	KCNE1/MinK	Loss	Long QT
	JLN tipo2	AR	KCNE1	Loss	Long QT, deafness
Channel Ikr	LQT2	AD	KCNH2 (HERG)	Loss	Long QT
	SQTS 1	AD	KCNH2/(HERG	Gain	Short QT, AF
	LQT6	AD	KCNE2/MiRP	Loss	Long QT
Channel IK1	LQT7	AD	KCNJ2/Kir2.1	Loss	Long QT, periodic paralysis, dysmorphism
	SQTS3	AD	KCNJ2/Kir 2.1	Gain	Short QT
Channel Ina	LQT3	AD	SCN5A	Gain	Long QT
	Brugada syndrome	AD	SCN5A	Loss	ECG types 1,2,3
	Lenegre syndrome	AD	SCN5A	Loss	Conduction disturbances
	SSS	AR	SCN5A	Loss	Sinus node dysfunction
Channel If	SSS	?	HCN4	Loss	Sinus node dysfunction
Ankyrin B, anchoring protein	LQT4	AD	ANK2	Loss	Long QT, AF
Ca^{2+} channel α-subunit	LQT8		CACNA1c/CaV1.2	Gain	Long QT, syndactyly, septal defect, mental retardation
Intracellular Ca++ Movement	CPVT 1	AD	RyR2	Calcium release	CPVT
	CPVT 2	AR	CASQ2	Calcium storage	CPVT

AD, Autosomal dominant; *AR*, autosomal recessive; *AF*, atrial fibrillation; *SSS*, sick sinus syndrome. For abbreviations of LQTS, SQTS, JLN, CPVT, see text

be associated with deafness in the Jerwell and Lang-Neelsen syndrome (JLNS) [2], which comprises two variants, JLNS1 and JLNS2.

The incidence of major events before age 40 years (syncope, cardiac arrest, sudden death) ranges between 30 and 46% according to genotype (LQT1 30%, LQT2 46%, LQT3 42%).

LQT1 and LJNS are characterized by the occurrence of malignant arrhythmias almost exclusively during effort and in general during catecholamine stimulation. In LQT2, arrhythmias can occur at rest and during effort and are frequently initiated by additive stress. In LQT3, arrhythmias generally occur at rest or during sleep.

Short QT Syndrome

A gain of function of the K channels IKs, IKr and IK1 is the mechanism behind SQTS [9–11]. Three main forms related to different genetic mutations have been identified: SQTS1, SQTS2, and SQTS3. It is interesting to note that thesame gene, is involved in LQT1 and SQTS2, LQT2 and SQTS1, and LQT7 and SQT3. That is KCNQ1/KvLQT1, KCNH2/HERG and KCNJ2/*Kir1-2*, respectively. This syndrome can be complicated by both atrial and ventricular fibrillation.

Brugada Syndrome

The loss of Na-channel function that occurs in BS [12–17] is due to a mutation of the *SCN5A* gene. This mutation is found in about 18–30% of cases. The syndrome is characterized by ST-segment elevation in the V1–V3 leads and right ventricular conduction delay. BS patients may present with ventricular tachycardia (VT)/ventricular fibrillation (VF) at rest. Fever and the use of class IC anti-arrhythmic drugs can disclose and/or enhance the ECG signs characteristic of BS. The typical ECG pattern is type 1 (coved pattern, J > 2 mm, negative T wave). Type 2 (saddle back pattern, J > 2 mm, positive T wave) and type 3 (minor J elevation) are considered diagnostic only if they are converted into a type 1 pattern by the administration of class 1C anti-arrhythmics.

Catecholaminergic Polymorphic Ventricular Tachycardia

In CPVT [18, 19] there are defects in intracellular calcium release or storage. The condition is complicated by malignant arrhythmias, which are typically induced by effort.

Genetic Cardiomyopathies

This group of diseases includes hypertrophic cardiomyopathies, dilated cardiomyopathies, and arrhythmogenic right ventricular cardiomyopathy. In all of these, the arrhythmias are the consequence of the organic anomalies arising from the genetic defects. In other words, the arrhythmias are not genetically determined per se, but are secondary to the genetic mutation. For this reason, this group of diseases is not further discussed here.

Identification of Risk Factors in Genetic Arrhythmias

In channelopathies, the risk of sudden death, beyond being due to the phenotype itself, is related to multiple factors, which probably only partially have been identified. A familial history of sudden death is generally considered a major risk factor, although some clinicians do not consider it as an independent factor (e.g., in BS) [16].

Gender can be a risk factor in particular conditions. For example, in LQTS gender can influence the prognosis associated with the different genetic defects [8]. In particular, male sex is a strong risk factor in LQT3 and female sex is a strong risk factor in LQT2.

The presence of symptoms such as syncope, pre-syncope, or dizziness is an important risk factor that has been frequently correlated to self-limited brief episodes of malignant arrhythmias.

Comorbidity can increase the risk under particular conditions. For example, deafness (present in JLNS) [2] and a post-partum condition increase the risk of arrhythmia in LQTS.

The entity of ECG changes in the basal tracing are generally correlated with a risk of arrhythmia. In LQTS, lengthening of the QT interval is strongly correlated with risk [8], with subjects showing a QTc > 500 ms being at highest risk. In BS, the presence in the basal ECG of a clear type 1 pattern is correlated to a higher risk of arrhythmia, while type 2 and 3 patterns imply a lower risk [14–16].

Effort test may be useful in LQTS in order to document the absence of adaptation of the QT interval during increasing heart rate. It is also useful in CPVT as it frequently reproduces ventricular arrhythmias at a fixed threshold.

Holter monitoring is generally not informative. However, in SQTS it can aid in the recognition of a short QT interval during phases of bradycardia.

Electrophysiological study (EPS) has no role in the diagnosis of LQTS or CPVT. In SQTS, EPS frequently induces VT/VF in symptomatic subjects [10],

but the prognostic significance of this finding in asymptomatic patients is unknown.

The prognostic significance of EPS in BS is controversial. According to Brugada et al., EPS is useful to predict the risk of sudden death [14]. These authors suggested that the results of EPS are closely correlated with the clinical characteristics of the patients. In fact, VT/VF is inducible in 81% of patients with a previous history of aborted sudden death, in 61% of patients with a previous history of syncope, and in 34% of asymptomatic individuals. Furthermore, a significant positive predictive value of EPS that varied in different categories of patients was observed: 54% in individuals with a history of aborted sudden cardiac death, 23% in patients with syncope, and 12% in asymptomatic patients, during a mean follow-up of 31 ± 41 months. It is important to note that while a 12% predictive value in asymptomatic individuals may seem low, it refers to both otherwise healthy and asymptomatic individuals. Our own experience [17], in a more limited number of cases, is similar to that of Brugada et al. [14].

Nonetheless, not all clinicians are in agreement with those findings. Instead, some have suggested that EPS reproducibility is only 70%, probably because of the variability of Na-channel function in these patients [20]. Other authors have rejected the usefulness of EPS completely [21, 22]. However it must be emphasized that in the latter series the number of patients was small, with a high percentage being asymptomatic.

Risk Stratification on the Basis of a Polyparametric Approach

Among the LQTS subjects at highest risk (> 50% probability of experiencing a major event before age 40) are those with a QTc > 500 ms independent of gender in LQT1 and LQT2, and in males with LQT3 [8]. Other factors increase the risk: previous VT/VF, deafness (JLNS) and post-partum. At lowest risk (< 30%) are patients with a QTc < 500 ms, with LQT1, and males with LQT2.

In SQTS, symptomatic subjects with a familial history are probably at highest risk.

In BS, according to Priori et al. [15], three groups of patients with decreasing risk can be identified: (1) patients with a typical ECG pattern and a history of syncope; (2) asymptomatic patients with a typical ECG pattern; (3) asymptomatic patients whose ECG reveals the Brugada pattern only after anti-arrhythmic drug challenge.

Brugada et al. [23] published a study in which 547 individuals with typical ECG pattern and no previous cardiac arrest were prospectively followed.

The study considered three major risk factors: typical ECG pattern in the basal ECG, syncope, and inducible VT/VF during EPS. By logistic regression analysis of these variables, eight groups were identified, with a risk of cardiac arrest during a 2-year follow-up varying from 0.5 to 27.2%. The highest-risk group (27.2%) consisted of individuals with a typical ECG, at least one syncopal episode, and positive EPS. In the lowest-risk group (0.5%) was one subject with an ECG that was diagnostic only after drug administration, who was otherwise asymptomatic, and had a negative EPS. An asymptomatic subject, with a typical ECG pattern and a positive EPS, had an intermediate risk (14%).

In CPVT, the association of family history and syncope identifies subjects at highest risk.

Behaviors That Can Prevent Sudden Death

In some genetic diseases, particularly LQT1 and CPVT, sports activities can facilitate the occurrence of malignant arrhythmias.

Certain drugs can be deleterious in some diseases. For this reason, all drugs that prolong the QT interval should be avoided by patients with LQTS. Ajmaline and class IC anti-arrhythmic drugs should be avoided in patients with BS.

Pharmacologic Prevention of Sudden Death

Beta-blockers are recommended by current guidelines [24] for patients with LQTS (especially LQT1 and LQT2) and CPVT (class I, evidence B and C). They have no effect in SQTS or BS.

Quinidine may prolong the QT interval in SQTS and modify ECG changes in BS [25]. In the latter pathology, it may reduce the inducibility of VT/FV [25, 26]. However, prospective randomized studies are not available to establish the efficacy of quinidine in preventing sudden death.

ICD Implantation To Prevent Sudden Death

Implantable cardioverter-defibrillators (ICDs) are the most effective method for preventing sudden death. Current guidelines [24] recommend ICD implantation for secondary prevention in patients with previous cardiac arrest (class I, evidence A–C in various diseases).

In patients with LQTS and syncope, an ICD can reduce sudden death also

in patients on beta-blockers (class IIa, evidence B). In patients with BS type 1 pattern with syncope or VT without cardiac arrest, ICD implantation is considered reasonable (class IIa, evidence C).

In primary prevention, ICD is not generally recommended in asymptomatic patients without documented malignant arrhythmias.

Some clinicians have suggested the implantation of an ICD in patients at higher risk. The problem is that it is not always easy to precisely predict risk in a single patient. Furthermore, in contrast to other more common pathologies, such as ischemic heart disease or heart failure, randomized primary prevention trials for patients with genetic arrhythmias are not available.

Nonetheless, in asymptomatic LQTS, ICD may be suggested for patients in the highest risk categories (class IIb, evidence B). In asymptomatic BS, the role of EPS in identifying candidates for ICD implantation is still considered to be controversial (class IIB, evidence C).

References

1. Sarkozy A, Brugada P (2005) Sudden cardiac death and inherited arrhythmia syndromes. J Cardiovasc Electrophysiol 16:S8-S20
2. Jervell A, Lange-Nielsen F (1957) Congenital deaf mutism, functional heart disease with prolongation of the QT interval and sudden death. Am Heart J 54:59–68
3. Romano C, Gemme G, Pongiglione R (1963) Aritmie cardiache rare dell'età pediatrica, II: accessi sincopali per fibrillazione ventricolare parossistica. Clin Pediatr (Bologna) 45:656–683
4. Schwartz PJ (1985) Idiopathic long QT syndrome: progress and questions. Am Heart J 109:399–411
5. Marks ML, Trippel DL, Keating MT (1995) Long QT syndrome associated with syndactyly identified in females. Am J Cardiol 76:744–745
6. Duggal P, Vesely MR, Wattanasirichaigoon D et al (1998) Mutation of the gene for IsK associated with both Jervell and Lang-Nielsen and Romano-Ward forms of long QT syndromes. Circulation 97:142–146
7. Locati EH, Zareba W, Moss AJ et al (1998) Age- and sex-related differences in clinical manifestations in patients with congenital long-QT syndrome: findings from the International LQTS Registry. Circulation 97:2237–2244
8. Priori SG, Schwartz PJ, Napolitano C et al (2003) Risk stratification in the long-QT syndrome. N Engl J Med 348:1866–1874
9. Napolitano C, Bloise R, Priori S (2006) Long QT syndrome and short QT syndrome: how to make correct diagnosis and what about eligibility for sport activity. J Cardiovasc Med 7:250–256
10. Gaita F, Giustetto C, Bianchi F et al (2003) Short QT syndrome. A familial cause of sudden death. Circulation 108:965–970
11. Brugada R, Hong K, Dumaine R et al (2004) Sudden death associated with short-QT syndrome linked to mutations in HERG. Circulation 109:30–35
12. Brugada P, Brugada J (1992) Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome. J Am Coll Cardiol 20:1391–1396

13. Brugada R, Brugada J, Antzelevitch C et al (2000) Sodium channel blockers identify risk for sudden death in patients with ST-segment elevation and right bundle branch block but structurally normal hearts. Circulation 101:510–515
14. Brugada P, Brugada R, Mont L et al (2003) Natural history of Brugada syndrome: the prognostic value of programmed electrical stimulation of the heart. J Cardiovas Electrophysiol 14:455–457
15. Priori SG, Napolitano C, Gasparini M et al (2002) Natural history of Brugada syndrome. Insight for risk stratification and management. Circulation 105:1342–1347
16. Antzelevitch C, Brugada P, Borggrefe M et al (2006) Brugada syndrome. Report of the second consensus conference. Circulation 111:659–670
17. Delise P, Marras E, Bocchino M (2006) Brugada-like electrocardiogram pattern: how to stratify the risk for sudden cardiac death. Is sport activity contraindicated? J Cardiovasc Med 7:239–245
18. Coumel P, Fidelle J, Lucet V et al (1978) Catecholaminergic-induced severe ventricular arrhythmias with Adams-Stokes syndrome in children: report of four cases. Br Heart J 40:28–37
19. Leenhardt A, Lucet V, Denjoy I et al (1995) Catecholaminergic polymorphic ventricular tachycardia in children. A 7-year follow-up of 21 patients. Circulation 91:1512–1519
20. Gasparini M, Priori S, Mantica M et al (2002) Programmed electrical stimulation in Brugada syndrome: how reproducible are the results? J Cardiovasc Electrophysiol 13:880–887
21. Kanda M, Shimizu W, Matsuo K et al (2002) Electrophysiologic characteristics and implications of induced ventricular fibrillation in symptomatic patients with Brugada syndrome. J Am Coll Cardiol 39:1799–1805
22. Eckardt L, Probst V, Smits JP et al (2005) Long-term prognosis of individuals with right precordial ST-segment elevation Brugada syndrome. Circulation 111:257–263
23. Brugada J, Brugada R, Brugada P (2003) Determinants of sudden death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. Circulation 108:3092–3096
24. ACC/AHA/ESC (2006) 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death – Executive summary. Eur Heart J 27:2099–2140
25. Belhassen B, Viskin S, Fish R et al (1999) Effects of electrophysiologic-guided therapy with Class IA antiarrhyhtmic drugs on the long term outcome of patients with idiopathic ventricular fibrillation with or without the Brugada syndrome. J Cardiovasc Electrophysiol 10:1301–1312
26. Hermida JS, Denjoy I, Clerc J et al (2004) Hydroquinidine therapy in Brugada Syndrome. J Am Coll Cardiol 43:1853-1860

Cost-Effectiveness of ICD Therapy in the Prevention of Sudden Death in CAD and/or HF Patients

Andrea Pozzolini

Introduction

Sudden cardiac death (SCD) is one of the most common causes of death in Western countries [1, 2], and its prevention poses a major challenge to both policymakers and health-care providers. The fundamental principle of evidence-based medicine is that clinical practice should rest on a sound scientific foundation established by clinical studies involving human subjects. The strategies of primary and secondary prevention of SCD with the implantable cardioverter defibrillator (ICD) have received increased attention in the last few years, mainly because multiple prospective randomized clinical trials (RCT) [3, 4] have yielded concordant and consistent results showing that ICD therapy is highly effective in reducing SCD and all-cause mortality in selected patients with impaired left ventricular function on optimized medical treatment (OMT), including post-MI patients as well as patients with nonischemic cardiomyopathy. It is now known that in such patients ICDs reduce mortality by approximately one-third over and above OMT [3–8]. Faced with this evidence, recently updated practice guidelines [9–11] have suggested a broadening of the indications for prophylactic ICD use; but opinions diverge on the desirability for expansion of this expensive therapeutic strategy, whose widespread implementation threatens to impact heavily on public health-care spending. Thus nowadays, due to the high cost of ICDs and the large population of patients potentially eligible to receive them, the debate on ICDs has moved from issues of feasibility and effectiveness to questions about costs and cost-effectiveness. The persisting controversy reflects the evolution from *evidence-based* to *value-based* medicine

Cardiology Operative Unit, Santa Croce Hospital, Fano (PU), Italy

[12]. Since health-care resources are limited, when therapies are both effective and expensive, it is both reasonable and necessary for health-care providers and purchasers to quantify the expected benefits for the money they spend, particularly when in the face of the many competing programs in an atmosphere of cost containment. The basic assumption is that clinical efficacy does not necessarily imply public priority. The challenge to health-policymakers is to conjugate equity in distribution with efficiency in allocation of health-care resources. Newer therapies are typically more expensive than older ones; thus, an important question is whether patient outcomes are improved sufficiently to justify the added expense [13]. The academic discipline of formal cost-effectiveness analysis is the best available approach to the question, which it seeks to answer by comparing alternative therapeutic strategies, calculating the ratio of incremental cost to incremental effectiveness (incremental cost-effectiveness ratio, ICER) and expressing clinical outcomes in terms of "years of added life" or "quality-adjusted life years" (QALY) gained [14–18]. Comparisons to other therapies are then possible. The lower the ICER, the better the use of resources and the more cost-effective the therapy. The typical upper-limit benchmark conventionally used to identify therapies that provide good value is US$ 50,000 per life-year saved (per QALY gained), which is the cost of dialysis treatment for end-stage renal disease [19]. An ICER of US$ 100,000 or more is typically considered a poor value for the money. Nowadays, in a context of cost-overburdened health-care systems, health economics is considered an integral part of clinical science, and includes an assessment of whether an intervention is worthwhile given the resources and alternative options available. The subsequent decisions drive and support societal decision-making for resource allocation in those cases in which not everything that is potentially possible can be done.

ICD Cost-Effectiveness: the Evidence from Randomized Clinical Trials

We will now consider the clinical and economic evidence from the major individual ICD trials, always bearing in mind that cost-effectiveness depends on the population being studied, and that comparing the results from cost-effectiveness analyses of trials enrolling appreciably different patients requires caution and careful consideration of design features [20, 21].

Early clinical studies showed that the implantation of ICDs reduced mortality in the small population of patients who had survived a spontaneous episode of ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) [22].

The AVID Trial [6] concluded that ICD therapy reduces mortality compared with anti-arrhythmic drugs (AADs) in survivors of serious ventricular tachyarrhythmias. However, by confining its length of follow-up to only 1.5 years, rather than patient life-expectancy or device longevity, the base-case ICER was found to be moderately expensive: at 3 years of follow-up, the expected survival for patients treated with the ICD was 0.21 years longer than for AAD at an incremental cost of US$ 14,101, yielding an ICER of US$ 66,677 per life-year saved (LYS) by the ICD over AADs [23].

The *Canadian Implantable Defibrillator Study* (CIDS) demonstrated a trend toward a lower risk of death with ICD therapy vs amiodarone (20% relative reduction, $p = 0.14$) over an average follow-up of 36 months in survivors of life-threatening ventricular arrhythmias [24]. The 4.3% absolute reduction in mortality rates translated in a number needed to treat (NNT) to save one life of 23 patients, significantly higher than the NNT of 9 at 3 years of follow-up of AVID, while the smaller survival benefit (0.23-year, not achieving statistical significance) and an increased cost difference (US$ 31,925) between ICD- and amiodarone-treated patients resulted in a CIDS base-case ICER over 6.3 years of follow-up of US$ 138,803, roughly twice as high as the AVID trial and economically unattractive [25]. This notwithstanding, the long-term follow-up study of a subset of 120 CIDS patients by Bokhari et al. [26] showed how long-term efficacy at up to 11 years (mean 5.9 years) may be higher than at mid-term, with a reduction in the relative risk of mortality of 43%, compared with 20% at 3 years in the original CIDS study [24]. Boriani et al. [27] calculate that such an increase in long term efficacy would reduce the NNT to save one life to just five patients (at the long-term follow-up of Bokhari's sub-study).

After the clinical evaluation of ICD therapy for the secondary prevention of SCD, eventually other trials evaluated the therapy as a means of primary prevention of SCD in high-risk patients with ischemic and non-ischemic heart disease and reduced left ventricular ejection fraction (EF); the results of these primary prevention trials provide unequivocal proof of the survival benefits of ICD therapy. Economic analyses were conducted to evaluate the incremental cost-effectiveness ratio of ICD for primary prevention of SCD compared to optimal medical treatment.

Economic analysis of the MADIT population (patients at high risk of sudden arrhythmic death, with EF $\leq$ 35% and spontaneous as well as inducible ventricular arrhythmias) resulted in an ICER of US$ 27,000/LYS [28]. The ICER (corrected to 1997 dollars) in MADIT was less than half that found in AVID, US$ 30,337/LYS vs US$ 66,677/LYS, mainly because the survival difference was 3.6 times greater in MADIT.

The MADIT II study highlighted the possibility of effective primary prevention of sudden death in those patients with coronary artery disease who were selected by straightforward clinical data and without expensive screening, such as electrophysiological study. For patients with healed myocardial infarction and EF < 30%, ICD therapy was shown to reduce mortality risk by approximately 31% in the following 2 years compared with drug therapy [5]. The study raised concern about its impact on health-care systems, because 32,000–66,000 people in the US annually fit its eligibility requirements [29, 30].

As reported by Al-Khatib et al. [30] in a study based on data from published literature, databases owned by Duke University Medical Center and Medicare data, without use of cost information from the trial, ICDs were projected to improve survival in MADIT II-like patients by 1.80 discounted years, with a marginally attractive ICER of US$ 50,500/LYS (US$ 57,000/QALY). Sensitivity analysis suggested that the ratio could vary greatly depending on the assumptions made, with the cost of replacing ICD batteries and leads exerting the greatest effect on cost-effectiveness.

A cost-effectiveness analysis combining patient outcome and economic data from the MADIT II trial [31] included 1,095 US patients with complete data relating to clinical costs, including number of office visits, diagnostic tests and procedures, hospitalizations, emergency department visits, medications, and other health-care services. During the 3.5-year period of the study, the average survival gain for the ICD arm was 0.167 years (2 months), clearly smaller than that seen in MADIT, which randomized only those patients who had inducible ventricular arrhythmias in response to invasive electrophysiology (EP) studies; the additional costs were US$ 39,200, and the ICER of ICD therapy was in the "very expensive" range (US$ 235,000/LYS). However, three alternate projections extrapolated to 12 years of follow-up revealed incremental cost-effectiveness ratios ranging from US$ 78,600 to US$ 114,000/LYS. The authors concluded that the estimated cost per year of life saved by ICD therapy in the MADIT-II study was high, at 3.5 years, but it was considerably lower based on projections for longer intervals.

The COMPANION trial [7] was the first trial that was sufficiently powered to evaluate the effects of cardiac resynchronization therapy (CRT) on the incidence of death and hospitalization, and demonstrated that CRT either without (CRT-P) or with the addition of an ICD function (CRT-D) reduced the combined risk of all-cause mortality or first hospitalization among patients with advanced heart failure and intraventricular conduction delays [7]. Investigators from the COMPANION trial modeled the trial data on an intention-to-treat basis to estimate the incremental cost-effectiveness

of CRT-P and CRT-D plus OMT relative to OMT alone over a base-case 7-year treatment episode [32]. Over 2 years, follow-up hospitalization costs were reduced by 29% for CRT-D. With extension of the cost-effectiveness analysis to a 7-year base-case time period, the ICER for CRT-D was US$ 46,700/LYS and US$ 43,000/QALY gained relative to OMT [32], below the benchmark of US$ 50,000, generally accepted to identify therapies that provide good value. This suggests that the clinical benefits of CRT-D can be achieved at a reasonable cost. In a recent work, Yao et al. [33] assessed the long-term cost-effectiveness of CRT-P compared OMT alone, and the cost-effectiveness of CRT-D plus OMT compared with CRT-P plus OMT, on incremental cost per QALY and life-year using data from the CARE-HF [34] and the COMPANION [7] studies. Using a decision-analytic model based on a Markov model and a Monte Carlo simulation, and taking into account the estimated additional benefit of an ICD on survival, as determined by COMPANION, the authors concluded that long-term treatment with CRT-P for patients with heart failure and cardiac dyssynchrony is much more cost-effective than medical therapy (ICERs of US$ 9528/QALY gained and US$ 7011/LYS). Meanwhile, the ICERs of CRT-D compared with CRT-P were US$ 62,067/QALY gained and US$ 46,456/LYS, suggesting that from a lifetime perspective, the addition of an ICD function, assuming the patient has a reasonable life expectancy if he or she receives effective treatment for heart failure, may further reduce the risk of sudden death, and may also be more cost-effective than CRT-P plus OMT [33].

Considered a landmark study, the *Sudden Cardiac Death in Heart Failure Trial* (SCD-HeFT) [8] enrolled patients with NYHA class II/III HF of ischemic or nonischemic origin and a left ventricular EF ≤ 35% who were on OMT. Patients were randomized to receive ICD therapy (single-chamber, shock-only ICDs implanted in an outpatient setting), amiodarone anti-arrhythmic drug treatment, or placebo. Over a 5-year follow-up, the study demonstrated a significant, 7% absolute reduction in all-cause mortality and a 23% decline in relative risk in the ICD arm vs the placebo arm, whereas those who received amiodarone showed no mortality benefit over placebo. Analyses of the subgroups showed that the majority of the ICD mortality benefit was obtained by patients with less severe, NYHA class II disease; these patients showed a 46% reduction in relative risk. NYHA class III patients demonstrated no significant mortality benefit from ICD therapy [8]. An economic analysis was designed and conducted to determine the long-term cost-effectiveness of ICD for prevention of SCD in patients with heart failure who were enrolled in the study [35]. Cost-effectiveness was calculated from cost and survival data gathered in the trial. Lifetime cost-effectiveness was estimated using projec-

tions of cost and life-expectancy beyond the mean study follow-up of 46 months. The results indicated that: (a) the projected life expectancy from time of randomization was 10.9 years in the ICD arm and 8.4 years in the placebo arm; (b) amiodarone did not prolong survival compared to placebo; (c) there was no evidence that ICD patients had significantly more hospitalizations, major cardiac procedures, or outpatients visits over the first 5 years of follow-up than patients in the placebo arm; (d) ICD cost-effectiveness, expressed as the incremental lifetime cost to save a life-year relative to placebo, was US$ 38,389/LYS. This cost varied depending on survival time: US$ 127,503/LYS at 5 years, US$ 88,657/LYS at 8 years, and US$ 58,510/LYS at 12 years. When NYHA class II patients were analyzed separately, the analysis yielded an even better discounted ICD ICER of US$ 29,872/LYS, due to the greater survival benefit in this group. The cost-analysis concluded that prophylactic use of conservatively programmed, single-lead ICDSs for primary prevention of SCD in HF patients with an ejection fraction ≤ 35% is an "economically efficient" way to improve patient outcomes based on the currently established benchmarks, provided that the devices are implanted in stable, moderately symptomatic patients (particularly NYHA class II) and that patients survive at least 8 years following implantation [35].

The cost-effectiveness of the ICD in the population of patients represented in eight primary-prevention ICD trials was assessed by Sanders et al. [36]. Based on a Markov model, the cost, quality of life, survival, and ICER of the ICD for primary prevention of sudden death were compared with medical therapy among patients with survival and mortality rates similar to those in each of the clinical trials. The efficacy of the ICD was modeled as a reduction in the relative risk of death on the basis of the hazard ratios reported in the individual clinical trials. The results showed that use of the ICD increased lifetime costs in every trial. In two trials in which no survival benefit was associated with ICD therapy, DINAMIT [37] and the CABG Patch trial [38], the authors concluded that the prophylactic implantation of an ICD did not reduce the risk of death and thus was both more expensive and less effective than control therapy. For the other six trials showing clinical benefit (MADIT I, MADIT II, MUSTT, DEFINITE, COMPANION, and SCD-HeFT), use of an ICD was projected to add between 1.01 and 2.99 QALY and between US$ 68,300 and US$ 101,500 in cost. With these base-case assumptions, the authors found that the ICER of the ICD as compared with control therapy in these six populations ranged from US$ 34,000 to US$ 70,200 per QALY gained [36]. Further sensitivity analyses showed that this ICER would remain below US$ 100,000 per QALY as long as the ICD reduced mortality rates for 7 or more years. On the basis of their analysis, it was concluded that prophylactic implantation of an ICD has an ICER below US$ 100,000 per

QALY gained in populations in which a significant device-related reduction in mortality is demonstrated [36].

ICDs and the Real World: the SEARCH-MI Registry

The generalizability of randomized clinical trials, that is, whether the results of the economic analyses from landmark trials such as MADIT II and SCD-HeFT apply to the real-world population of patients, has been raised as a concern [39]. The objections are based on the fact that selection bias is very difficult to eliminate from any clinical trial, and real-world patients are older and generally sicker than patients included in trials [40]. Generalizability is best assessed through the evaluation of outcomes in clinical practice.

A comparison of the data from 556 patients enrolled from July 2002 to April 2005 in the Italian sub-study of the prospective Multicenter *Survey to Evaluate Arrhythmia Rate in so-Called High-risk Myocardial Infarction Patients* (Search-MI) Registry with data from the ICD arm of MADIT II showed comparable results, both in terms of appropriate shocks and overall mortality, thus confirming in real-world practice the benefits of primary prevention in "MADIT II-like" patients [41]. Describing an economic analysis based on real expenditure data from 2002 to 2005, as recorded in the Search-MI Registry, Boriani et al. [42] estimated the daily costs associated with the device and leads. Over a 5–7 year time horizon, the average daily cost was estimated to be € 4.60–€ 6.70. Translation of these figures into US market conditions results in a daily cost of around US$ 7.90–11.40. It is important to bear in mind that these estimates only refer to hardware costs and do not take into account hospitalization and physicians' fees at the time of implant, nor were costs secondary to complications and device replacement included in the calculations; therefore, the cited values somewhat underestimate the entire cost of treatment [42]. Nevertheless, the dilution in terms of daily costs over a predefined time horizon of the high initial expenditure of ICD purchase and implant makes it somewhat easier to compare such costs with those generated by the continuous use of chronic pharmacological treatment, and thereby to evaluate the affordability of ICD.

The Influence of Risk Stratification among Patients on the Cost-Effectiveness of ICDs

Although expensive, in appropriate patients ICDs provide value. Ideally, ICDs would be placed only in patients who are likely to develop life-threatening

ventricular arrhythmias and would not be placed in those who are not destined to have such arrhythmias. However, given the number of patients now eligible for ICD implantation, based on the EF alone, there is a need to identify the clinical characteristics or diagnostic tests that will enable clinicians to select patients who are at increased risk for sudden death but whose low competing risks of death would allow them to benefit the most from receipt of an ICD.

Conversely, from a societal perspective, identification of the MADIT II-like patients least likely to benefit from ICD implantation might allow for substantial cost savings with a small or even negligible sacrifice in population life expectancy [43]. Furthermore, as cost-effectiveness needs to be adjusted for the tolerability of the therapy by the patients, i.e., quality-adjusted, better selection might decrease the percentage of patients in whom an ICD will only lower quality-of-life, producing inappropriate discharges and other undesirable effects, thus affecting cost-utility analyses [44]. Although multiple clinical, electrocardiographic, and electrophysiologic parameters have been assessed as potential markers to stratify risk for VT/VF and SCD, scarce progress has been made over the last years in this field by researchers.

Promising results have been recently obtained with microvolt T wave alternans (MTWA) testing, which potentially could be employed to improve cost-effectiveness [45]. The MTWA test noninvasively measures beat-to-beat microvolt variations in the shape, amplitude, or timing of the ECG T wave that are linked with the development of clinical ventricular arrhythmias. The test has a high negative predictive value, that is, a negative test result identifies a patient at very low risk of fatal SCD.

In the absence of direct studies examining whether there is any benefit to be derived from implanting ICDs among the patients testing negative for microvolt T wave alternans, Chan et al. [45] used a mathematical model based on recent studies to compare the lifetime costs and benefits of a medical therapy strategy to prevent death by implanting ICDs in all currently eligible MADIT II-like patients, or implanting defibrillators in only those patients considered to be at higher risk according to the MTWA test and using drugs to treat the rest. Overall, they calculated that, on average, patients who received an ICD would live almost one-and-a-half "quality-adjusted" years longer than patients on drug therapy (7.3 vs 5.9 years) and the additional cost per QALY would be about US$ 56,000. However, when the screening test was factored, the authors found that almost all the benefits went to high-risk patients, and that the patients testing negative and who received defibrillators would live only slightly longer than if they were treated with medical therapy.

The ICER for implanting an ICD in the lower risk group testing negative for microvolt T wave alternans was closer to US$ 90,000/QALY, which would not be considered cost-effective by commonly accepted thresholds. In contrast, implanting an ICD in an eligible MADIT II-like population that tests non-negative would be less than US$ 50,000/QALY. Thus, a strategy of making ICDs available to all eligible patients according to MADIT II criteria would be less cost-effective than a more discriminating strategy of implanting ICDs only among those testing MTWA non-negative [45].

Conclusions

Although there is consistency among the majority of primary- and secondary-prevention ICD studies regarding the effectiveness of the device, calculated figures on cost-effectiveness in different trials vary significantly [31, 35, 36], as cost-effectiveness depends on the population being studied. As we have already stressed, comparing the results from cost-effectiveness analyses of trials enrolling appreciably different patients requires caution and careful consideration of design features [20, 21]. Furthermore, most ICD clinical trials underestimate the cost-effectiveness of ICD therapy because the follow-up periods are short. In fact, failure to consider therapy duration can incorrectly alter cost-effectiveness findings. Compared with medical treatment, ICD therapy has a high up-front cost but very few costs thereafter. Many trials, such as MADIT II, have follow-up periods of only 18 months. Given a current battery life of 7 years, only 20% of the life of the device will be used by the end of a typical follow-up period, yet the full cost of the device is used in cost-effectiveness calculations.

In the end, in the range of survival benefit observed in randomized clinical studies, ICD therapy appears to be acceptably cost-effective and economically attractive by conventional standards in the patients indicated by current clinical guidelines. Although the ICD is expensive, it can be justified when considered in the context of other accepted therapies (revascularization procedures, antihypertensive treatment) [46], and, at least in certain subsets of patients, ICD therapy falls under US$ 50,000/LYS, which is the commonly accepted benchmark to identify therapies that provide good value [31, 35]. Conversely, one must also consider that cost-effective does not mean inexpensive. There is diffuse concern among policymakers that the large number of patients eligible for ICDs under currently accepted criteria may strain societal ability to perform and pay for these procedures.

Undoubtedly, ICD therapy would be more attractive if certain modifications in the factors affecting ICD cost-effectiveness occurred, i.e., reduced

cost, extended longevity and improved reliability of the hardware, reduced length of hospitalization, and better risk-stratification. The latter issue is of paramount importance, as the use of more selective, more efficient risk-stratifiers would lead to lower NNT to prevent one premature death, and would result in fewer cases in which patients receive ICDs although they do not stand to benefit from them as well as fewer patients exposed to unnecessary risks. Furthermore, the use of biventricular ICDs for cardiac resynchronization therapy (CRT-D) in selected patients with severe heart failure and ventricular electromechanical dyssynchrony substantially improves quality-of-life, modifies disease progression, and favorably influences both hospitalization for heart failure and mortality [7]. This, in turn, would make the ICER of ICDs used for cardiac resynchronization therapy more attractive than that for ICDs implanted only to prevent SCD [32, 47].

As for the general problem of how the results of clinical trials can be transposed in the real world, data from the prospective multicenter registries in the USA on ICD use in primary prevention [48] and the already available data from the multicenter European SEARCH-MI Registry [42] will allow better clinical as well as economical evaluation of ICD use in the coming years.

References

1. Zheng ZJ, Croft JB, Giles WH et al (2001) Sudden cardiac death in the United States, 1989 to 1998. Circulation 104:2158–2163
2. Josephson M, Wellens HJ (2004) Implantable defibrillators and sudden cardiac death. Circulation 109:2685–2691
3. Nanthakumar K, Epstein A, Kay GN et al (2004) Prophylactic implantable cardioverter-defibrillator therapy in patients with left ventricular systolic dysfunction: a pooled analysis of 10 primary prevention trials. J Am Coll Cardiol 44:2166–2172
4. Desai A, Fang J, Maisel W et al (2004) Implantable defibrillators for the prevention of mortality in patients with nonischemic cardiomyopathy: a meta-analysis of randomized controlled trials. JAMA 292:2874–2879
5. Moss AJ, Zareba W, Hall WJ (2002) Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 346:877–883
6. The Antiarrhythmic Versus Implantable Defibrillator (AVID) Investigators (1997) A comparison of antiarrhythmic drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. N Engl J Med 337:1576–1583
7. Bristow M, Saxon L, Boehmer J et al (2004) Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 350:2140–2150
8. Bardy GH, Lee KL, Mark DB et al (2005) Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 352:225–237

9. Hunt SA, Abraham WT, Chin MH et al (2005) ACC/AHA 2005 Guideline update for the diagnosis and management of chronic heart failure in the adult : a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 46:e1-e82
10. Zipes DP, Camm AJ, Borggrefe M et al (2006) ACC/AHA/ESC 2006 Guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death – executive summary. J Am Coll Cardiol 48:1064–1108
11. Lunati M et al (2005) Linee guida AIAC all'impianto di pacemaker, dispositivi per la resincronizzazione cardiaca (CRT) e defibrillatori automatici impiantabili (ICD). Giornale italiano di Aritmologia e Cardiostimolazione 8:1–58
12. Brown GC, Brown MM, Sharma S (2003) Value-based medicine: evidence-based medicine and beyond. Ocul Immunol Inflamm 11:157–170
13. Boriani G, Biffi M, Martignani C et al (2003) Cardioverter-defibrillators after MADIT II: the balance between weight of evidence and treatment costs. Eur J Heart Failure 5:419–425
14. Meltzer MI (2001) Introduction to health economics for physicians. Lancet 358:993–998
15. Mark DB, Hlatky MA (2002) Medical economics and the assessment of value in cardiovascular medicine. Part I. Circulation 106:516–520
16. Mark DB, Hlatky MA (2002) Medical economics and the assessment of value in cardiovascular medicine. Part II. Circulation 106:626–630
17. Boriani G, Biffi M, Martignani C et al (2001) Cost-effectiveness of implantable cardioverter-defibrillators. Eur Heart J 22:990–996
18. Boriani G, Larsen G (2006) Cost-effectiveness of implantable cardioverter-defibrillators. In: Priori S, Zipes DP (eds) Sudden cardiac death. Blackwell Publishing, Malden, pp 263–279
19. Stange PV, Sumner AT (1978) Predicting treatment costs and life expectancy for end-stage renal disease. N Engl J Med 298:372–378
20. Spath MA, O'Brien BJ (2002) Cost-effectiveness of the implantable cardioverter defibrillator therapy versus drug therapy for patients at high risk of sudden cardiac death. Pharmacoeconomics 20:727–738
21. Weinstein MC, Siegel JE, Gold MR et al (1996) Recommendations of the Panel on cost-effectiveness in health and medicine. JAMA 276:1253–1258
22. Ezekowitz JA, Armstrong PW, McAlister FA (2003) Implantable cardioverter defibrillators in primary and secondary prevention: a systematic review of randomized, controlled trials. Ann Intern Med 138:445–452
23. Larsen G, Hallstrom A, McAnulty J et al (2002) Cost-effectiveness of the implantable cardioverter-defibrillator versus antiarrhythmic drugs in survivors of serious ventricular tachyarrhythmias: results of the Antiarrhythmic Versus Implantable Defibrillators (AVID) economic analysis substudy. Circulation 105:2049–2057
24. Connolly SJ, Gent M, Roberts RS et al (2000) Canadian Implantable Defibrillator Study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 101:1297–1302
25. O'Brien BJ, Connolly SJ, Goeree R et al (2001) Cost-effectiveness of the implantable cardioverter-defibrillator: results from the Canadian Implantable Defibrillator Study (CIDS). Circulation 103:1416–1421
26. Bokhari F, Newman D, Greene M et al (2004) Long term comparison of the implantable cardioverter defibrillator versus amiodarone: eleven-year follow-up of a subset of patients in the Canadian Implantable Defibrillator Study (CIDS). Circulation 110:112–116

27. Boriani G, Biffi M, Martignani C (2005) Letter regarding article by Bokhari et al "Long-term comparison of the implantable cardioverter defibrillator versus amiodarone: eleven-year follow-up of a subset of patients in the Canadian Implantable Defibrillator Study (CIDS)". Circulation 111:e26
28. Mushlin AI, Hall WJ, Zwanziger J et al (1998) The cost-effectiveness of automatic implantable cardiac defibrillators: results from MADIT. Multicenter Automatic Defibrillator Implantation Trial. Circulation 97:2129–2135
29. Centers for Medicare and Medicaid Services (2003) Decision memorandum: national coverage determination (NCD) on implantable defibrillators, pp 1–37
30. Al-Khatib SM, Anstrom KJ, Eisenstein EL et al (2005) Clinical and economic implications of the Multicenter Automatic Defibrillator Implantation Trial-II. Ann Intern Med 142:593–600
31. Zwanziger J, Hall WJ, Dick AW et al (2006) The cost-effectiveness of implantable cardioverter-defibrillators: results from the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II. J Am Coll Cardiol 47:2310–2318
32. Feldman AM, de Lissovoy G, Bristow MR et al (2005) Cost effectiveness of cardiac resynchronization therapy in the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. J Am Coll Cardiol 46:2311–2321
33. Yao G, Freemantle N, Calvert MJ et al (2007) The long-term cost-effectiveness of cardiac resynchronization therapy with or without an implantable cardioverter-defibrillator. Eur Heart J 28:42–51
34. Cleland JG, Daubert JC, Erdmann E et al (2005) The effect of cardiac resynchronization on morbidity and mortality in heart failure. N Engl J Med 352:1539–1549
35. Mark DB, Nelson CL, Anstrom KJ et al (2006) Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). Circulation 114:135–142
36. Sanders GD, Hlatky MA, Owens DK (2005) Cost-effectiveness of implantable cardioverter-defibrillators. N Engl J Med 353:1471–1480
37. Hohnloser SH, Kuck KH, Dorian P et al (2004) Prophylactic use of an implantable cardioverter-defibrillator after acute myocardial infarction. N Engl J Med 351:2481–2488
38. Bigger JT Jr (1997) Prophylactic use of implanted cardiac defibrillators in patients at high risk for ventricular arrhythmias after coronary-artery bypass graft surgery. N Engl J Med 337:1569–1575
39. Buxton AE (2003) The clinical use of implantable cardioverter defibrillators: where are we now? Where should we go? Ann Int Med 138:512–514
40. Tavazzi L (2000) Ventricular pacing: a promising new therapeutic strategy in heart failure. For whom? Eur Heart J 21:1211–1214
41. Boriani G (2006) From MADIT II to Search-MI Registry for primary prevention of sudden death in ischemic patients. Presented at the XII International Symposium on progress in clinical pacing, Rome
42. Boriani G, Biffi M, Russo M et al (2006) Primary prevention of sudden cardiac death: can we afford the cost of cardioverter-defibrillators? Data from the Search-MI Registry-Italian Sub-study. Pacing Clin Electrophysiol 29:S29-S34
43. Owens DK, Sanders GD, Heidenreich PA et al (2002) Effect of risk stratification on cost-effectiveness of the implantable cardioverter-defibrillator. Am Heart J 144:440–448

44. Gould PA, Krahn AD (2006) Complications associated with implantable cardioverter-defibrillator replacement in response to device advisories. JAMA 295:1907–1911
45. Chan PS, Stein K, Chow T et al (2006) Cost-effectiveness of a microvolt T wave alternans screening strategy for implantable cardioverter-defibrillator placement in the MADIT II-eligible population. J Am Coll Cardiol 48:112–121
46. Hlatky MA (2004) Evidence based use of cardiac procedures and devices. N Engl J Med 350:2126–2128
47. Stevenson LW (2006) Implantable cardioverter-defibrillators for primary prevention of sudden death in heart failure. Are there enough bangs for the bucks? Circulation 114:101–103
48. Sweeney MO, Schoenfeld MH, Cannom DS (2005) Rules of evidence: CMS and primary prevention of sudden cardiac death in systolic heart failure. Pacing Clin Electrophysiol 28:81–88

Hemodynamic Impact of Right Ventricular Pacing

Raúl Chirife, G. Aurora Ruiz, M. Cristina Tentori

Introduction

Right ventricular apical pacing has been the standard for cardiac pacing in view of lead mechanical stability and low pacing thresholds. Patients receiving rate-adaptive dual chamber pacemakers because of high-degree atrioventricular (AV) block and/or severe chronotropic incompetence have thus obtained the benefits of rate control for many decades, without any appreciable hemodynamic adverse effects, for as long as the device was appropriately programmed. Dual-chamber pacing provides the AV-block patient with normal sinus function the benefit of physiological rate response and restoration of AV sequence. Thus, the improvement of quality-of-life of DDDR in patients with clear pacing indications is beyond question. Nonetheless, in recent years there have been numerous studies showing the deleterious effects of right ventricular apical pacing [1–5]. Some of these studies, however, are not in agreement with clinical observations, mostly because experience shows that, in prolonged follow-up, patients with DDD devices and permanent right ventricular apical pacing do not necessarily end up with cardiac dilatation and heart failure, even after decades of pacing. If the patients do not have a clear indication for pacing and left ventricular (LV) function is already impaired, such as was the case in the David study [6], it is likely that artificial pacing will cause only side effects and offer no clinical benefit. Therefore, it is apparent to us that many questions remain to be answered.

Cardiology Department, Fernández Hospital, Buenos Aires, Argentina

What Do We Expect from DDDR Pacing?

DDDR pacemakers are primarily designed to offer the patient physiological rate adaptation and conservation of AV sequence. The former is accomplished by tracking sinus rate in patients with normal sinus function or by the use of a rate-adaptive sensor for patients with chronotropic incompetence. Regarding the latter, DDD pacemakers have nominal AV parameters similar to physiological PR intervals, resulting in a surface ECG with a "normal" P/QRS sequence.

What Do We Really Get from DDDR Pacemakers?

Rate adaptation is physiological only for patients with preserved sinus function and various degrees of AV block. All modern pacemakers can track sinus function either with a single VDD lead or with a two-lead system. However, if the patient has chronotropic incompetence, a rate-adaptive sensor is required. In practice, most of these sensors are not sufficiently sensitive or specific, or they have a slow response, since they use extra-cardiac markers of metabolic demand (body motion, respiration). False-positive responses are common in accelerometer-based sensors, since the pacing rate frequently increases unnecessarily with passive body motion (i.e., traveling by car). False-negative responses occur in cases of isometric effort, which increases metabolic demands in the absence of important body motion. Finally, delayed responses are observed with minute ventilation and QT sensors.

Conservation of AV sequence is also not achieved entirely. Although the nominal value of programmed AV is similar to normal PR, a "normal" AV sequence is accomplished only for the right heart, where pacing leads are placed. The left-heart AV interval, or better the mechanical left AV (the sequence between left atrial and LV contraction), may not necessarily be physiological with a "normal" right heart AV interval. This is because of the known sensing and pacing-induced delays [7–10]. These delays are:

1. *P-sense offset* (PSO), which is the time from the true onset of the right atrial P wave to the detection point by the atrial sensing amplifier of the pacemaker. Most pacemakers use a default PSO of around 30 ms, which on average is the time required by the pacemaker to detect the presence of a P wave. By virtue of this delay, the true AV interval is longer than the programmed one.
2. Right atrial pacing is known to lengthen the *interatrial delay* (IAD). This is because the right atrial lead is placed in the right atrial appendage

(longer delay), lateral wall, or interatrial septum (shorter delay). For practical reasons, this delay is measured from the onset of right atrial P to the onset or end of atrial transport (best detected by transmitral Doppler flow). This delay causes a shorter left-heart AV interval than programmed.

3. An *interventricular delay* (IVD) arises from the fact that right ventricular pacing, especially if done from the apex, causes a delay in LV depolarization. Because of this delay, the resulting left heart AV interval is longer than programmed.

From the above, it is clear that in most instances we do not get what we expect from DDDR pacing, unless it is meticulously programmed and a physiological rate-adaptive sensor is used. Nevertheless, even in those cases in which rate response is physiological and AV interval has been optimized, are there side effects of cardiac pacing?

What Is the Hemodynamic Impact of Acute Right Ventricular Apical Pacing?

Publications describing the effects of right ventricular pacing on LV function are not only abundant but controversial as well. Although it is well-known that the contraction wavefront of the left ventricle is affected whenever the depolarization wavefront is, many patients with DDDR pacemakers followed-up for decades show no demonstrable deleterious hemodynamic or clinical impact of right ventricular (RV) pacing on cardiac function. In fact, patients with long periods of bradycardia preceding pacemaker implantation may show reverse remodeling of the left ventricle after DDDR implant. It is our intention to clarify several concepts related to pacing and cardiac function by offering specific examples of typical acute and chronic effects of RV pacing on LV function.

Effect of Pacing Rate

Since currently used rate-adaptive sensors are "non-physiological", it may be expected that the pacing rate governed by the sensor may not always be appropriate. If the pacing rate is too slow, metabolic demands may not be met, and if it is too fast, such as in a false-positive sensor response, symptoms may arise and blood pressures and cardiac output may drop. In the example of Fig. 1, a DDDR pacemaker implanted for complete AV block was programmed to optimize the AV interval. The DDD pacing rate was

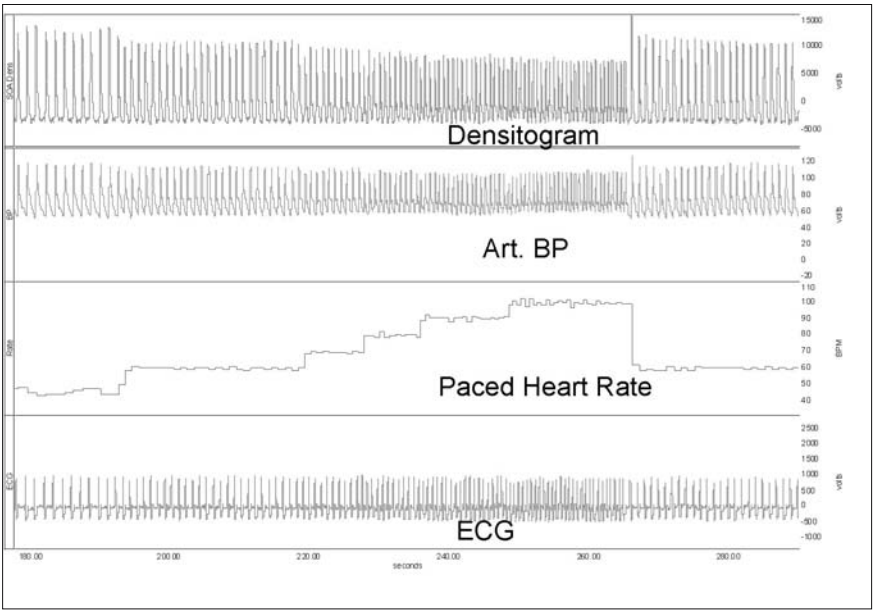


Fig. 1. Effect of rate of cardiac hemodynamics. Patient with a DDD pacemaker. Rate was increased from 50 to 100 bpm, while blood pressure was recorded with a noninvasive blood-pressure monitor allowin beat-by-beat measurements (channel 2). Channel 1 is a photoplethysmographic recording of the right supraorbital artery, channel 3 is a marker of prevailing heart rate, and channel 4 is the surface ECG lead II. As rate is increased, it can be seen that systolic blood pressure drops and diastolic blood pressure rises slightly. The peak-to-peak changes in the photodensitogram are directionally similar to blood pressure changes and suggest a drop in stroke volume during higher pacing rates

increased from 50 to 100 bpm, while blood pressure was recorded with a noninvasive blood-pressure monitor that allows beat-by-beat measurements (channel 2). Channel 1 is a photoplethysmographic recording of the right supraorbital artery, channel 3 is a marker of prevailing heart rate, and channel 4 is the surface ECG lead II. It can be seen that, as the rate is increased, systolic blood pressure drops and diastolic blood pressure rises slightly. The peak-to-peak changes in the photodensitogram are directionally similar to blood-pressure changes and suggest a drop in stroke volume during higher pacing rates. Figure 2 is a plot of the changes in the same patient. Systolic pressure area, a surrogate of stroke volume [11], and its product with heart rate (surrogate of cardiac output) drop during incremental pacing. From these experiments it is inferred that faster pacing rates do not necessarily increase cardiac output, at least in patients who do not have heart failure.

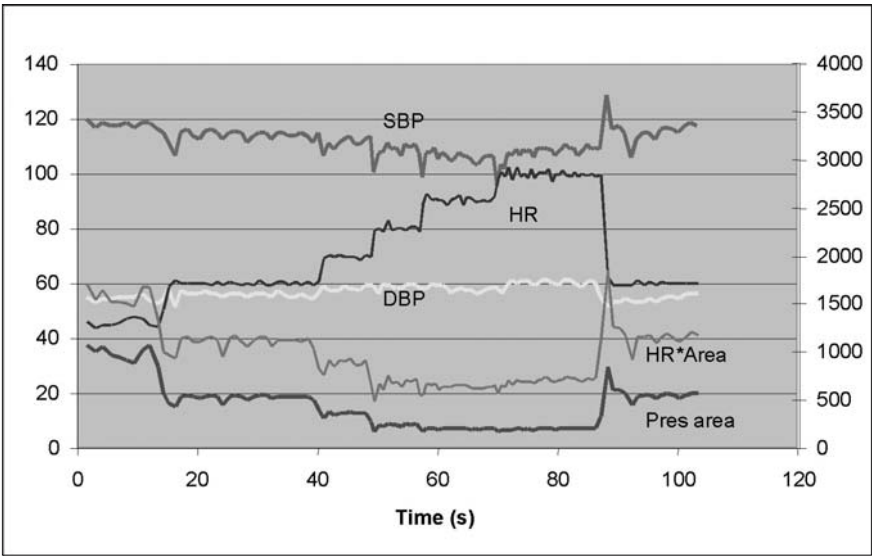


Fig. 2. Effect of rate of cardiac hemodynamics. Plot of hemodynamic changes in the same patient as Fig. 1. Systolic pressure area, a surrogate of stroke volume, and its product with heart rate (surrogate of cardiac output) drop during unnecessary incremental pacing at rest

The effect of incremental pacing on arterial blood pressure is, however, different in the experimental animal (Fig. 3). For example, in a dog instrumented for another study, the animal had high-fidelity pressure catheters inserted in the aorta and right ventricle, and fluid-filled catheter in the right atrium. An electromagnetic probe was inserted in the pulmonary artery for continuous monitoring of pulmonary flow. A bipolar screw-in pacemaker lead was inserted in the right atrial appendage and another in the RV apex. Intracardiac impedance was used to assess instantaneous RV volume changes [12] (transvalvular impedance, measured from the right atrial ring to the RV ring electrodes). The tracings reveal that incremental pacing increases blood pressure in the dog (probably due to the Bowditch effect), but stroke volume is reduced due to the Starling effect (shorter filling time), as indicated by the reduced flow amplitude in the pulmonary artery.

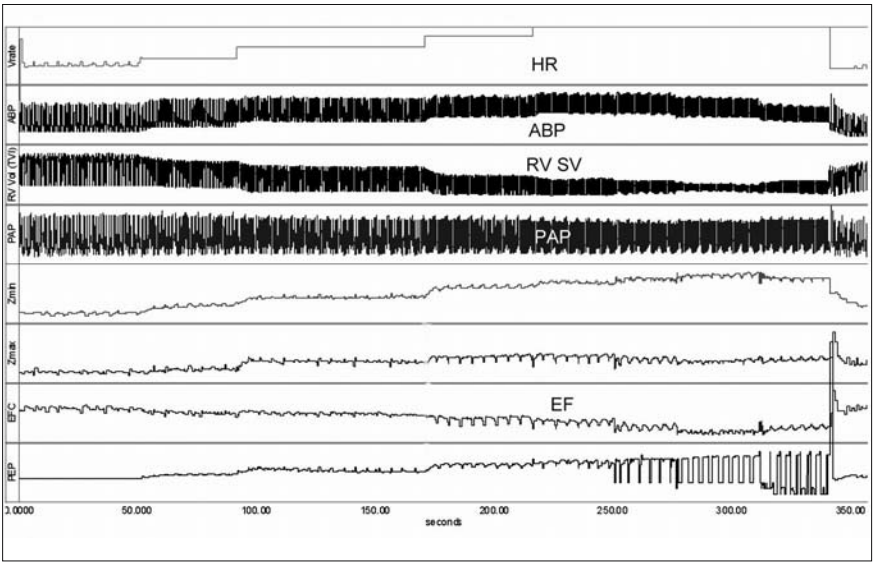


Fig. 3. Effect of rate of cardiac hemodynamics. Dog instrumented for another study, with high-fidelity pressure catheters in the aorta and right ventricle, and fluid-filled catheter in the right atrium. A flow probe was placed in the pulmonary artery. A bipolar screw-in pacemaker lead was inserted in the right atrial appendage and another in the RV apex. Intracardiac impedance was used to assess instantaneous RV volume changes [12]; transvalvular impedance (TVI), measured from the right atrial ring to the RV ring electrodes. It can be seen that incremental pacing at rest increases blood pressure (probably due to the Bowditch effect), but stroke volume and ejection fraction (EF) measured from TVI are reduced as well

Direct Effect of RV Pacing on LV Function

Figure 4 shows an example in a patient with sick sinus syndrome and normal QRS morphology. After a 5-min stabilization period with atrial pacing at 70 bpm and normal AV conduction, RV pacing was started by shortening the AV interval, while insuring that the left-heart AV interval remained unchanged (see "How Should the Heart Be Paced?"). RV pacing was switched on and off at the arrows by shortening or lengthening the AV interval. Although no gross change in systolic (channel 1) or diastolic (channel 3) blood pressure is noted outside of the natural fluctuations, closer observation of the beat-to-beat blood pressure changes following the switch to RV pacing (Fig. 5) reveals significant morphological changes in the arterial pulse: Peak systolic pressure drops and the pulse becomes narrower (shorter ejection time) for the first few beats. After the fourth beat, systolic and diastolic blood pres-

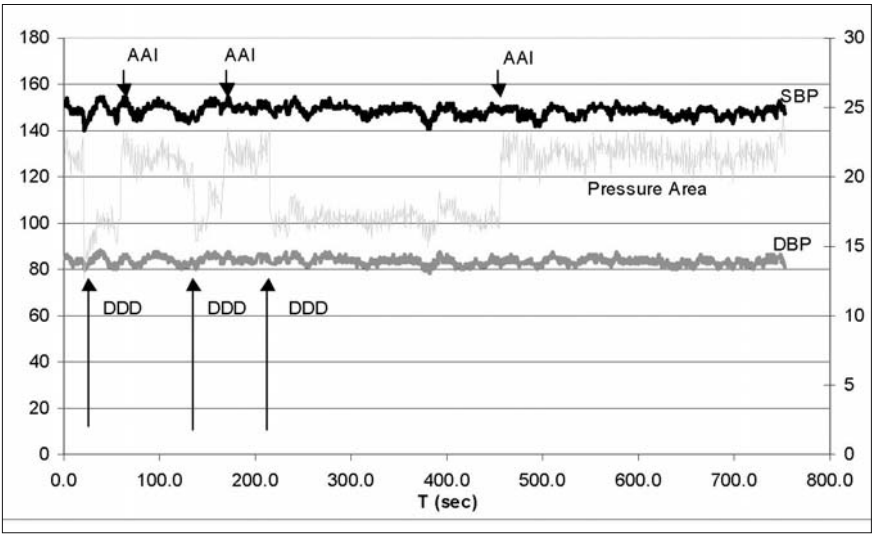


Fig. 4. Effect of RV pacing on cardiac hemodynamics. Patient with sick sinus syndrome and normal QRS morphology, after a 5-min stabilization period with atrial pacing at 70 bpm and normal AV conduction. RV pacing was switched on and off at the arrows by shortening or lengthening the AV interval. Although no gross change in systolic (channel 1) or diastolic (channel 3) blood pressure is noted outside, the area under pressure pulse (channel 2) is decreased, indicating a reduction in SV

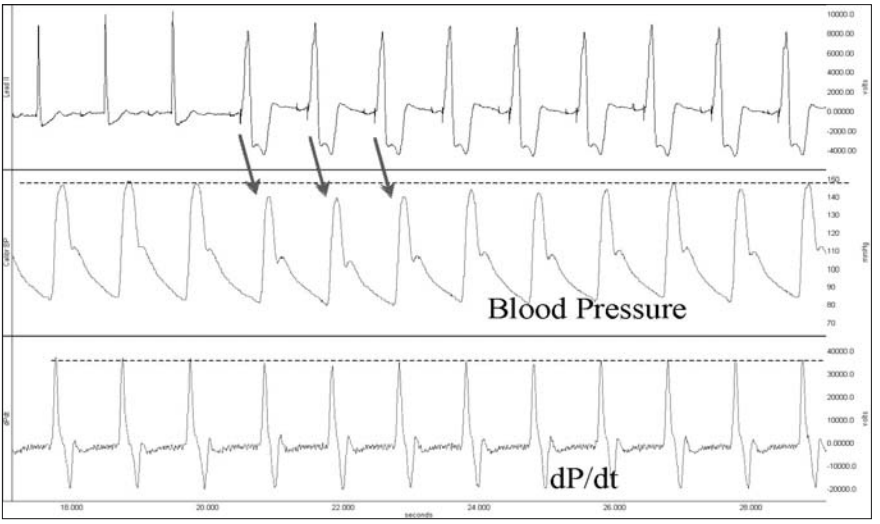


Fig. 5. Effect of RV pacing on cardiac hemodynamics. Same patient as in Fig. 4. Closer observation of the beat-to-beat blood pressure changes with RV pacing reveals significant morphological changes in the arterial pulse: peak systolic pressure drops and the pulse becomes narrower (shorter ejection time) for the first few beats. After the fourth beat, systolic and diastolic blood pressures return towards normal, probably as a consequence of the baroreflex

sures return towards normal, probably as a consequence of the homeostatic mechanisms, but the beat-by-beat area under blood pressure curve (a surrogate of stroke volume), drops and remains low. Although systolic pressure returns to normal, the area under the pulse remains low for at least 8 min of RV pacing. In addition to blood-pressure changes, RV pacing causes a significant lengthening of the left pre-ejection interval, a marker of interventricular dyssynchrony, as seen in the example of Fig. 6. In this case, the LV pre-ejection interval lengthened by 70 ms during RV stimulation.

To study the net effect of RV pacing on RV and LV function in the dog experiment described above, the animal was subjected to alternate (beat by beat) intrinsic and RV pacing in order to prevent baroreflex compensatory mechanisms. The animal was atrial paced at 10 beats above intrinsic throughout the experiment to maintain a constant heart rate, and the AV interval was lengthened and shortened in alternate beats. During RV pacing, the left heart AV interval remained unchanged compared to the atrial-paced rhythm. The following observations can be made regarding the hemodynamic effects of RV pacing, as seen in Fig. 7: (1) there is a drop in systolic arterial pressure; (2) RV stroke volume, as measured by intracardiac transvalvular impedance, is reduced; (3) pulmonary-artery flow is reduced; (4) there is a reduction in the area under pulse pressure (a surrogate of stroke volume); (5) the LV pre-ejection interval is prolonged; (6) RV pressure is reduced; and (7) the RV pre-ejection interval is prolonged.

In summary, from this experiment it can be concluded that RV pacing indeed causes deterioration of both RV [13] and LV performance [1–6].

Effect of AV Interval on LV Function

If the left-heart mechanical AV interval is either too short or too long it may be associated with deleterious hemodynamic effects. A normal left-heart AV interval can be defined as that causing left atrial transport to be completed just before LV contraction. If the AV interval is too short, atrial contraction may overlap with LV isometric contraction; if it is too long, atrial contraction may overlap with isometric relaxation of the preceding cardiac cycle. These two conditions impair cardiac performance by two different mechanisms. The first is related to the Starling principle; it is more evident when the AV interval is too long and atrial contraction takes place too early in diastole, causing inadequate LV filling (ineffective atrial kick). The other results from overlap of left atrial and LV pressures; in this case, atrial contraction takes place while the LV pressure is too high to be overcome, such as during isometric relaxation and contraction. When this happens, atrial

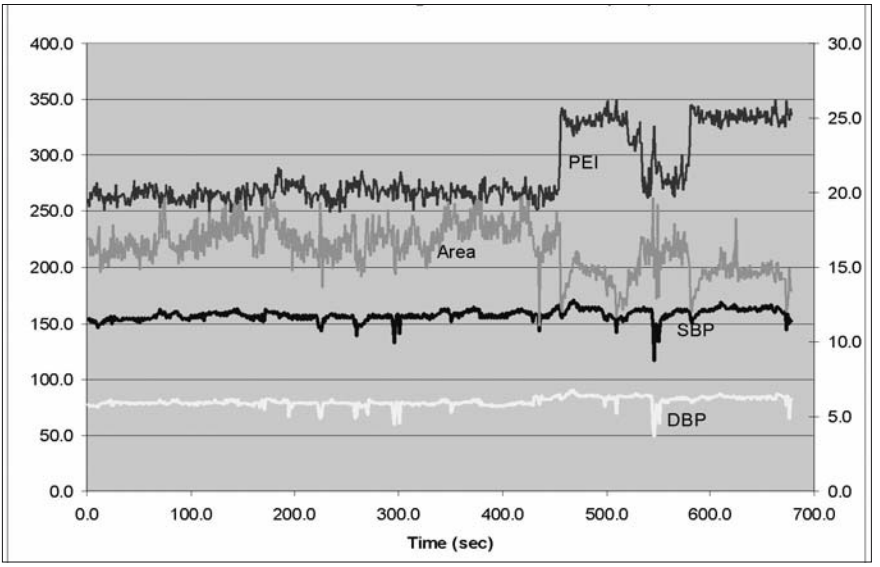


Fig. 6. Effect of RV pacing on cardiac hemodynamics. In addition to blood-pressure changes, RV pacing causes a significant lengthening of the left pre-ejection interval (PEI), a marker of interventricular dyssynchrony. In this case, PEI lengthened by 70 ms during RV stimulation

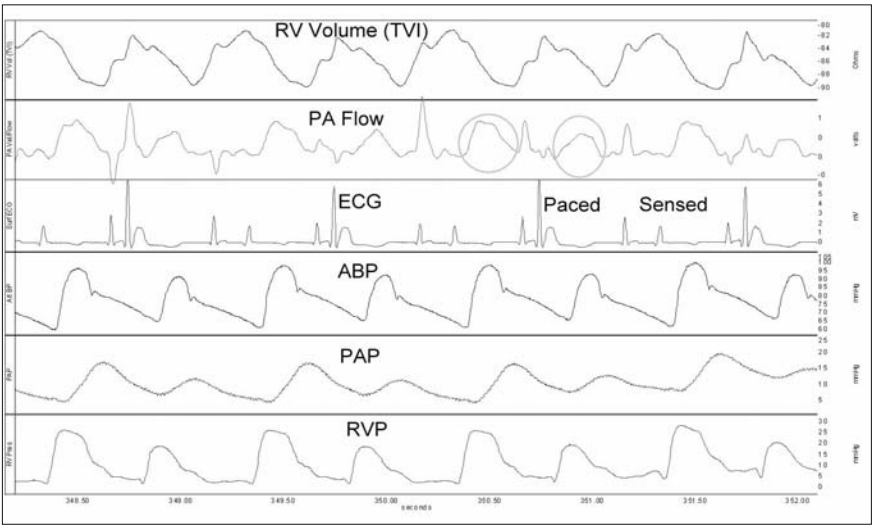


Fig. 7. Effect of RV pacing on cardiac hemodynamics, dog experiment. The following changes are seen during RV apical pacing: (1) drop in systolic arterial pressure; (2) drop in RV stroke volume (as measured by TVI) is reduced; (3) reduction of pulmonary-artery flow (4) there is a reduction in the area under pulse pressure (a surrogate of stroke volume); (5) the LV pre-ejection interval is prolonged; (6) RV pressure is reduced; and (7) the RV pre-ejection interval is prolonged. In summary, this experiment reveals that RV pacing causes deterioration of both RV [13] and LV performance [1–6]

transport is severely limited or absent (thus affecting LV filling by the Starling mechanism). Also, all of the left-atrial contraction pressure backs up into the pulmonary circulation, causing an increase in pulmonary wedge pressure. This phenomenon may explain symptoms in patients with first-degree AV block during exercise, when P waves overlap T waves, the so-called pacemaker syndrome without a pacemaker [14].

What Is the Hemodynamic Impact of Chronic RV Apical Pacing?

From a database of 869 patients with chronically implanted pacemakers, 272 patients with measurements of LV diastolic dimension (LVDD) and left atrial dimension (LAD) in two ECGs obtained at least 6 months apart after pacemaker implant were included in the study [15]. Changes in LV and left atrial diameters were evaluated after long follow-up periods in two groups: (1) RV-paced group (RVP), comprising patients with > 60% RV pacing on Holter function of the pacemaker and (2) RV sensing group (RVS), comprising patients with < 60% RV pacing. The two groups were similar in age, clinical diagnosis, and pacing mode (all p values were non-significant). Follow-up time was 55 ± 37 months in the RVP group and 48±32 months in the RVS group (p = non-significant). Since in the RVP group 51% of the subjects were males vs. 28% in the RVS group ($p = 0.0051$), patients were separated by gender for analysis. At the end of follow-up it was found that male patients receiving RVP had more left atrial and LV dilatation than those with RV sensing. However, in the RVP group, 40% of patients had either no change (11%) or a reduction of LV size (29%) (Fig. 8).

How Should the Heart Be Paced?

If the patient needs a DDDR device, and atrial and ventricular leads are in the right atrial appendage and RV apex, respectively, several actions can be taken to minimize the side effects of DDDR pacing:

Rate Response

For patients with chronotropic incompetence, the use of a physiological sensor that parallels neurohormonal changes associated with increased metabolic demands is ideal. One such sensor is under evaluation in Europe (Sophòs 151, Medico SpA, Padova, Italy). It is based on transvalvular impedance, which calculates ejection fraction (contractility marker) from relative

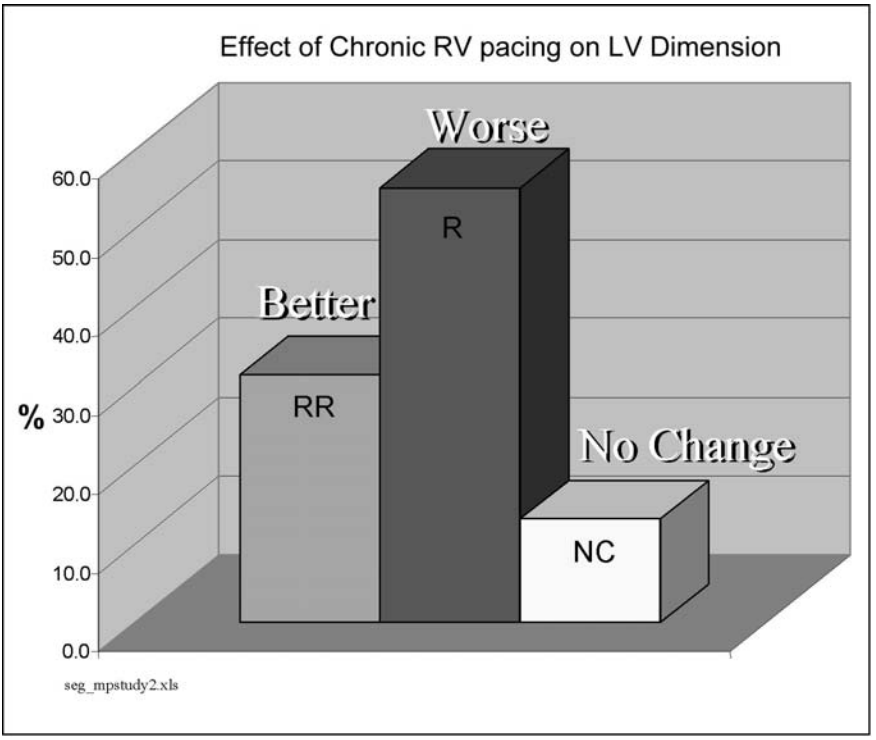


Fig. 8. Effect of chronic RV pacing on LV dimension. Long-term RV apical pacing produces mixed results regarding LV chamber size: After a mean follow-up time 55 ± 37 months, 60% of patients had LV dilatation, while 29% of patients had reduction and 11% no change in chamber size. This indicates that there is an interaction between the benefits of pacing and the adverse effects of ventricular pacing. *RR*, Reverse remodeling; *R*, remodeling; *NC*, no change

ventricular volume changes. The mode of operation is relatively simple: the device measures end-diastolic time velocity integration (TVI) (a surrogate of end-diastolic volume) and end-systolic TVI (a surrogate of end-systolic volume). Based on these measurements, changes in the relative ejection fraction are calculated [12]. This sensor is expected to minimize false positive and false negative responses leading to patient's symptoms. Other contractility markers may be valuable as well.

AV Interval Optimization

This procedure is critical to avoid pacemaker syndrome. One simple way would be to offset the delays caused by atrial and ventricular sensing and

pacing (see above). A previously published equation [8, 16] could be used to evaluate patients with complete AV block: *Right AV = IATD – PSO – IVD*. In this equation, IATD is the interatrial transport delay, the time from the onset of right-atrial P (or pacing pulse) to the end of left-atrial transport (approximately the peak of mitral Doppler A wave); PSO is the P-sense offset, the time needed by the pacemaker to detect the onset of the P wave; and IVD is the interventricular delay, measured as the extension of left pre-ejection interval caused by RV apical pacing. With this calculation, the shortest possible AV interval is used that allows atrial transport to end just before the onset of LV contraction. Since IATD is longer with right atrial pacing (about 50 ms) than with intrinsic P waves, the resulting right-heart AV interval during atrial pacing will necessarily be longer. By restoring the left-heart AV interval to a normal value, some of the hemodynamic consequences of RV pacing can be diminished.

Minimizing RV Pacing

Important side effects of RV apical pacing are the inter- and intraventricular mechanical dyssynchronizations caused by the ectopic origin of the depolarization wavefront. This causes unequivocal hemodynamic changes, as described above. Some of these may be compensated by the baroreflex, but in patients with already deteriorated LV function these minor changes may be of importance. From a hemodynamic standpoint, it seems preferable to have a long PR with intrinsic AV conduction and narrow QRS rather than pacing the RV with an optimal AV interval. However, how long an AV is too long? The maximal duration of AV (or PR) depends on several factors, as previously shown. These are heart rate and interatrial and interventricular delays (the latter will dictate the duration of electromechanical systole). Whenever right ventricular pacing is inevitable, such as in complete AV block or severe 1st degree AV block during exercise, it must be done with a normalized mechanical left AV interval as described above, to avoid pacemaker syndrome. Therefore, all the available algorithms to reduce ventricular pacing must be used with caution in order to avoid pacemaker syndrome at faster rates. In the presence of left bundle branch block, which has similar hemodynamic implications as RV pacing, avoidance of pacing may not be as important, since dyssynchrony is already present. In this case, it is expected that simultaneous RV and LV stimulation with biventricular pacemakers may improve, at least in part, inter- and intraventricular dyssynchrony.

Conclusions

From the above observations, it is apparent that cardiac pacing offers both benefits and side effects that have to be carefully weighed for each individual patient. If the right ventricle must be paced, it has to be done with a normalized AV interval and only when strictly necessary. The need for RV pacing is determined not only by the presence of complete AV block but also in situations of first-degree AV block during exercise, to avoid "pacemaker syndrome without a pacemaker" [14]. In patients with left bundle branch block, there is so far no evidence that RV pacing further deteriorates LV function. Thus, avoidance of RV pacing in these patients does not theoretically provide any clinical benefit except for increased device longevity.

References

1. Thambo JB, Bordachar P, Garrigue S et al (1999) Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. Pacing Clin Electrophysiol 22(8):1234–1239
2. Ritter O, Koller ML, Fey B et al (2002) Progression of heart failure in right univentricular pacing compared to biventricular pacing. Europace 4(1):61–65
3. Szili-Torok T, Kimman GP, Theuns D et al (2006) Deterioration of left ventricular function following atrio-ventricular node ablation and right ventricular apical pacing in patients with permanent atrial fibrillation. Indian Pacing Electrophysiol J 6(3):142–152
4. Tantengco MV, Thomas RL, Karpawich PP (2006) Left ventricular dysfunction after long-term right ventricular apical pacing in the young. Rev Esp Cardiol 59(6):553–558
5. Lee MA, Dae MW, Langberg JJ et al (2003) Effects of long-term right ventricular apical pacing on left ventricular perfusion, innervation, function and histology. J Cardiovasc Electrophysiol 14(11):1180–1186
6. Wilkoff BL; Dual Chamber and VVI Implantable Defibrillator trial investigators (2006) The Dual Chamber and VVI Implantable Defibrillator (DAVID) Trial: rationale, design, results, clinical implications and lessons for future trials. Kardiol Pol 64(10):1082–1091
7. Chirife R, Ortega DF, Salazar AI (1991) Nonphysiological left heart AV intervals as a result of DDD and AAI "physiological" pacing. Pacing Clin Electrophysiol 14(11 Pt 2):1752–1756
8. Chirife R (1995) Proposal of a method for automatic optimization of left heart atrioventricular interval applicable to DDD pacemakers. Pacing Clin Electrophysiol 18(1 Pt 1):49–56
9. Chirife R (1994) Left heart function during right heart pacing. Pacing Clin Electrophysiol 17(9):1451–1455 (Editorial, 2002 25:888–896)
10. Chirife R (1998) Importance of interatrial and interventricular delays in the performance of dual chamber pacemakers. In: Barold S, Mujica J (eds) Recent advances in cardiac pacing. Goals for the 21st century. Vol 4. Futura, Armonk NY

11. Wesseling KH, Jansen JRC, Settels JJ, Schreuder JJ (1993) Computation of aortic flow from pressure in humans using a non-linear, three-element model. J Applied Physiol 74:2566–2573
12. Chirife R, Ortega DF, Salazar AI (1993) Feasibility of measuring relative right ventricular volumes and ejection fraction with implantable rhythm control devices. PACE 16:1673–1678
13. Dwivedi S, Bansal S, Puri A et al (2001) Diastolic and systolic right ventricular dysfunction precedes left ventricular dysfunction in patients paced from right ventricular apex. J Am Coll Cardiol 37(8):2093–2100
14. Chirife R, Ortega DF, Salazar AI (1990) "Pacemaker syndrome" without a pacemaker. Deleterious effect of first degree AV block. R Eur Tech Biomed 12:22
15. Chirife R, Ruiz A, Tentori C, Sztyglic E (2006) Does chronic right ventricular pacing cause further remodeling of left heart chambers? J Cardiac Failure 12:S65
16. Chirife R. US Pat #5,179,949

Hemodynamics in Standard Cardiac Pacing

Milos Taborsky

Early Experiences with Rate-Responsive Pacing

The first rate-responsive pacing systems were introduced by Center [1] and Lagergren [2] in 1964–1966. Both systems used P waves, which were detected with an atrial electrode positioned by thoracotomy or mediastinoscopy to trigger the ventricular pacing after a short delay. A comparison of the acute data with VVI pacing showed that the cardiac index increased by 10–30%. Despite these promising data, atrioventricular (AV) synchronous pacemakers were not widely used until the late 1970s.

The first extensive study of the acute hemodynamic effect of AV synchronous pacing was carried out by Karlöf [3] in a study of 25 patients. With a change from fixed-rate ventricular pacing of 70 bpm to AV synchronous pacing, cardiac output increased by 20%. The change in cardiac output was obtained without an increase in left ventricular filling pressure.

One of the first comparisons between the acute and long-term hemodynamic effects of ventricular and AV pacing was made by Kruse [4]. No significant differences were found between acute and long-term results based on an acute invasive study of hemodynamics at rest and during exercise in AV synchronous pacing. The increases in cardiac output and stroke volume were significantly lower in patients with fixed-rate ventricular pacing.

Since the 1980s, dual chamber pacing and DDD/DDDR modes have become the standard for physiological pacing. DDD/R mode has two fundamentals advantages: (1) AV synchrony and restoration of atrial function, and (2) adaptation of heart rate to the sensed atrial activity. However, the ques-

Cardiology Department, Na Homolce Hospital, Prague, Czech Republic

tion remains: are these advantages truly physiologic, especially in patients with depressed left ventricular function and right apical pacing?

Heart Rate and Atrioventricular Synchrony

The importance of increasing heart rate to increase cardiac output during exercise has been clearly documented in several studies [5, 6]. Since the improvement in exercise performance is due predominantly to an increase in heart rate, it is expected that favorable hemodynamic results will be obtained by rate-adaptive systems.

In the era of ventricular rate-responsive pacing (VVIR), a number of different sensors have been incorporated into pacemakers. Many investigations have compared the exercise hemodynamics between sensor-driven VVIR pacing and those of VVI pacing. Percentage improvements of heart rate and exercise duration during symptoms-limited exercise in the VVIR and VVI pacing modes was determined in several large series for currently available rate-adaptive systems. The results showed variable but consistent increases of 69% in rate and 32% in exercise tolerance in patients with VVIR pacing [7, 8]. Early comparisons of patients with VVI and VVIR pacing consisted of rather small series and mixed patient populations in terms of pacemaker indications, symptoms of heart failure, and degree of ventricular dysfunction.

The use of an atrial sensing electrode to synchronize ventricular stimulation with intrinsic sinus node discharge (atrial synchronous ventricular pacing, VAT) resulted in a more physiologic mode of pacing [9, 10]. Addition of a ventricular sensing capability to this pacing mode resulted in the development of the VDD mode as a combination of VAT plus VVI.

The standard approach to the management of complete symptomatic heart block involves the use of pacemaker units that provide not only basic ventricular pacing support but also adaptation of the pacing rate to physiologic needs. Two patterns of hemodynamic response to higher rates of ventricular pacing have been described. In the *flat response,* after an initial increase in heart rate and cardiac output (rate increase from 30 to 60 bpm), cardiac output remains relatively constant as stroke volume decreases with further rises in heart rate [11]. This response occurs most often in individuals with normal cardiac function and indicates that cardiac output is relatively independent of heart rate. In the *peaked response,* cardiac output increases progressively until the optimal pacing rate is achieved and further increases are not possible [12]. The peaked response is more commonly observed in patients with myocardial disease, in whom cardiac output is

more sensitive to changes in preload, afterload, myocardial contractility, and distensibility. The major factors limiting the increase in resting cardiac output that can be achieved by pacing rate alone are shortened diastolic filling time, reduced left ventricular compliance at higher rates of ventricular pacing, and increased systematic resistance [7, 8].

AV Block and Ventricular Pacing

In patients with acquired complete heart block, cardiac output is less than in patients with a normal heart rate [13]. As a result, compensatory increases in sympathetic tone and end-diastolic ventricular volume occur, leading to higher atrial rates, enhanced ventricular contractility, and increased stroke volume [14].

The importance of the duration of overload is confirmed by the observation that the frequency of congestive heart failure symptoms in patients with complete heart block correlates with the duration of heart block. Congestive heart failure has been described during chronic complete heart block even in patients with normal ventricular function. In two-thirds of patients with complete heart block and congestive heart failure, symptoms were induced by ventricular pacing alone, and no additional medical therapy was required [15]. Janousek described that, in pediatric patients with congenital heart block, implantation of a pacemaker and right apical pacing resulted in increased left ventricular dilatation and the development of heart failure [16]. However, longer-lasting ventricular pacing in hearts with AV block may lead to left ventricular dilatation and hypertrophy secondary to the effect of asynchronous activation in the adult population as well [17–19]. These data strongly suggest that in the patient with AV block the short- and long-term effects of RV pacing are different, indicating that the choice of apical or septal right ventricular pacing together with algorithms minimizing ventricular pacing may be essential.

Role of Optimal AV Interval During Pacing

An optimally timed atrial contraction (before the isovolumetric contraction phase) maximizes filling and thereby its output, according to the Frank-Starling principle. Premature atrial contraction (as in the case of first-degree AV block and dual-chamber pacing with long AV intervals) decreases the pump function of the atrium. In addition, it may initiate early mitral valve closure, thereby limiting ventricular diastolic filling time. This observation

can be explained by the importance of three factors collaborating to achieve optimal closure of the AV valves: (1) termination of transvalvular flow at the end of the atrial contraction forces the valvular leaflets to approach one another; (2) at the beginning of ventricular contraction, the anulus of the AV valve contracts, as do the papillary muscles that hold the leaflets; (3) at the start of ventricular contraction, ventricular pressure rises above atrial pressure, and the valves close. When these factors are misaligned, the opportunity for diastolic and systolic mitral regurgitation arises [20].

AV Interval in Patients with Normal Left Ventricular Function

The AV interval that maximizes resting cardiac output during dual-chamber pacing varies widely among patients, and has been reported in most studies to be between 125 and 200 ms [21, 22]. Optimal AV interval can be determined in most patients during dual-chamber pacing by means of several different invasive and noninvasive measurements. Most commonly, optimal AV interval is assessed by left ventricular outflow recording with Doppler echocardiography [23].

The optimal AV interval determined with Doppler echocardiography correlates well with the optimal AV interval determined with radionuclide ventriculography. Many factors, in addition to interpatient variability, may influence the determination of optimal AV interval in the same patient, such as heart rate, paced or sensed atrial event, posture, and exercise [24, 25]. During the lifetime of a patient, there may be situations in which the optimal AV interval is different from the AV interval considered to be physiologic. Optimal hemodynamics at AV intervals in the range of 80–120 ms for complete heart block complicating an acute myocardial infarction or after cardiac surgery reflect intrinsic catecholamine levels or the administration of inotropic drugs and reduced left ventricular compliance in these acute situations.

AV Interval in Patients with Depressed Left Ventricular Function

In patients with depressed left ventricular function, relaxation is slower than in normal hearts. Less blood enters the ventricles during the rapid filling phase, as can be observed from the lower E waves on Doppler echocardiograms. Therefore, failing hearts are more dependent on properly timed atrial contraction than normal hearts.

The actual role of atrial contraction in patients with dilated ventricles

and low ejection fraction varies among individuals. The systolic pump function of the left atrium is described as a "shoulder" in the left ventricular pressure tracing, and the left ventricle does not start contracting immediately after atrial contraction. If this plateau lasts too long, diastolic mitral regurgitation may occur, as is the case in patients in whom a decrease in left ventricular pressure occurs after atrial contraction. About 20% of patients in heart failure studies for whom complete hemodynamic data are available show this type of diastolic left ventricular pressure waveform.

Examination and calculation of the cardiac output with Doppler echocardiography, as is easily and frequently done in patients with dual-chamber pacemakers, is more problematic in patients with depressed left ventricular ejection fraction [25]. The number of repetitions required to obtain a reproducible evaluation of the optimal AV interval makes this method impractical for patients with depressed ejection fraction [26, 27].

Hemodynamic Consequences of Ventricular Asynchrony

Abnormal asynchronous activation causes abnormal contraction patterns, inefficient and depressed pump function, and, later, ventricular remodeling. Wiggers recognized the importance of normal electrical activation of the ventricle for optimal pump function in 1925 [28]. In the 1960s, Kosowsky compared right ventricular apex pacing with His-bundle pacing, the latter maintaining the normal activation but allowing variation of the AV interval. It was concluded that AV synchrony and proper sequence of activation are equally important [29].

The combination of acute adverse hemodynamic effects and long-term ventricular remodeling may explain why abnormal electrical activation and asynchronous electrical activation have major implications for the clinical status of the patient. Several studies have shown that morbidity and mortality are higher in patients with long-term AV apex pacing than in those with atrial pacing [30, 31]. In patients with sinus-node disease and good ventricular function, the risk for development of heart failure was significantly high after more than 7 years in a comparison of atrial pacing and right ventricular pacing [32]. In a similar population, the risk of hospitalization for heart failure within 3 years increased with the percentage of time the patients underwent pacing at the right ventricular apex [33]. The development of heart failure and atrial fibrillation was more sensitive to the percentage of pacing than to the pacing mode (single- or dual-chamber pacing). In patients who received an implantable cardioverter-defibrillator (ICD), the

incidence of heart failure was higher within a year in patients paced at VVI 70 bpm rather than in backup mode [34].

Experimental proof of the negative effect of left bundle branch block (LBBB) on hemodynamics has come from studies in an animal model of LBBB [35, 36]. The negative effect of LBBB on left ventricular pump function was shown in several studies [37–39]. Therefore, it appears that right ventricular apex pacing and LBBB are conditions that increase the risk of heart failure and cardiac death, especially in patients with already compromised function. For this reason, efforts to either prevent right ventricular apex pacing or correct LBBB are rapidly growing. With our knowledge of electrical impulse conduction (electroanatomical mapping and other techniques), it becomes obvious that the best solution may depend on whether the heart has normal or disturbed intrinsic conduction within the ventricles.

Long-term epidemiological studies determining cardiovascular morbidity have shown that LBBB always carries a poor prognosis. In a 29-year follow-up study of 3,983 pilots, the morbidity and cardiovascular mortality rate among those showing signs of LBBB was 17.2%, and the most common clinical event observed was sudden death without any previous symptoms (17%). These percentages are ten times higher than those in subjects without LBBB [40]. In the Framingham Study, cumulative cardiovascular mortality over 10 years was approximately five times higher in patients with LBBB than in those without LBBB [41].

The Role of Modern Physiological Sensors in Pacing Hemodynamics

The role of hemodynamic sensors is to assess the inotropic status of the heart and adapt the pacing rate to the contractility and exercise level. Most of the hemodynamic sensors available in implantable pacemakers are sensitive to different expressions of the strength of cardiac contraction, which depends in turn on myocardial contractility (controlled by the autonomic nervous system) and preload (independent of the autonomic nervous system), according to Starling's law [42]. Therefore, any hemodynamic parameter affected by the cardiac contraction strength can reliably reflect the input of the autonomic nervous system to the heart only if the preload is assessed and accounted for.

The issue has been addressed by a new sensing system based on transvalvular impedance (TVI), which is the impedance recorded between the right atrium and right ventricle. TVI reflects the hemodynamic changes that occur during the cardiac cycle, the minimum TVI being associated with the

maximum diastolic volume and the maximum TVI with the minimum systolic volume. In addition, TVI fluctuations are observed only in the presence of ventricular ejection [43]. The signal is missing whenever the volume does not change, as in the case of capture loss. Assuming an inverse relationship between TVI and ventricular volume, the signal can provide information on relative changes in end-diastolic volume, end-systolic volume, stroke volume, and ejection fraction.

Since changes in stroke volume and end-diastolic volume are monitored, the inotropic index can be derived from the relationship between the two parameters, a classic way to describe contractility while accounting for the effect of preload on pump function. Indeed, the TVI inotropic index differs from the one obtained from the ratio of the current stroke volume, corrected for preload changes with respect to basal conditions, and basal stroke volume. The product of the inotropic index times the resting rate and a programmable gain factor, added to the basic rate, defines the TVI-indicated pacing rate.

In addition to the standard pacing function, the pacemaker records TVI, determines the minimum and maximum value in each cycle, checks the data to confirm or deny ejection, averages the results over a programmable number of cycles, and calculates inotropic index and TVI, which after a smoothing process becomes the pacing rate applied by the device. Tests were performed under overdrive atrial pacing to exclude the possibility that the increase in the inotropic index could be dependent on a previous increase in cardiac rate. On the contrary, even if the sinus rate was suppressed, isoproterenol administration induced a clear-cut increase in inotropic index, TVI, and pacing rate. Moreover, an increase in cardiac rate independent of the adrenergic input, induced by reprogramming the pacemaker basic rate, had no effect on the inotropic index, demonstrating that the TVI rate-responsive system is not affected by positive feedback. Another important application of the TVI sensor is the confirmation of systolic ejection after ventricular sensing or pacing. The algorithm compares the maximums TVI detected in a rate-adapted systolic window with a reference value derived from the average end-diastolic TVI and end-systolic TVI recorded in eight previous cycles. If the reference is reached or exceeded, ejection is confirmed; otherwise it is denied and the stimulator activates an alarm modality [44].

TVI could be an effective tool for pacing rate auto-regulation based upon changes in cardiac inotropic state; it is adapted according to adrenergic input, either in the presence or absence of intrinsic rate changes. Furthermore, a TVI rate-responsive system is free of positive feedback effects [45]. Therefore, pacing algorithms based on TVI may offer a safe and

reliable alternative of rate-responsive pacing reflecting physiological hemodynamics in patients with both normal and depressed left ventricular function.

References

1. Center S, Nathan D, Wu CY et al (1964) Two years of clinical experience with the synchronous pacemaker. J Thorac Cardiovasc Surg 48:513–526
2. Lagergren H, Johansson L, Karlof J et al (1966) Atrial-triggered pacemaking without thoracotomy. Acta Chir Scand 132: 678–695
3. Karlöf I (1975) Hemodynamics effect of atrial triggered versus fixed rate pacing at rest and during exrecise in complete heart block. Acta Med Scand 197:195–210
4. Kruse I, Bevegård S, Ovenfors CO et al (1982) A comparison of acute and long-term hemodynamics effects of ventricular inhibited and atrial synchronous pacing. Circulation 65:846–855
5. Kristensson B, Arnman K, Ryden L et al (1985) The hemodynamic importance of atrioventricular synchrony and rate increase at rest and during exercise. Eur Heart J 6:773–778
6. Perhsson SK (1983) Influence of heart rate and atrioventricular synchrony on maximal work tolerance in patients treated with artificial pacemakers. Acta Med Scand 214:311–315
7. Benchimol A, Li YB, Simone EG (1964) Cardiovascular dynamics in complete heart block at various heart rates. Circulation 30:542–543
8. Sowton E (1964) Hemodynamic studies in patients with artificial pacemakers. Br Heart 26:737–746
9. Videem JS, Juany SK, Bazgan ID et al (1986) Hemodynamic comparison of ventricular pacing, atrioventricular sequential pacing and atrial synchronous ventricular pacing using radionuclide ventriculography. Am J Cardiol 57:1305–1308
10. Norlander R, Pehrsson SK, Astrom H et al (1987) Myocardial demands of atrial-triggered versus fixed-rate ventricular pacing in patients with complete heart block. Pacing Clin Electrophysiol 10:1154–1159
11. Leclercq C, Gras D, Le Helloco A et al (1995) Hemodynamic importance of preserving the normal sequence of ventricular activation in permanent cardiac pacing. Am Heart J 129:1133–1141
12. Rowe GG, Stenlund RR, Thomsen JH et al (1969) Coronary and systemic hemodynamic effects of cardiac pacing in man with complete heart block. Circulation 40:839–845
13. Brockman SK (1965) Cardiodynamics of complete heart block. Am J Cardiol 16:72–83
14. Vos MA, de Groot SH, Verduyn SC et al (1998) Enhanced susceptibility for acquired torsade de pointes arrhythmias in the dog with chronic, complete atrio-ventricular block is related to cardiac hypertrophy and electrical remodeling. Circulation 98:1125–1235
15. Brockman SK, Stoney WS (1969) Congestive and heart failure and cardiac output in heart block and during pacing. Ann NY Acad Sci 167:534–545
16. Janousek J, Tomek V, Chaloupecky V et al (2004) Dilated cardiomyopathy associated with dual-chamber pacing in infants: improvement through either left ventricular cardiac resynchronization or programming the pacemaker off allowing

intrinsic normal conduction. J Cardiovasc Electrophysiol 15:470–474
17. Tantengco MV, Thomas RL, Karpawich PP (2001) Left ventricular dysfunction after long-term right ventricular apical pacing in the young. J Am Coll Cardiol 37:2093–2100
18. Thambo JB, Bordachar P, Garrigue S et al (2004) Detrimental ventricular remodeling in patients with congenital complete heart block and chronic right ventricular apical pacing. Circulation 110:3766–3772
19. Peschar M, March AM,Verbenek X et al (2004) Site of right ventricular pacing determines left ventricular remodeling in patients with atrio-ventricular block. Heart Rhythm 1:245
20. Faerestrand S, Ohm O-J (1985) A time-related study of the hemodynamic benefit of atrioventricular synchronous pacing evaluated by Doppler echocardiography. Pacing Clin Electrophysiol 8:838–848
21. Bowman AW, Kovacs SJ (2004) Left atrial conduction volume is generated by deviation from the constant volume state of the left heart: a combined MRI-echocardiographic study. Am J Physiol Heart Circ 286:H2416-H2424
22. Mehta D, Gilmour S, Ward DE et al (1989) Optimal atrioventricular delay at rest and during exercise in patients with dual chamber pacemakers: a non-invasive assessment by continuous wave Doppler. Br Heart J 61:161–166
23. Ritter P, Dib JC, Mahaut V et al (1995) New method for determining the optimal atrio-ventricular delay in patients paced in DDD mode for complete atrioventricular block. Pacing Clin Electrophysiol 18(Part II):237
24. Sutton R (1992)The atrioventricular interval: what considerations influence its programming? Eur Cardiac Pacing Electrophysiol 3:169
25. Dupot WD, Plummer WD Jr (1998) Power and sample size calculations for studies involving linear regression. Control Clin Trials 19:589–601
26. Bedotto JB, Grayburn PA, Black WH et al (1990) Alterations in left ventricular relaxation during atrioventricular pacing in humans. J Am Coll Cardiol 15:658–664
27. Tanabe A, Mohri T, Ohga M et al (1990) The effects of pacing-induced left bundle branch block on left ventricular systolic and diastolic performances. Jpn Heart J 31:309–317
28. Wiggers CJ (1925) The muscular reactions of the mammalian ventricles to artificial surface stimuli. Am J Physiol 73:346–378
29. Kosovsky BD, Scherlag BJ, Samaro AN (1968) Re-evaluation of the atrial contribution to ventricular function. Am J Cardiol 21:518–524
30. Nielsen JC, Andersen HR, Thomsen PEB et al (1998) Heart failure and echocardiographic changes during long-term follow-up of patients with sick-sinus syndrome randomized to single-chamber atrial or ventricular pacing. Circulation 97:987–995
31. Santini M, Alexidou G, Ansalone G et al (1990) Relation of prognosis in sick sinus syndrome to age, conduction defects and modes of permanent cardiac pacing. Am J Cardiol 65:729–735
32. Andersen HR, Nielsen JC, Thomsen PEB et al (1997) Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick sinus syndrome. Lancet 350:1210–1216
33. Sweeny MO, Hellkamp AS, Ellenbogen KA et al (2003) Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 107:2932–2937
34. Wilkoff BL, Cook JR, Epstein AE et al (2002) Dual-chamber pacing or ventricular back-up pacing in patients with an implantable defibrillator. JAMA 288:3115–3123

35. Verbenek X, Vernooy K, Pesar M et al (2002) Quantification of interventricular synchrony during LBBB and ventricular pacing. Am J Physiol 283:H1370-H1378
36. Liu L, Tockman B, Girouard S et al (2002) Left ventricular resynchronization therapy in a canine model of left bundle branch block. Am J Physiol 282:H2238-H2244
37. Hirzel HO, Senn M, Nuesch K et al (1984) Thalium-201 scintigraphy in complete left bundle branch block. Am J Cardiol 53:764–769
38. Kaas DA, Chen CH, Curry C et al (1999) Improved left ventricular mechanics from acute VDD pacing in patients with dilated cardiomyopathy and ventricular conduction delay. Circulation 99:1567–1573
39. Dekker AL, Phelps B, Dijkam A et al (2004) Epicardial left ventricular lead placement for cardiac resynchronization therapy: optimal pace site selection with pressure-volume loops. J Thorac Cardiovasc Surg 27:1642–1647
40. Rabkin SW, Mathewson FAL, Tate RB (1980) Natural history of left bundle-branch block. Br Heart 43:164–169
41. Schneider JF, Thomas HE Jr, Sorlie P et al (1981) Comparative features of newly acquired left and right bundle branch block in general population. The Framingham Study. Am J Cardiol 47:931–940
42. Khoury D, McAlister H, Wilkoff B et al (1989) Continuous right ventricular volume assessment by catheter measurement of impedance for antitachycardia system control. Pacing Clin Electrophysiol 12:1918–1926
43. Chirife R, Ortega DF, Salazar A (1993) Feasibility of measuring relative right ventricular volumes and ejection fraction with implantable rhythm control device. Pacing Clin Electrophysiol 16:1673–1683
44. Gasparini M, Denis A, Mantica M et al (2001) Hemodynamic sensors: what clinical value do they have in heart failure. In: Raviele A (ed) Cardiac arrhythmias. Springer Verlag Italia, Milan, pp 576–585
45. Artur W, Kaye GC (2001) Clinical use of intracardiac impedance: current applications and future perspectives. Pacing Clin Electrophysiol 24(Pt I):500–506

Hemodynamic Assessment with an Implanted Pacing Device

Maria Grazia Bongiorni[1], Ezio Soldati[1], Giuseppe Arena[1], Giulio Zucchelli[1], Andrea Di Cori[1], Alberto Barbetta[2], Franco Di Gregorio[2]

Introduction

Continuous hemodynamic monitoring could be highly valuable in the treatment of cardiac diseases characterized by a deterioration of pump function, allowing detection of the early signs of heart failure and thus prompt adaptation of the pharmacological regimen to the patient's changing clinical condition [1]. Therefore, specific implantable devices have been developed to record right ventricular blood pressure and dP/dt in the outflow tract, in order to assess diastolic pulmonary pressure [2]. Indications of the pressure sensor were shown to be correlated with invasive hemodynamic measurements and anticipated the clinical course of the disease, predicting and potentially reducing the need for hospitalization [2–4]. However, an increasing proportion of heart-failure patients have already received implantable rhythm-control devices (pacemakers and defibrillators), which are often designed to provide cardiac resynchronization therapy. In such patients, the same hardware needed for cardiac stimulation could be used to also assess the hemodynamic state. For instance, a system intended to reveal fluid accumulation in the lung based on thoracic impedance measurements by an implanted biventricular defibrillator was recently introduced in the clinical setting. Impedance is assessed between the defibrillation coil placed in the right ventricle and the device case in the left pectoral region. An inverse correlation with both pulmonary capillary wedge pressure and net change in body fluids during hospital care was reported [5]. The decrease in intrathoracic impedance started approximately 2 weeks before the manifestation of pulmonary congestion symptoms requiring hospitalization.

[1]Cardiothoracic Department, University of Pisa, Pisa; [2]Clinical Research Unit, Medico Spa, Rubano (PD), Italy

Cardiac Impedance as Volume Sensor

Similar to thoracic impedance, cardiac impedance can be measured with the same electrodes used for pacing or defibrillation. Different configurations have been proposed, including unipolar impedance (derived between the tip ventricular electrode and the stimulator can), bipolar ventricular impedance (derived between the tip and ring ventricular electrodes of standard bipolar pacing leads, or between two ring electrodes of a special tripolar lead, while the testing current is applied between the tip electrode and the stimulator can), transvalvular impedance (derived between the atrial ring and either the tip or the ring ventricular electrode in dual-chamber pacing systems). In all recording configurations, impedance changes during the cardiac cycle are assumed to reflect the mechanical activity of the ventricle [6]. However, the unipolar impedance waveform has not been related to the specific aspects of cardiac hemodynamics; the only claim being that any waveform change with respect to a reference signal can be taken as an indication of increased myocardial contractility and applied to drive rate-responsive pacing in a closed-loop system [7, 8]. In contrast, bipolar ventricular and transvalvular recording configurations provide impedance waveforms of predictable shape, supporting the hypothesis of an inverse relationship with ventricular volume [9, 10]. In particular, the transvalvular impedance (TVI) has drawn increasing attention due to its remarkably high signal stability and resolution. It is generally lower in diastole and higher in systole, increasing after an R wave or a ventricular pacing spike throughout the QT interval to reach the maximum peak right at the end of the T wave, when the ventricular volume is at a minimum. TVI then decreases back to the diastolic level in two steps, related to passive and active ventricular filling [11]. Since the TVI signal is not high-pass filtered, changes in absolute end-diastolic and end-systolic values (EDTVI and ESTVI, respectively) can be detected. EDTVI decreases when the ventricular filling time is prolonged (Fig. 1) and increases when it is shortened (for instance, in the event of an ectopic beat). Moreover, EDTVI increases under conditions of reduced venous return (e.g., with the patient in the standing position) and decreases when venous return is known to be increased (e.g., with the patient in the supine position or during skeletal muscle activity). Therefore, EDTVI can be proposed as a marker of beat-by-beat preload modifications and, possibly, of long-term changes in ventricular volume as well [12]. In addition, TVI excursion from diastole to systole (i.e., the difference between absolute ESTVI and EDTVI) can be correlated with the stroke volume (SV). Indeed, when the SV increases or decreases, the TVI waveform peak–peak amplitude is correspondingly increased or decreased

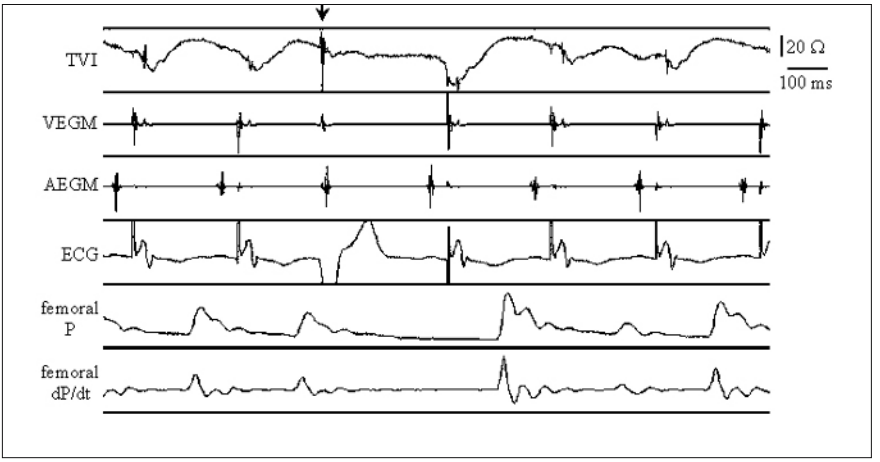


Fig. 1. From *top* to *bottom*: transvalvular impedance (*TVI*) recorded in atrial ring–ventricular ring configuration, right ventricular and atrial electrograms (*VEGM* and *AEGM*, respectively), surface *ECG*, blood pressure in the femoral artery (*femoral P*), and its time derivative (*femoral dP/dt*). The recording was obtained with an external device during the implantation of a biventricular stimulator in a patient with dilated cardiomyopathy and left bundle branch block (LBBB). The left ventricle is paced in VDD. TVI recorded in the right heart shows the usual features, increasing in the QT interval and decreasing after the end of the T wave (passive filling). A clear-cut change in slope is observed after P-wave detection and indicates active filling. After two regular cycles, a PVC (premature ventricular contraction) (*arrow*) fails to produce a pressure pulse, suggesting that no ejection takes place. Consistently, TVI fluctuation is virtually abolished. The next cycle shows a long filling time and a large stroke volume (as suggested by high pulse pressure). The corresponding TVI fluctuation is also increased, mainly due to a decrease in the minimum diastolic value (a preload indicator). The following cycle shows a small pressure pulse, probably due to a weak contraction. At the same time, TVI fluctuation is depressed and a reduction in the end-systolic value (a contractility indicator) is noticed.

(Fig. 1). If SV changes are induced by changes in preload, according to Starling's law, peak–peak TVI modifications result from changes in EDTVI only, while ESTVI remains constant. In contrast, when SV changes are due to stimulation or depression of myocardial contractility, peak–peak TVI modifications are associated with changes in ESTVI (Fig. 2). The relationship between the difference in peak–peak TVI and EDTVI with respect to reference conditions (putative SV and preload indicators, respectively) reflects the inotropic state and has proven effective in the assessment of acute changes in adrenergic tone [13].

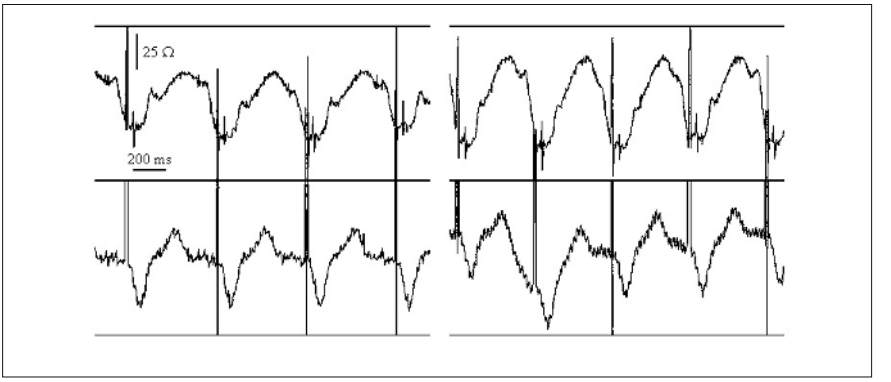


Fig. 2. TVI recorded in atrial ring–ventricular tip configuration (*upper tracing*) and surface ECG (*lower tracing*) before (*left panel*) and during a stress test on an ergometric bicycle (*right panel*); VDD pacing. Physical exercise induces an increase in end-systolic TVI, reflecting increased myocardial contractility, and a decrease in end-diastolic TVI, due to the increased venous return

Hemodynamic Monitoring with TVI

The feasibility of deriving complex information on ventricular volumes and related hemodynamic parameters, such as preload, SV, and ejection fraction, by recording absolute values of cardiac impedance in telediastole and telesystole was originally proposed by Chirife and coworkers [9]. In their model, which was tested in vitro, volume was proportional to a negative power of the measured impedance. The actual quantitative relationship between volume and impedance in the beating heart has so far only been determined with multipolar catheters used in acute hemodynamic studies [14]. However, a new family of pacemakers equipped with the TVI sensor is now available in the clinical setting (Sophòs models 151 and 155, Medico, Padua, Italy) and could allow evaluation of the reliability of impedance recording by conventional pacing leads in the assessment of acute and chronic changes in ventricular volume. Studies have already been undertaken to compare TVI indications and echocardiographic evidence during hemodynamic challenges based on variation in pacing mode, stimulation rate, and AV delay. In addition, patients will be followed-up in the long term to verify whether TVI can reveal or predict significant changes in clinical condition and hemodynamic performance. Promising results have recently been reported with bipolar impedance measurements in a 1-year follow-up of heart-failure patients. Pacing impedance changes in the right ventricular apex showed positive and negative correlation, respectively, with changes in

left-ventricular ejection fraction (LVEF) and NYHA functional class [15].

In conclusion, theoretical considerations and acute experimental evidence support the use of TVI for continuous hemodynamic monitoring of pacemaker patients. The sensing system is based on the same hardware implanted to provide cardiac stimulation, with no need of dedicated pacing leads. Hemodynamic monitoring is important in heart-failure patients and could suggest timely adaptations in the pharmacological treatment or in the programming configuration of a cardiac resynchronization device. However, this new option may also be valuable in the pacing therapy of rhythm disorders, especially if a high prevalence of ventricular pacing is expected, as early warning could be obtained in case of hemodynamic deterioration [16, 17].

References

1. Brinker JA (2005) Implantable hemodynamic monitors: success in the pursuit of failure? Pacing Clin Electrophysiol 28:743–746
2. Magalsky A, Adamson P, Gadler F et al (2002) Continuous ambulatory right heart pressure measurements with an implantable hemodynamic monitor: a multicenter 12-month follow-up study of patients with chronic heart failure. J Card Fail 8:63–70
3. Braunschveig F, Linde C, Eriksson MJ et al (2002) Continuous haemodynamic monitoring during withdrawal of diuretics in patients with congestive heart failure. Eur Heart J 23:59–69
4. Adamson PB, Magalsky A, Braunschveig F et al (2003) Ongoing right ventricular hemodynamics in heart failure: clinical value of measurements derived from an implantable monitoring system. J Am Coll Cardiol 41:565–571
5. Yu CM, Wang L, Chau E (2005) Intrathoracic impedance monitoring in patients with heart failure. Circulation 112:841–848
6. Arthur W, Kaye GC (2001) Clinical use of intracardiac impedance: Current applications and future perspectives. Pacing Clin Electrophysiol 24(Pt 1):500–506
7. Osswald S, Cron T, Gradel C et al (2000) Closed-loop stimulation using intracardiac impedance as a sensor principle: correlation of right ventricular dP/dt max and intracardiac impedance during dobutamine stress test. Pacing Clin Electrophysiol 23:1502–1508
8. Griesbach L, Gestrich B, Wojciechowski D et al (2003) Clinical performance of automatic closed-loop stimulation systems. Pacing Clin Electrophysiol 26(Pt 1):1432–1437
9. Chirife R, Ortega DF, Salazar A (1993) Feasibility of measuring relative right ventricular volumes and ejection fraction with implantable rhythm control devices. Pacing Clin Electrophysiol 16:1673–1683
10. Chirife R, Tentori MC, Mazzetti H, Dasso D (2001) Hemodynamic sensors: are they all the same? In: Raviele A (ed) Cardiac arrhythmias 2001. Springer, Milan, pp 566–575
11. Di Gregorio F, Morra A, Finesso M, Bongiorni MG (1996) Transvalvular impedance (TVI) recording under electrical and pharmacological cardiac stimulation. Pacing Clin Electrophysiol 19(Pt 2):1689–1693

12. Bongiorni MG, Soldati E, Arena G et al (2005) Haemodynamic assessment by transvalvular impedance recording. In: Gulizia MM (ed) Emerging pathologies in cardiology. Springer, Milan, pp 323–330
13. Gasparini G, Curnis A, Gulizia M et al (2005) Rate-responsive pacing regulated by cardiac haemodynamics. Europace 7:234–241
14. Applegate RJ, Cheng CP, Little WC (1990) Simultaneous conductance catheter and dimension assessment of left ventricular volume in the intact animal. Circulation 81:638–648
15. Stambler BS, Ellenbogen KA, Liu Z et al (2005) Serial changes in right ventricular apical pacing lead impedance predict changes in left ventricular ejection fraction and functional class in heart failure patients. Pacing Clin Electrophysiol 28:S50-S53
16. Sweeney MO, Hellkamp AS, Ellenbogen KA et al (2003) Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 107:2932–2937
17. Nielsen JC, Kristensen L, Andersen HR et al (2003) A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. J Am Coll Cardiol 42:614–623

Hemodynamic Optimization of Pacing Configuration in Bradyarrhythmias

Gianfilippo Neri[1], Rolando Zamprogno[1], Diego Vaccari[1], Giuliano Masaro[1], Alberto Barbetta[2], Franco Di Gregorio[2]

Introduction

The electric treatment of cardiac bradyarrhythmias by an implanted pacemaker is mandatory whenever the reduction in ventricular rate results in a functional impairment affecting health, safety, and quality of life [1]. Nevertheless, it is well-known that electrical stimulation of the heart may have disadvantages and drawbacks, which have been progressively identified and brought to attention as a consequence of increasing clinical experience and medical knowledge. Parallel improvements in pacing technology have allowed many essential issues to be addressed and solved, such as the prevention of competitive pacing and synchronization of atrial and ventricular stimulation to maintain physiological sequential activation. In the last decade, the increasing use of biventricular pacing in the therapy of heart failure has underlined the relevance of interventricular and intraventricular synchronization for effective pump function. However, conventional single-site pacing in the right ventricular apex (RVA) necessarily implies myocardial conduction of the evoked action potential, resulting in deep modification of the ventricular activation pattern and delayed contraction of the left ventricle (LV), as indicated by the altered axis and increased duration of the QRS complex and confirmed by echocardiographic observation. The short- and long-term impacts of RVA pacing on cardiac hemodynamics have therefore become major concerns in the care of patients presenting with bradycardia [2].

[1]Cardiology Department, Carretta Hospital, Montebelluna (TV); [2]Clinical Research Unit, Medico Spa, Rubano (PD), Italy

Hemodynamic Implications of Ventricular Pacing

Ventricular dyssynchrony induced by RVA pacing can increase myocardial stress and mitral regurgitation and affect coronary perfusion, thus leading to long-term cardiac remodeling, atrial enlargement, and an increased incidence of atrial fibrillation and heart failure [2–7]. However these deleterious effects are often associated with pre-existing conditions of ventricular function impairment [8]. Provided that baseline hemodynamics had been preserved at the time of implantation, the clinical consequences of ventricular pacing were found to be negligible in a cohort of pacemaker patients affected by atrioventricular (AV) block and continuously paced along a 3-year follow-up [9, 10].

To keep as low as possible the incidence of ventricular pacing in patients provided with intrinsic AV conduction, dedicated algorithms have been designed, including AV delay hysteresis (a mechanism by which the programmed AV delay is prolonged by a defined interval as long as intrinsic AV conduction is detected) and mode switch from AAI to DDD and back, depending on the absence or presence of intrinsic R waves [11, 12]. Although these systems have been shown to be effective in implantable cardioverter defibrillators (ICD) as well as in the pacing therapy of patients with sick sinus syndrome, they cannot be applied to the treatment of permanent AV block, in which ventricular stimulation is required to avoid asystole or to speed up AV conduction in order to improve ventricular filling, especially at high cardiac rates. In these cases, the hemodynamic contraindications to ventricular pacing can only be addressed by replacing the RVA with another stimulation site, where lower pacing-induced ventricular desynchronization is expected to occur. Promising results have been obtained by stimulating the right ventricular outflow tract (RVOT), the interventricular septum or the bundle of His [13–16], and with left-ventricular and biventricular pacing [7, 17, 18]. However, all of these techniques are, at present, more difficult than conventional RVA pacing and the risk of adverse events is higher. They are therefore better applied in selected patients, in whom RVA pacing might prove particularly detrimental.

At present, assessing whether RVA pacing is well-tolerated and what the best-suited alternative pacing site may be in each individual patient is difficult and time-consuming, as the acute hemodynamic effects of electrical stimulation should be evaluated by echocardiography or cardiac catheterization during either the implantation procedure or a previous electrophysiological study. This is virtually impossible in the actual clinical setting, where information on ventricular mechanics would be of practical value only if it was inexpensive and quickly obtained. Since implantable hemodynamic sen-

sors can be considered for this purpose, we have tested the application of transvalvular electric impedance (TVI) in the detection of pacing-induced ventricular desynchronization.

Tailoring the Pacing System with TVI

TVI is recorded between right atrium and ventricle with either tip or ring conventional pacing electrodes and is claimed to reflect changes in right ventricular volume. Indeed, TVI increases throughout ventricular systole and decreases during passive and active ventricular filling. In addition, end-diastolic TVI was shown to increase under conditions of decreased preload, while end-systolic TVI increased when myocardial contractility was enhanced by adrenergic stimulation [19–21]. We compared the TVI waveform properties under intrinsic AV conduction and RVA pacing in eight patients affected by sick sinus syndrome, with or without AV block, and implanted with the pacemaker Sophòs 151 (Medico, Padova, Italy), a dual-chamber rate-responsive device equipped with the TVI sensor. Immediately after TVI recording by pacemaker telemetry, diastolic and systolic function was assessed by two-dimensional and Doppler echocardiography under the same pacing conditions (i.e., intrinsic conduction in sinus rhythm vs. atrium-driven RVA pacing with 80-ms AV delay). Interventricular and intraventricular desynchronization was expressed, respectively, as the delay between the onset of pulmonary and aortic flow and between basal septum and LV lateral-wall contraction, as detected by tissue Doppler imaging.

The average delay of aortic vs pulmonary flow (0.9 ± 24 ms with intrinsic AV conduction) showed a non-significant acute increase after transition to RVA pacing (15 ± 21 ms). Similarly, a non-significant increase in average intraventricular delay was observed (from 7 ± 18 to 20 ± 22 ms). However, the sensitivity to RVA pacing differed among patients and evidence of ventricular desynchronization was clearly obtained in some of them (Fig. 1). Stroke volume (assessed as velocity-time integral of LVOT flow) was significantly decreased from 127 ± 40 to 118 ± 38 ml ($p < 0.05$, paired Student's t test), but the individual reduction was not correlated with either the interventricular or intraventricular desynchronization level.

The TVI waveform recorded during intrinsic AV conduction generally showed the expected physiological time-course, characterized by a progressive increase in the ejection phase with the maximum peak occurring within the T-wave decay (Figs. 2–3a). RVA pacing entailed morphological modifications in the TVI waveform, including a faster rate of rise and the presence of more peaks in the Q-T interval. These changes were more pronounced in patients

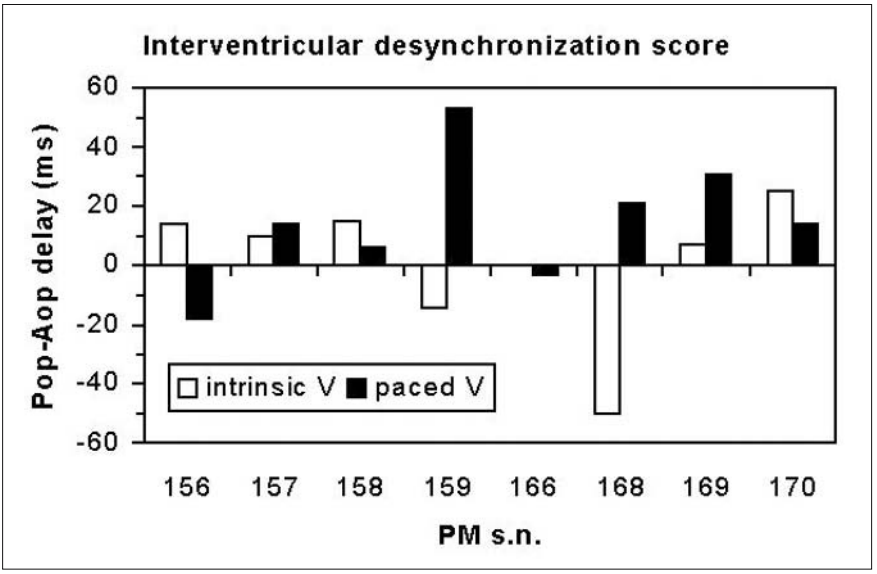


Fig. 1. Time interval from the onset of pulmonary flow (*Pop*) to the onset of aortic flow (*Aop*), during intrinsic atrioventricular (AV) conduction (*open bars*) or atrium-driven pacing in the right ventricular apex (*RVA*), with 80-ms AV delay (*full bars*). Each case is identified by the serial number of the implanted pacemaker. The impact of pacing on interventricular synchronization differed in different patients

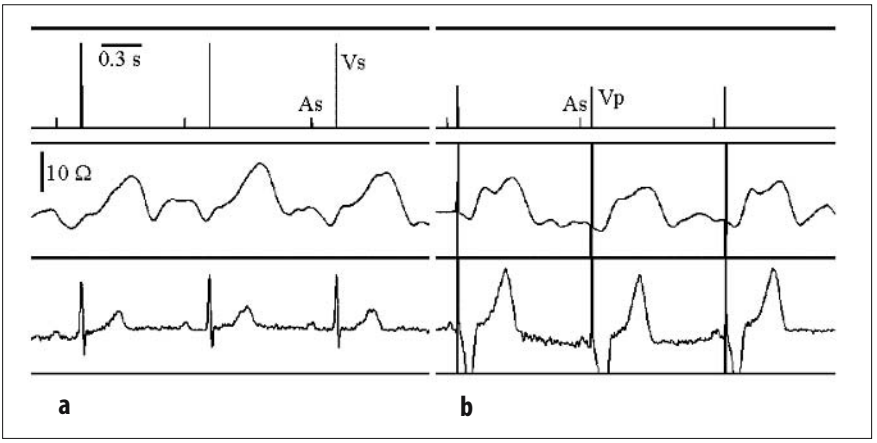


Fig. 2a, b. From *top* to *bottom*: pacemaker event markers (*As*, atrial sensing; *Vs*, ventricular sensing; *Vp*, ventricular pacing), TVI waveform, surface electrocardiogram, recorded during intrinsic AV conduction (**a**) and VDD pacing in RVA with 80 ms AV delay (**b**), in the patient implanted with Sophòs 151 number 157. In this case, the interventricular desynchronization induced by RVA pacing was negligible (Fig. 1). TVI was recorded in atrial ring–ventricular ring configuration, with a sampling current of 20 μA. The waveform showed a physiological time-course after both ventricular sensing and pacing

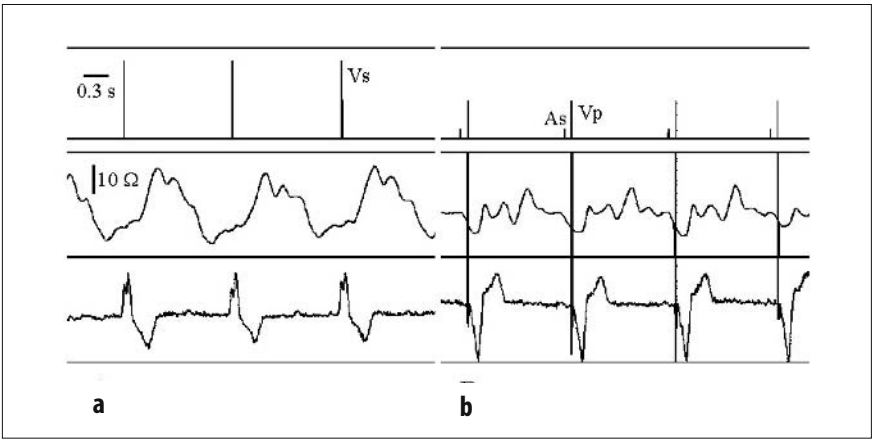


Fig. 3a, b. Patient implanted with Sophòs 151 number 159, in whom a maximum delay in left ventricular contraction induced by RVA pacing was observed (Fig. 1). The patient presented with trifascicular block and long PR; therefore, the pacemaker was temporarily programmed in VVI at 40 bpm to inhibit ventricular stimulation (**a**). TVI was recorded in atrial ring–ventricular tip configuration, with a sampling current of 20 μA. The waveform showed a physiological time-course after ventricular sensing, but was heavily modified by RVA pacing (**b**)

showing echocardiographic evidence of interventricular desynchronization (Figs. 2–3b). The peak-peak amplitude of TVI fluctuation from diastole to systole was decreased by 14 ± 13% ($p < 0.05$, paired Student's t test) and the individual reduction was linearly correlated with the delay of aortic vs pulmonary flow observed during atrium-driven RVA stimulation ($r = 0.68$).

Conclusions

High interpatient variability characterizes the acute effects of RVA pacing on cardiac hemodynamics. Changes in the TVI waveform associated with the transition from intrinsic conduction to ventricular stimulation can reflect pacing-induced alterations in ventricular mechanics and help to quickly identify patients who might require an alternative stimulation site or the upgrading to biventricular pacing during the implantation procedure, when echocardiographic analysis is not practicable. In chronic conditions, the TVI sensor available in Sophòs pacemakers may allow permanent monitoring of the patient's hemodynamic efficiency and detect early signs of a possible deterioration, which could be timely counteracted by correcting the drug regimen, pacemaker programming, or pacing system configuration.

References

1. Lunati M, Bongiorni MG, Boriani G et al (2005) Linee Guida AIAC 2006 all'impianto di pacemaker, dispositivi per la resincronizzazione cardiaca (CRT) e defibrillatori automatici impiantabili (ICD). Giornale Italiano di Aritmologia e Cardiostimolazione 8(4)
2. Gillis AM, Chung MK (2005) Pacing the right ventricle: to pace or not to pace? Heart Rhythm 2:201–206
3. Tse HF, Lau CP (1997) Long-term effect of right ventricular pacing on myocardial perfusion and function. J Am Coll Cardiol 29:744–749
4. Nunez A, Alberca MT, Cosio FG et al (2002) Severe mitral regurgitation with right ventricular pacing, successfully treated with left ventricular pacing. Pacing Clin Electrophysiol 25:226–230
5. Sweeney MO, Hellkamp AS, Ellenbogen KA et al (2003) Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 107:2932–2937
6. Nielsen JC, Kristensen L, Andersen HR et al (2003) A randomized comparison of atrial and dual-chamber pacing in 177 consecutive patients with sick sinus syndrome: echocardiographic and clinical outcome. J Am Coll Cardiol 42:614–623
7. Simantirakis EN, Vardakis KE, Kochiadakis GE et al (2004) Left ventricular mechanics during right ventricular apical or left ventricular-based pacing in patients with chronic atrial fibrillation after atrioventricular junction ablation. J Am Coll Cardiol 43:1013–1018
8. Lieberman R, Padeletti L, Eastman W et al (2005) Greater sensitivity of cardiac function to ventricular pacing lead location in patients with vs without left ventricular dysfunction. J Am Coll Cardiol 45:100A (abs)
9 Moro E, Marcon C, Degan P et al (2006) Conventional dual chamber apical pacing in patients with advanced atrio-ventricular block and preserved basal left ventricular function: a prospective long-term study. Giornale Italiano di Aritmologia e Cardiostimolazione 9(4):40 (abs)
10. Moro E, Marcon C, Sciarra L et al (2006) Long term evaluation of conventional dual chamber pacing in patients with advanced atrio-ventricular block and different hemodynamic configurations. Giornale Italiano di Aritmologia e Cardiostimolazione 9(4):64 (abs)
11. Melzer C, Sowelam S, Sheldon TJ et al (2005) Reduction of right ventricular pacing in patients with sinus node dysfunction using an enhanced search AV algorithm. Pacing Clin Electrophysiol 28:521–527
12. Sweeney MO, Ellenbogen KA, Casavant D et al (2005) Multicenter, prospective, randomized safety and efficacy study of a new atrial-based managed ventricular pacing mode (MVP) in dual chamber ICDs. J Cardiovasc Electrophysiol 16:811–847
13. de Cock CC, Meyer A, Kamp O, Visser CA (1998) Hemodynamic benefits of right ventricular outflow tract pacing: comparison with right ventricular apex pacing. Pacing Clin Electrophysiol 21:536–541
14. Mera F, DeLurgio DB, Patterson RE et al (1999) A comparison of ventricular function during high right ventricular septal and apical pacing after His-bundle ablation for refractory atrial fibrillation. Pacing Clin Electrophysiol 22:1234–1239
15. Tse HF, Yu C, Wong KK et al (2002) Functional abnormalities in patients with permanent right ventricular pacing: the effect of sites of electrical stimulation. J Am Coll Cardiol 40:1451–1458

16. Deshmukh P, Casavant DA, Romanyshyn M, Anderson K (2000) Permanent, direct His-bundle pacing: a novel approach to cardiac pacing in patients with normal His-Purkinje activation. Circulation 101:869–877
17. Doshi RN, Daoud EG, Fellows C et al (2005) Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol 16:1160–1165
18. Hay I, Melenovsky V, Fetics BJ et al (2004) Short-term effects of right-left heart sequential cardiac resynchronization in patients with heart failure, chronic atrial fibrillation, and atrioventricular nodal block. Circulation 110:3404–3410
19. Di Gregorio F, Morra A, Finesso M, Bongiorni MG (1996) Transvalvular impedance (TVI) recording under electrical and pharmacological cardiac stimulation. Pacing Clin Electrophysiol 19:1689–1693
20. Bongiorni MG, Soldati E, Arena G et al (2005) Haemodynamic assessment by transvalvular impedance recording. In: Gulizia MM (ed) Emerging pathologies in cardiology. Springer, Milan, pp 323–330
21. Gasparini G, Curnis A, Gulizia M et al (2005) Rate-responsive pacing regulated by cardiac haemodynamics. Europace 7:234–241

Applications of TVI Sensing in Cardiac Stimulation

Eraldo Occhetta[1], Miriam Bortnik[1], Franco Di Gregorio[2], Alberto Barbetta[2], Paolo Marino[1]

Introduction

Permanent cardiac stimulation has become increasingly complex, and modern pacing devices are now equipped with a wide set of functions aimed at reproducing as closely as possible the physiological control of cardiac rhythm, including dual-chamber and three-chamber architecture, sensor-driven rate-response, careful management, and rate-adaptation of the atrioventricular delay. Special algorithms have been developed to allow pacing and sensing autoregulation, self-limitation of unnecessary ventricular stimulation, pacing-mode switch in the event of supraventricular tachyarrhythmias, overdrive pacing aimed at preventing atrial fibrillation, etc. However, in spite of the improved effectiveness in sensing and processing cardiac electric signals, standard pacemakers do not take into account the associated mechanical activity, which is the final expression of ventricular function. So far, a few special models have been equipped with hemodynamic sensors, which are used to assess changes in myocardial contractility and accordingly regulate rate-responsive pacing [1–4]. However, no attempt has been made to acquire information on the heart's hemodynamic activity on a beat-by-beat basis.

The Transvalvular Impedance Sensor

A new hemodynamic sensor has been brought to the attention of the medical community in recent years: the transvalvular impedance (TVI). TVI is the

[1]Division of Cardiology, School of Medicine, Università degli Studi del Piemonte Orientale, Novara; [2]Clinical Research Unit, Medico Spa, Rubano (PD), Italy

electrical impedance derived between the right atrium and right ventricle with standard pacing electrodes. The measurement shows regular periodic fluctuation along the cardiac cycle, increasing in the QT period (systole) and decreasing in diastole and after a P wave [5, 6]. The signal time-course thus suggests an inverse relationship with ventricular volume [7–9], which was confirmed by TVI recording in experimental animal models. When right ventricular systolic ejection was prevented by reversible clamping of the pulmonary artery, cyclic TVI fluctuation was virtually abolished, notwithstanding the presence of ventricular electrical activity and isometric myocardial contraction. Recording in human patients has consistently showed that TVI rises after a spontaneous R wave or a ventricular pacing spike only if an effective ejection occurs, as demonstrated by the detection of a pressure pulse signal [6]. Due to its stability and remarkably high signal-to-noise ratio, TVI can be measured without the need of high-pass filtering, so that absolute impedance values are recorded (DC coupling). This way, the minimum and maximum TVI detected in a cardiac cycle can reflect, respectively, the level of diastolic ventricular filling and the residual systolic volume. Indeed, end-diastolic TVI increases under conditions of decreased preload, and end-systolic TVI increases if myocardial contractility is enhanced [9–11].

Ejection Surveillance with TVI

Since TVI fluctuation is specifically related to systolic ejection, this sensor has been proposed as a tool for the hemodynamic check of pacing effectiveness by a pacing device [5, 10]. As long as ventricular capture is achieved, each pacing pulse entails a properly timed increase in TVI. By contrast, in case of capture failure, TVI remains at baseline or even continues to decrease as a result of prolonged ventricular filling (Fig. 1). If the TVI response to ventricular pacing is missing, the stimulator should automatically react by increasing the energy of the next pulse to be released. This algorithm was initially tested by an external pacemaker provided with the TVI sensor. In order to identify a proper discriminant of true TVI responses from background noise, the signal amplitude detected within an appropriate time-window after each pacing spike was compared with the average amplitude measured in eight previous paced cycles. The lower limit of TVI relative variation in the presence of an evoked response was found to be 65%. Accordingly, a cut-off level of 50% was proposed to maximize both sensitivity and specificity in capture-loss recognition [12].

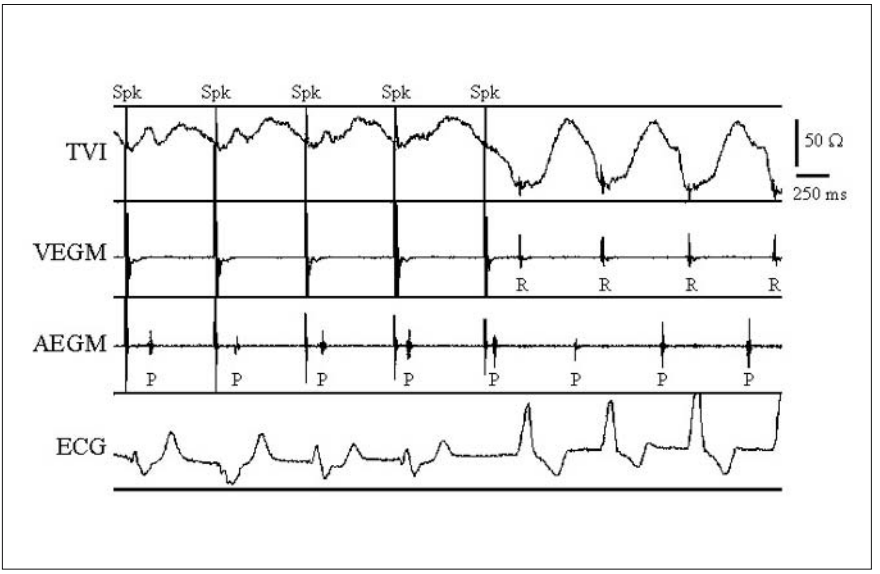


Fig. 1. From *top* to *bottom*: transvalvular impedance (*TVI*), ventricular electrogram (*VEGM*), atrial electrogram (*AEGM*), and surface ECG, recorded with an external device during pacemaker implantation. TVI is derived between the atrial and ventricular ring electrodes. Progressive pulse amplitude reduction during VVI pacing at 90 bpm. Effective stimulation resulted in P wave occurrence in the QT interval and atrial contraction with closed atrioventricular valves. The last spike (spk) failed to capture the ventricle and did not entail an increase in TVI. By contrast, diastolic TVI continued to decrease as the passive filling time was prolonged and showed a further steep reduction during active filling. Thereafter, the fluctuation of TVI kept pace with the intrinsic ventricular activation (R waves)

An ejection check at every heartbeat is valuable after either ventricular pacing or sensing. In the former case, it can be applied to restore effective stimulation by increasing pulse energy; in the latter, it may represent the ultimate solution to prevent false inhibition of ventricular pacing. Indeed, any sensing event that is not followed by a TVI increase can be regarded as putative electromagnetic interference (EMI) from the external environment (portable phones, antitheft devices, metal detectors, etc.) or from extracardiac physiological sources (myopotentials). Alternatively, it is possible that a true ventricular depolarization does not entail systolic ejection, as the developed contraction strength is too small to overcome aortic or pulmonary pressure. This is more likely to occur in the presence of early premature ven-

tricular contractions. Therefore, an algorithm designed to protect pacemaker-dependent patients from the risk of oversensing should be triggered by a repetitive lack of ejection in a series of cycles and not by an isolated event, especially if ventricular sensing is not sequential to previous atrial activity.

An ejection check based upon the TVI sensor is available in the implantable pacemakers of the Sophòs family (Medico, Padova, Italy), either as diagnostic feature (Sophòs model 151) or for the actual regulation of pacing function (Sophòs model 155). The algorithm can be enabled after ventricular pacing, sensing, or both. Sophòs 155 reacts to the lack of TVI-indicated ejection within the expected time-window after ventricular stimulation by replacing the current pulse parameters with a "safety pulse" of higher energy, to be applied from the following pacing cycle. After safety stimulation for 16 cycles, a threshold test is automatically performed in an attempt to restore the programmed pacing pulse. In case missing ejection is noticed after ventricular sensing in three consecutive cycles, Sophòs 155 will temporarily switch to asynchronous dual-chamber pacing at 100 bpm, in order to ensure non-competitive overdrive stimulation of the heart. The procedure can be repeated up to three times with a 1-min maximal duration – a timeframe that should allow removal of the electrical interference affecting the pacemaker's sensing function.

Both Sophòs models can optionally perform ventricular threshold analysis at the follow-up under TVI control. In case of capture loss, the energy scan is automatically broken and programmed pulse parameters are promptly resumed, while the test is closed and threshold values are stored in memory (Fig. 2). TVI effectiveness and reliability in capture-loss recognition during threshold analysis is presently assessed by a multicenter registry. Each patient is tested four times in different body positions: supine, right and left lateral decubitus, and sitting upright. The system sensitivity is defined by the ratio of the procedures successfully closed by TVI over the total number of performed procedures. Specificity is derived from the pacemaker diagnostic data collected in 20 min, while the patient changes posture and performs physical exercise (walking). Throughout the observation period, the ventricular pulse amplitude is programmed beyond twice the threshold; therefore, no capture loss is expected to occur. Under this assumption, the specificity in capture surveillance is expressed as the complement to 1 of the ratio between the number of presumed capture-loss episodes recorded by the device (regarded as false-alarms) and the total number of paced ventricular cycles. Preliminary results have shown 100% sensitivity and 99.9% specificity, but the sample size at present is too small to draw any conclusions.

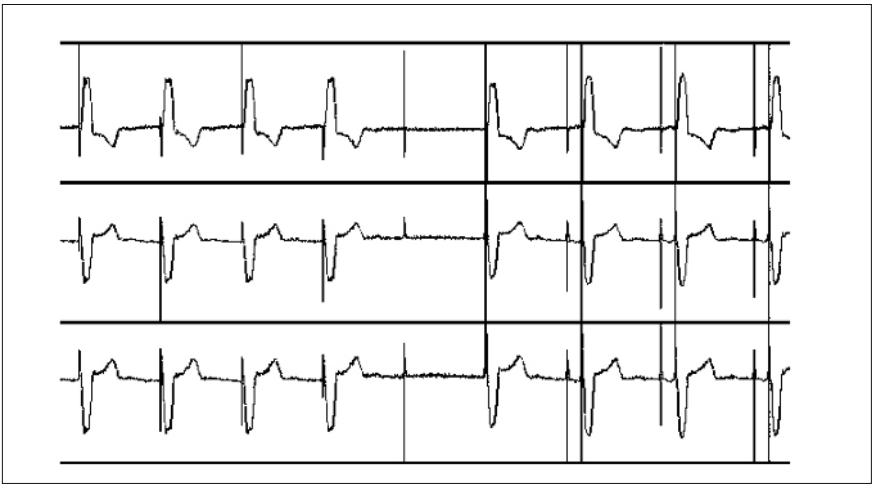


Fig. 2. ECG limb leads showing ventricular threshold analysis controlled by the TVI sensor in a patient implanted with a Sophòs 151 pacemaker. A pulse amplitude scan was performed in VVI pacing at 70 bpm. After one ineffective spike, the stimulation energy was automatically increased so that capture was regained. The procedure was then closed and the pacing mode switched back to DDD

Benefits and Limitations of Ejection Checking

Capture recognition based on the electrical evoked response to ventricular pacing is often ineffective in the presence of fusion beats [13, 14]. By contrast, the TVI-driven ejection check is equally responsive to paced or sensed ventricular activity and the risk of false-alarms is minimized. On the other hand intrinsic AV conduction might mask a condition of capture failure, unless it is delayed enough with respect to the spike emission to entail a TVI increase outside the expected systolic window (Fig. 1). In addition, since the ejection occurrence must be verified hundreds of milliseconds after the pacing spike, the pulse energy can be increased in the event of capture loss starting with the following cardiac cycle, and no back-up pulse is delivered beforehand (Fig. 2). The above considerations make TVI better-suited to the surveillance of ventricular activity aimed at increasing patient safety, rather than to continuous assessment of the minimum effective pacing energy.

The ejection check after ventricular sensing is certainly a valuable task in itself, which can only be accomplished by an advanced hemodynamic sensor.

This feature can be applied to protect the patient from false ventricular inhibition, by mode-switching from inhibited to asynchronous dual-chamber pacing or from atrial to dual-chamber pacing in case of paroxysmal AV block. Most importantly, ascertaining the presence or absence of ventricular ejection during a tachycardia burst might become a key factor to correctly discriminate ventricular fibrillation, thus reducing the risk of inappropriate discharge by implantable defibrillators.

References

1. Bennett T, Sharma A, Sutton R et al (1992) Development of a rate adaptive pacemaker based on the maximum rate-of-rise of right ventricular pressure (RV dP/dtmax). Pacing Clin Electrophysiol 15: 219-234
2. Rickards AF, Bombardini T, Plicchi G et al (1996) An implantable intracardiac accelerometer for monitoring myocardial contractility. Pacing Clin Electrophysiol 19:2066–2071
3. Osswald S, Cron T, Gradel C et al (2000) Closed-loop stimulation using intracardiac impedance as a sensor principle: correlation of right ventricular dP/dt max and intracardiac impedance during dobutamine stress test. Pacing Clin Electrophysiol 23:1502–1508
4. Occhetta E, Magnani A, Bortnik M et al (2003) Hemodynamic sensors: their impact in clinical practice. In: Raviele A (ed) Cardiac Arrhythmias 2003. Springer, Milan, pp 713–718
5. Di Gregorio F, Morra A, Finesso M, Bongiorni MG (1996) Transvalvular impedance (TVI) recording under electrical and pharmacological cardiac stimulation. Pacing Clin Electrophysiol 19:1689–1693
6. Gasparini M, Curnis A, Mantica M et al (2001) Hemodynamic sensors: what clinical value do they have in heart failure? In: Raviele A (ed) Cardiac Arrhythmias 2001. Springer, Milan, pp 576-585
7. Chirife R, Ortega DF, Salazar A (1993) Feasibility of measuring relative right ventricular volumes and ejection fraction with implantable rhythm control devices. Pacing Clin Electrophysiol 16:1673–1683
8. Chirife R, Tentori MC, Mazzetti H, Dasso D (2001) Hemodynamic sensors: are they all the same? In: Raviele A (ed) Cardiac Arrhythmias 2001. Springer, Milan, pp 566–575
9. Di Gregorio F, Curnis A, Pettini A et al (2002) Trans-valvular impedance (TVI) in the hemodynamic regulation of cardiac pacing. In: Mitro P, Pella D, Rybár R, Valočik G (eds) Cardiovascular Diseases 2002. Monduzzi Editore, Bologna, pp 53–57
10. Bongiorni MG, Soldati E, Arena G et al (2005) Haemodynamic assessment by transvalvular impedance recording. In: Gulizia MM (ed) Emerging pathologies in cardiology. Springer, Milan, pp 323–330
11. Gasparini G, Curnis A, Gulizia M et al (2005) Rate-responsive pacing regulated by cardiac haemodynamics. Europace 7:234–241
12. Bongiorni MG, Soldati E, Arena G et al (2003) Transvalvular impedance: does it allow automatic capture detection? In: Raviele A (ed) Cardiac Arrhythmias 2003. Springer, Milan, pp 733–739
13. Duru F, Bauersfeld U, Schüller H et al (2000) Threshold tracking pacing based on

beat by beat evoked response detection: clinical benefits and potential problems. J Intervent Cardiol Electrophysiol 4:511–522

14. Candinas R, Liu B, Leal J et al (2002) Impact of fusion avoidance on performance of the automatic threshold tracking feature in dual chamber pacemakers: a multicenter prospective randomized study. Pacing Clin Electrophysiol 25:1540–1545

The Ideal Pacemaker for Complete AV Block

I. Eli Ovsyshcher

Since the initial description of the use of a transvenous endocardial lead for pacing in humans, in 1959 [1], the right ventricular apex (RVA) has served as the traditional site for lead positioning. However, RVA pacing produces an abnormal pattern of ventricular depolarization and there is growing evidence that pacing from this site is associated with adverse functional and structural changes in the left ventricle. This is manifested clinically in the deterioration of left ventricular (LV) function and increased morbidity and mortality. The results of numerous studies have described these observations, which were summarized in a recent review [2].

Obviously, in light of the potential harmful effects of ventricular (V) pacing, every effort should be made to avoid it, if possible. However, V-pacing is necessary in many patients because of unreliable or absent AV conduction, i.e., in patients with advanced or complete AV block. V-pacing from the RV outflow tract (RVOT), RV septum (RVS), His and para-His bundle area, biventricular (BV) or LV pacing appears to have hemodynamics benefits compared to RVA pacing.

In a recent paper, Lieberman et al. [3] attempted to identify the optimal V-pacing site in patients with or without LV dysfunction. The authors studied the acute hemodynamic effects of AV synchronous pacing at three different RV sites (apex, free wall, and septum), at the LV free wall, and at both the RV septum and the LV free wall (BV) during electrophysiological studies in patients with or without preexisting LV dysfunction. All of these patients had normal QRS duration and no conventional indication for cardiac pacing. During the acute pacing protocol, invasive hemodynamic assessment of the

Electrophysiology, Faculty of Health Sciences, Ben Gurion University of the Negev, BeerSheva, Israel

LV pressure-volume loop was obtained. The results showed that acute cardiac hemodynamics and functions were better during LV and BV pacing than during RV pacing at all three sites, especially in patients with preexisting LV dysfunction. In patients with LV dysfunction, acute RV pacing at any site resulted in worsening cardiac performance. However, in patients without LV dysfunction, individual optimization of RV pacing sites could preserve cardiac performance. There were substantial individual variations in the optimal RV pacing sites. Thus, the study suggested that V-pacing sites need to be individually optimized. In patients with preexisting LV dysfunction, an LV-based pacing approach can avoid RVA-pacing-induced LV dyssynchrony and may further improve LV performance. However, the clinical implications of this finding remain unclear. In patients with conventional indications for CRT, an acute hemodynamic benefit did not predict the long-term response [4]. Additionally, the pacing sites tested in this study were imprecisely defined.

With the recent advances in the active-fixation endocardial lead systems, alternative RV pacing sites have been explored in order to replace the RVA. In patients without significant distal conduction abnormalities, such as those who have undergone AV node ablation for atrial fibrillation, His or para-His bundle pacing has been shown to preserve the LV activation sequence and LV function [5]. A recent study [6] showed that pacing at the RVS with a screw-in electrode can stimulate ventricles antegradely and may result in a normal LV activation sequence (interestingly, the RV septum site was used by S. Furman in the first human implantation of the endocardial pacing lead [1]). However, the technique for achieving successful RVS, His or para-His bundle pacing remains challenging. One of the major issues related to pacing in these sites is that it is difficult to define the optimal site for lead placement. Moreover, data regarding acute and long-term effects of pacing at sites other than that of RVA, are conflicting [7, 8]. Therefore, future studies are needed to define the potential role of alternative RV pacing sites for long-term pacing [2, 7, 8].

It seems evident from the MOST and DAVID trials that conventional RV pacing (in all the large randomized trials the position of the lead in RV was not defined) is harmful for some patients [2]. In the MOST study, only 10% of DDD patients with sinus-node dysfunction had heart failure (HF) during follow-up, and they were more likely to have a lower ejection fraction, to be post-myocardial-infarction, and have a worse New York Heart Association (NYHA) functional class than patients who did not experience HF [9]. Thus, a significant group of RV pacing patients tolerates this approach for many years without experiencing deleterious effects on LV function. Therefore, it

would be essential and useful before pacemaker implantation to identify the subset of patients susceptible to the adverse effects of RV pacing.

The recently published *Ablate and Pace in Atrial Fibrillation* (APAF) study [10] attempted to resolve this problem. It evaluated the extent to which pacing from the RVA affects LV electromechanical activation and assessed whether the extent of LV asynchrony during RV pacing could be predicted by clinical, ECG, or echo findings obtained during sinus rhythm. The authors evaluated 56 patients with normal QRS and preserved AV conduction who received permanent backup RV pacing. Intra-LV electromechanical activation was assessed during sinus rhythm and during RV pacing. An abnormal electromechanical LV delay was found in 27% of patients during sinus rhythm and in *only* 50% of patients during RV pacing ($p < 0.001$). An abnormal baseline electromechanical LV delay and QRS > 85 ms were independent predictors of an abnormal electromechanical LV delay during RV pacing. Thus, RVA pacing induces asynchrony of LV contractions in a substantial percentage of patients, but by no means in all of them. Although normal baseline electromechanical LV activation cannot exclude the development of significant asynchrony during RV pacing, the presence of preimplant LV asynchrony predicts a worsening of this detrimental effect.

In a subgroup analysis of the DAVID trial [11], patients with abnormal conduction (QRS ≥ 110 ms) had worse outcomes from RVA pacing than patients with narrow QRS. These important observations [10, 11] reaffirm the necessity to search for additional electromechanical indices that predict a negative response to RVA paging, as well as a positive response to cardiac resynchronization therapy in patients with conventional pacemakers. The data can also explain why only some patients with RV pacing develop HF. As was demonstrated in the MOST and DAVID trials, the development of HF strongly depends on the cumulative percentage of RV pacing beats [2]. It may be that a combination of these two factors, that is, LV dyssynchrony, which can be detected by echo (or other cardiac imaging) techniques or ECG, and a high percentage of RV pacing beats, can lead to a deterioration of LV function, resulting in HF. Conversely, the absence of one of these factors may postpone or preserve developing HF.

Currently, only patients with preexisting LV dysfunction seem more likely to develop progressive HF after RV pacing. In those patients, LV-based pacing should be recommended to prevent deterioration of LV function (RV pacing can be used if solid evidence emerges that any alternative site[s] in RV can prevent the weakening of heart function). This recommendation is in complete agreement with the results of a recent randomized prospective

study (30 patients) showing that prophylactic BV pacing in patients with AV block resulted in better LV function (reduced LV end-diastolic, $p = 0.022$, and end-systolic volumes, $p < 0.001$), better quality of life and exercise capacity, and reduced N-terminal pro-B-type natriuretic peptide level ($p < 0.002$) when compared with RV apical pacing [12]. The benefit of BV over RV pacing was similar for patients with ($n = 9$) and without ($n = 21$) AF. RV function was not affected by BV pacing. Similar results were demonstrated in two additional controlled studies on patients with AF and spontaneous [13] or AV node ablation bradycardia [13–15].

However, except in a subset of pacemaker patients, as previously discussed, the routine use of LV-based pacing for an entire cohort of patients with AV block is impractical due to numerous disadvantages of BV pacing, such as the longer procedure time, shorter battery life, lead dislodgement, and higher cost and complication rates. Moreover, BV or LV pacing induces dyssynchrony in hearts with normal ventricular conduction [3, 16] and reduces LV pumping function in patients with no baseline dyssynchrony. Therefore, BV or LV pacing is not the ideal and not even an optimal solution for many patients with AV block.

Recent studies have shown that 31–50% of pacemaker patients have asymptomatic LV dysfunction [17, 18]. This is an important cohort of patients who are potential candidates for LV-based pacing. Therefore, all patients with AV block and RV pacing should be closely monitored for worsening of LV function [17]. Recent studies have shown that upgrading to BV pacing can improve functional status and cardiac function in those patients in whom HF developed after RVA pacing [19].

Conclusions

There is no ideal pacing for patients with complete AV block. However, based on our current knowledge we can suggest optimal pacing for these patients. Patients with AV block who need permanent pacing should be evaluated on the issues of LVEF and LV dyssynchrony presence. Patients with normal, or close to normal, LV function and without dyssynchrony should be treated by RV pacing. In patients with normal, or close to normal, LV dysfunction and signs of LV dyssynchrony, EF should be closely monitored.

Patients with preexisting LV dysfunction (LVEF 40–45%) seem more likely to develop progressive HF after RV pacing. In these patients in NYHA class III–IV, LV-based pacing should be considered; in NYHA class I–II patients, LV-based pacing may be recommended to prevent deterioration of LV function.

References

1. Furman S, Schwedel JB (1959) An intracardiac pacemaker for Stokes-Adams Seizures. N Engl J Med 261:943–948
2. Sweeney MO, Prinzen FW (2006) A New Paradigm for Physiologic Ventricular Pacing. J Am Coll Cardiol 47:282–288
3. Lieberman R, Padeletti L, Schreuder J et al (2006) Ventricular pacing lead location alters systemic hemodynamics and left ventricular function in patients with and without reduced ejection fraction. J Am Coll Cardiol 48:1634–1641
4. Stellbrink C, Breithardt OA, Franke A et al (2001) Impact of cardiac resynchronization therapy using hemodynamically optimized pacing on left ventricular remodeling in patients with congestive heart failure and ventricular conduction disturbances. J Am Coll Cardiol 38:1957–1965
5. Occhetta E, Bortnik M, Magnani A et al (2006) Prevention of ventricular desynchronization by permanent para-Hisian pacing after atrioventricular node ablation in chronic atrial fibrillation: a crossover, blinded, randomized study versus apical right ventricular pacing. J Am Coll Cardiol 47:1938–1945
6. Laske TG, Skadsberg ND, Hill AJ et al (2006) Excitation of the intrinsic conduction system through His and interventricular septal pacing. Pacing Clin Electrophysiol 29:397–405
7. Lewicka-Nowak E, Dabrowska-Kugacka A, Tybura S et al (2006) Right ventricular apex versus right ventricular outflow tract pacing: prospective, randomized, long-term clinical and echocardiographic evaluation. Kardiologia Polska 64:1082–1090
8. McGavigan AD, Mond HG (2006) Selective site ventricular pacing. Curr Opin Cardiol 21:7–14
9. Sweeney MO, Hellkamp AS (2005) Baseline and post-implant risk scores for predicting heart failure hospitalization during pacemaker therapy for sinus node dysfunction. Heart Rhythm 2 (Suppl 2):75–76
10. Lupi G, Sassone B, Badano L et al; Ablate and Pace in Atrial Fibrillation (APAF) Pilot Echocardiographic Trial Investigators (2006) Effects of right ventricular pacing on intra-left ventricular electromechanical activation in patients with native narrow QRS. Am J Cardiol 98:219–222
11. Hayes JJ, Sharma AD, Love JC et al (2006) Abnormal conduction increases risk of adverse outcomes from right ventricular pacing. J Am Coll Cardiol 48:1628–1633
12. Kindermann M, Hennen B, Jung J et al (2006) Biventricular versus conventional right ventricular stimulation for patients with standard pacing indication and left ventricular dysfunction: the Homburg Biventricular Pacing Evaluation (HOBIPACE). J Am Coll Cardiol 47:1927–1937
13. Leclercq C, Walker S, Linde C et al (2002). Comparative effects of permanent biventricular and right-univentricular pacing in heart failure patients with chronic atrial fibrillation. Eur Heart J 23:1780–1787
14. Brignole M, Gammage M, Puggioni E et al (2005) Comparative assessment of right, left, and biventricular pacing in patients with permanent atrial fibrillation. Eur Heart J 26:712–722
15. Doshi RN, Daoud EG, Fellows C et al (2005) Left ventricular-based cardiac stimulation post AV nodal ablation evaluation (the PAVE study). J Cardiovasc Electrophysiol 6:1160–1165
16. Wyman BT, Hunter WC, Prinzen FW et al (2002) Effects of single- and biventricular pacing on temporal and spatial dynamics of ventricular contraction. Am J Physiol 282:H372-H379

17. O'Keefe JH Jr, Abuissa H, Jones PG et al (2005) Effect of chronic right ventricular apical pacing on left ventricular function. Am J Cardiol 95:771–773
18. Thackray SD, Witte KK, Nikitin NP et al (2003) The prevalence of heart failure and asymptomatic left ventricular systolic dysfunction in a typical regional pacemaker population. Eur Heart J 24:1143–1152
19. Ovsyshcher IE, Barold SS (2007) Should cardiac resynchronization be considered for the primary prevention of heart failure? In: Ritter P, Barold SS (eds) Devices for cardiac resynchronization. Technologic and clinical aspects. Springer (in press)

The Ideal Pacemaker for Elderly Patients

Gulmira Kudaiberdieva[1], Bulent Gorenek[2]

Introduction

The number of elderly people has been rapidly increasing for several decades. This increase in longevity has been accompanied by issues of health and quality-of-life. Among these, the proper treatment of cardiac diseases in the elderly has become an important concern. Sinus node dysfunction (SND) and atrioventricular block (AVB) due to development of conduction system fibrosis are the most common indications for cardiac pacing in elderly population [1].

Population-based studies have demonstrated that more than two-thirds of all pacemaker implantations are done in patients older than 65–70 years, with very elderly patients over 80 years of age receiving 30% of the implantations [1, 2]. Retrospective studies demonstrated that pacemaker implantation resulted in a reduction of disease symptoms, an improvement in functional state and health, and an increase in long-term survival rates in elderly and very elderly patients [2–6]. During the last few decades, there has been an increase in the number of atrial-based dual-chamber pacemakers (DDD, atrial and ventricular pacing and sensing, dual response) implanted in older patients, from 0–27% in the early 1980s to 37–76% by the mid-1990s [1, 7].

It is known that single-chamber ventricular-based pacing (VVI, ventricular pacing and sensing, inhibition response) has significant drawbacks due to a loss of atrioventricular synchrony, leading to hemodynamic deterioration and development of pacemaker syndrome. In contrast, physiological atrial-based pacing by preserving atrioventricular synchrony improves ventricular filling and optimizes cardiac output. Elderly patients may be more sensitive

[1]National Center of Cardiology and Therapy, Bishkek, Kyrgyzstan; [2]Cardiology Department, Eskisehir Osmangazi University, Eskisehir,Turkey

to hemodynamic compromise because of aging-associated changes in cardiovascular and autonomic function.

Trial and Study Results

Retrospective studies in very elderly patients suggested that the pacing mode was not an independent predictor of survival after adjustment for clinical variables and comorbidities, and had no prognostic influence on the long-term survival of patients undergoing pacemaker implantation [2, 3, 7].

Several randomized prospective studies have compared patient outcomes obtained with atrial-based and ventricular-based pacing modes, and recent meta-analysis has shown that atrial-based pacing was associated with a significant reduction in the incidence of atrial fibrillation (AF) and a borderline reduction in the risk of stroke, as compared with ventricular pacing [8–14].

Though many of the patients included in those studies [9, 12–14] were elderly, only two were randomized prospective studies [10, 11] designed to evaluate outcomes in different pacing modes in the elderly population. The PASE study included patients over 65 years with SND and AVB, and the UKPACE study included over 70 years with AVB. In the MOST trial [14] the inclusion criterion was age > 21 years; however, about 75% of the patients were > 67 years of age.

The PASE trial [10] compared clinical outcomes and quality of life during 18 months of follow-up in 407 patients > 65 years of age and with SND and AVB. Participants were assigned to either the VVIR or DDDR pacing modes. No significant differences were found in the rate of death from all causes, stroke or death or hospitalization due to heart failure (HF), or AF rate between VVIR and DDDR pacing modes groups. However, there were significant differences in the entire group with respect to overall quality-of-life measurements and health-related quality-of-life measurements favoring DDDR pacing mode.

In the PASE trial, the quality-of-life improved to a greater extent in the subgroup of patients with SND and DDDR pacing mode than in those with VVIR mode, while no such a difference was observed for AVB patients assigned to either pacing mode. The clinical outcome rates were not dependent on type of pacing mode, either in SND patients or in patients with AVB.

In patients with SND, quality-of-life scores (physical role, social function, and emotional function subscales) at 3 months were significantly better (p = 0.02, p = 0.03 and p = 0.002) for patients with atrial-based pacing than for those with ventricular-based pacing. There were no differences between VVIR and DDDR modes with respect to clinical outcomes, except for a bor-

derline significance in the incidence of AF ($p = 0.06$), which was somewhat less in the DDDR group (19 vs 28%). Further multivariate analysis of AF predictors in the PASE trial [15] showed that, after adjustment for baseline clinical variables, randomization for VVIR pacing mode was a significant clinical predictor of AF development along with hypertension and pre-implant supraventricular tachycardia. The adjusted risk of AF development was 2.55 times higher (95% CI 1.23, 5.29, $p = 0.01$) in patients with VVIR pacing than in those with DDDR pacing. However, the development of AF did not significantly affect the risk of death from all causes, or death or stroke or hospitalization due to HF, and AF was not associated with a worsening of quality-of-life scores or cardiovascular functional status.

In patients with AVB, there were no differences between VVIR and DDDR pacing modes in deaths from all causes (15 vs 17%), stroke or death from any cause, or hospitalization for HF and AF. There were also no differences in quality-of-life scores for patients with AVB with and without AV-synchronized pacing.

The incidence of pacemaker syndrome was 26% in patients with VVIR pacing mode. Complication rates in the PASE trial [16] were 6.1%, with the most frequent complications being pneumothorax (2%), ventricular lead dislodgement (1.7%), cardiac perforation, atrial lead dislodgement (0.5%), and subclavian vein thrombosis (0.5%). There were no significant clinical predictors for the development of complications, including mode of pacing, except for pneumothorax, which was associated significantly with age > 75 years, lower weight, higher trend of occurrence in females, and with subclavian approach. The length of hospital stay was dependent on the perioperative complication rates.

The MOST trial [14] was designed to compare the outcomes in 2,010 patients with SND assigned to either VVIR or DDDR pacing modes during a median 33.1 months of follow-up. There were no differences in primary outcome, death, or nonfatal stroke between patients with respect to the two pacing modes (DDDR -21.5% and VVIR -23%, $p = 0.48$), death, nonfatal stroke, or hospitalization for HF. However, there was a significantly lower incidence of AF in the DDDR group than in the VVIR group (21.4 vs 27.1%, HR-0.79, 95% CI 0.66–0.94, $p = 0.008$). After adjustment for clinical variables, including history of myocardial infarction, diabetes, congestive HF, and supraventricular tachycardia, multivariate analysis showed that the rate of reduction of AF incidence with DDDR pacing mode increased (HR-0.77, 95% CI 0.64–0.92, $p = 0.004$). Multivariate analysis also demonstrated an association of dual-chamber pacing with reduction of adjusted rate of hospitalizations for HF (HR-0.73, 95% CI 0.56–0.95, $p = 0.02$) and a reduction in the inci-

dence of combined clinical end-point (death, nonfatal stroke, or hospitalization for HF; HR-0.85, 95% CI 0.72–1.0, $p = 0.05$).

Dual-chamber pacing was associated with better health-related quality-of-life measurements (SF-36, Medical Outcomes Study 36-Item Short Form, General Heart Survey): role physical ($p < 0.0001$), role emotional ($p = 0.009$), and vitality ($p = 0.002$) during 4 years than obtained with ventricular pacing [17].

Pacemaker syndrome developed in 18.3% of 996 patients with VVIR pacing mode whose pacemaker modes were further reprogrammed for dual-chamber pacing mode. Predictors of the development of pacemaker syndrome were a higher percentage of paced beats, higher programmed low rate, and slower underlying spontaneous sinus rate [18]. As determined by multivariate analysis, only a higher percentage of paced ventricular beats was an independent predictor of pacemaker syndrome development ($p = 0.0001$). After switching to dual-chamber pacing, there was a significant improvement in quality-of-life scores, which led the investigators to suggest that the implantation of atrial leads in all patients may prevent pacemaker syndrome development.

The 30-day post-implantation complications rate was 4.8%, with the most frequent complications being atrial lead dislodgement (1.8%), pneumothorax (1.5%), and problems with ventricular leads (1.1%).

The recently completed UKPACE trial [11] was devoted to the assessment of the effects of single-chamber ventricular pacing (with and without rate adaptation) vs dual-chamber pacing (with and without sensor rate adaptation) on mortality, AF, HF, and composite stroke rates in elderly patients (> 70 years) with high-grade AVB. Among the 2,021 patients with high-grade AVB, 1,009 patients received single-chamber pacemakers (504 patients +VVI and 505 – VVIR) and 1,012 patients had dual-chamber pacemakers implanted. There were no differences among the two pacing-mode groups with respect to annual mortality rate (7.2% VVI pacing group vs 7.4% DDD pacing group) and death due to cardiovascular causes (3.9 vs 4.5%, $p = 0.07$) during 4.6 years of follow-up. Pacing mode did not affect the incidence of AF (3.0 and 2.8%, $p = 0.74$, for VVI and DDD pacing groups), HF (3.2 vs 3.3%, $p = .80$, for VVI vs DDD pacing groups), combined stroke outcome (stroke, transient ischemic attack, thromboembolism; 2.1 vs 1.7%, $p = 0.20$), or event rates for coronary artery disease and myocardial infarction.

However, in the group of patients that received VVI pacing without rate adaptation (subgroup of 505 patients), the annual event rate of combined stroke was significantly higher than in the DDD group (2.5 vs 1.7%, $p = 0.04$). In addition, the 3-year event-free survival for combined stroke was

1.58 (CI 1.03–2.42, $p = 0.04$) times lower for fixed-rate VVI pacing than in the DDD group. Event rates in the VVIR pacing group were similar to that of the DDD pacing group.

Procedural complication rates (7.8 vs 3.5%, $p < 0.001$), therapeutic intervention rate (8.8 vs 5.6%), and need for re-operation (4.2 vs 2.5%, $p = 0.04$) were higher for DDD pacing mode than for VVI pacing mode. The pacemaker syndrome rates have not yet been reported for the UKPACE trial.

Conclusions

Selection of the pacing mode in elderly patients should be based on an individual approach that takes into consideration the patient's quality of life, potential clinical outcome, and the complication rates of the procedure.

In elderly patients with SND, the primary outcomes, i.e., mortality and stroke rate, did not differ between patients with ventricular- and atrial-based pacing modes. However, dual-chamber pacing may be preferred to ventricular-based pacing because of greater improvement in the quality of life and the lower number of hospitalizations for HF and AF, although the latter does not ultimately worsen the quality of life or other clinical outcomes.

In patients with AVB, there were no differences in the incidence of death, stroke, HF, and AF between patients with dual-chamber pacing and those with ventricular single-chamber pacing modes. The differences in combined stroke, transient ischemic attack, and thromboembolism resulting from fixed-rate VVI pacing vs DDD pacing may recommend rate-adaptive ventricular-based pacing if single-chamber ventricular pacing is decided upon.

Another important factor that may affect the choice of an appropriate pacemaker is the high incidence (18.3–26%) of pacemaker syndrome due to loss of atrioventricular synchrony in elderly patients with single-chamber ventricular-based pacing. However, it is difficult to predict which patients will develop pacemaker syndrome, since the only independent predictor of this complication was the number of paced ventricular beats. This finding may favor the implantation of dual-chamber pacemakers [18].

Patients of advanced age are also prone to increased periprocedural and implantation complication rates (4.8–6.1%). In selecting the mode of pacing in elderly patients, the clinician should keep in mind that DDD pacemaker implantation is associated with a higher rate of complications, atrial leads dislodgement, and problems with ventricular leads, all of which necessitate careful monitoring during both the implant procedure and follow-up. Older (> 75 years) and sicker patients should be observed closely for the risk of developing pneumothorax.

In elderly patients, the absence of a clear benefit in primary outcome rates for DDD pacing vs VVI pacing modes may be explained in part by the fact that the advantage of AV synchrony provided by dual-chamber pacemakers could be masked by ventricular dyssynchrony resulted from right ventricular apical pacing. Recent results of the MOST trial [19–21] revealed that the incidence of HF in DDD pacing was closely related to the percentage of ventricular paced beats. The increased hospitalization rate for HF in patients with wide-paced QRS complex reported by the MOST trial also suggests a contribution of ventricular dyssynchrony. Further studies with optimal pacing sites and advanced modes are needed to find a solution for the undesirable consequences of right ventricular pacing and ventricular dyssynchrony in elderly patients.

References

1. Rosenheck S, Geist M, Weiss A et al (1995) Permanent cardiac pacing in octogenarians. Am J Geriatr Cardiol 4:42–47
2. Schmidt B, Brunner M, Olschewski M et al (2003) Pacemaker therapy in very elderly patients: long-term survival and prognostic parameters. Am Heart J 146:908–913
3. Shen WK, Hayes DL, Hammill SC et al (1996) Survival and functional independence after implantation of a permanent pacemaker in octogenarians and nonagenarians. A population-based study. Ann Intern Med 125:476–480
4. Lopez-Jimenez F, Goldman L, Orav EJ et al (2002) Health values before and after pacemaker implantation. Am Heart J 144:687–692
5. Shen WK, Hammill SC, Hayes DL et al (1994) Long-term survival after pacemaker implantation for heart block in patients > or = 65 years. Am J Cardiol 74:560–564
6. Lamas GA, Pashos CL, Normand SL, McNeil B (1995) Permanent pacemaker selection and subsequent survival in elderly Medicare pacemaker recipients. Circulation 91:1063–1069
7. Jahangir A, Shen WK, Neubauer SA et al (1999) Relation between mode of pacing and long-term survival in the very elderly. J Am Coll Cardiol 33:1208–1016
8. Healey JS, Toff WD, Lamas GA et al (2006) Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of randomized trials, using individual patient data. Circulation 114:11–17
9. Andersen HR, Nielsen JC, Thomsen PE et al (1997) Long-term follow-up of patients from a randomised trial of atrial versus ventricular pacing for sick-sinus syndrome. Lancet 350:1210–1216
10. Lamas GA, Orav EJ, Stambler BS et al (1998) Quality of life and clinical outcomes in elderly patients treated with ventricular pacing as compared with dual-chamber pacing. Pacemaker Selection in the Elderly Investigators. N Engl J Med 338:1097–1104
11. Toff WD, Camm AJ, Skehan JD; United Kingdom Pacing and Cardiovascular Events Trial Investigators (2005) Single-chamber versus dual-chamber pacing for high-grade atrioventricular block. N Engl J Med 353:145–155

12. Connolly SJ, Kerr CR, Gent M et al (2000) Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. N Engl J Med 342:1385–1391
13. Mattioli AV, Vivoli D, Mattioli G (1998) Influence of pacing modalities on the incidence of atrial fibrillation in patients without prior atrial fibrillation. Eur Heart J 19:282–286
14. Lamas GA, Lee KL, Sweeney MO et al (2002) Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 346:1854–1862
15. Stambler BS, Ellenbogen KA, Orav EJ et al; Pacemaker Selection in the Elderly Trial Investigators (2003) Predictors and clinical impact of atrial fibrillation after pacemaker implantation in elderly patients treated with dual chamber versus ventricular pacing. Pacing Clin Electrophysiol 26:2000–2007
16. Link MS, Estes NA 3rd, Griffin JJ et al (1998) Complications of dual chamber pacemaker implantation in the elderly. Pacemaker Selection in the Elderly (PASE) Investigators. J Interv Card Electrophysiol 2:175–179
17. Fleischmann KE, Orav EJ, Lamas GA et al (2006) Pacemaker implantation and quality of life in the Mode Selection Trial (MOST). Heart Rhythm 3:653–659
18. Link MS, Hellkamp AS, Estes NAM et al (2004) High incidence of pacemaker syndrome in patients with sinus node dysfunction treated with ventricular-based pacing in the Mode Selection Trial (MOST). J Am Coll Cardiol 43:2066–2071
19. Sweeney MO, Hellkamp AS, Ellenbogen KA et al; Mode Selection Trial Investigators (2003) Adverse effect of ventricular pacing on heart failure and atrial fibrillation among patients with normal baseline QRS duration in a clinical trial of pacemaker therapy for sinus node dysfunction. Circulation 107:2932–2937
20. Shukla HH, Hellkamp AS, James EA et al; Mode Selection Trial (MOST) Investigators (2005) Heart failure hospitalization is more common in pacemaker patients with sinus node dysfunction and a prolonged paced QRS duration. Heart Rhythm 2:245–251
21. Sweeney MO, Hellkamp AS (2006) Heart failure during cardiac pacing. Circulation 113:2082–2088

Update on ACC/ESC Criteria for Acute ST Elevation Myocardial Infarction

Peter W. Macfarlane

Introduction

In 2000, the European Society of Cardiology and the American College of Cardiology jointly published [1] guidelines defining myocardial infarction. The definition was based partly on the availability of new biomarkers to assist in detecting myocardial damage. As part of their report, the criteria for acute ST elevation myocardial infarction were established. These provided thresholds for abnormal ST elevation in the 12-lead ECG. Table 1 summarises these criteria.

Table 1. ESC criteria for ECG changes indicative of myocardial ischemia that may progress to myocardial infarction

Patients with ST elevation	New or presumed new ST segment elevation at the J point in two or more contiguous leads with the cut-off points ≥ 0.2 mV in leads V1, V2 or V3 and ≥ 0.1 mV in other leads. Contiguity in the frontal plane is defined by the lead sequence aVL, I, inverted aVR, II, aVF, III.
Patients without ST segment elevation	– ST segment depression – T-wave abnormalities only

Medical Sciences, University of Glasgow, Scotland, UK

Previous work in this laboratory had shown that the normal limits of ST amplitude were both age- and sex-dependent [2]. In 2001, a summary of the normal limits of ST junctional (STj) amplitude were published [3] in order to highlight this age and sex dependency. More recently, a separate study was undertaken in this laboratory to determine the upper limits of normal ST elevation in additional chest leads V7–V9 and V3R–V6R. No previous information on the normal limits in the former was available, although limited data [4] on right-sided chest leads V4R–V6R did not allow any conclusions to be drawn on the effect of age and gender.

The availability of all of this information has allowed us to further revise the criteria for abnormal ST elevation. As a result, it is hoped that the various cardiology authorities, such as the ESC/ACC/AHA, will acknowledge, in their next revision of ECG criteria for acute myocardial infarction, the fact that criteria should be age- and sex-dependent and that the current grouping [1] of leads to which criteria are applied is not optimal.

This short paper summarises some of the work aimed at enhancing the criteria for acute ST elevation myocardial infarction.

Methods

For the study of the conventional 12-lead ECG, apparently healthy volunteers were recruited from local government as well as from a small number of staff and students at the University of Glasgow. All were examined by a physician and none had any illness that affected the cardiovascular system.

With respect to the study on additional chest leads, individuals were recruited from staff and patients in Glasgow Royal Infirmary, all of whom had a healthy cardiovascular system. The additional chest leads were recorded in the resting position, with V7–V9 placed at the level of V4–V6 but with V7 at the posterior axillary line, V8 at the midscapular line and V9 at the parasternal line [5]. Leads V3R–V6R were placed on the right side of the chest in mirror image positions to V3–V6. All ECG measures were derived in an automated fashion using the University of Glasgow ECG analysis program [6]. The ST amplitude was defined as the amplitude at the junction of the QRS complex and the ST segment in each individual lead.

With respect to the standard 12-lead ECG, the normal limits of ST amplitude were used to obtain equations giving the age-dependent upper limit of the normal amplitude within individual leads for males. It was readily determined that the upper limits of normal in females were not age-dependent, although they were generally lower than in males. Therefore, revised upper limits of normal were separately established for females.

Results

The normal limits of ST amplitude in the 12 leads were derived from a cohort of 1,388 individuals, 731 males and 590 females, ages 17 years and over. Subjects were divided into four age ranges: 18–29, 30–39, 40–49 and 50 years and over. Further details are available elsewhere [3].

A separate group of 88 males, ages 42.2 ± 13.3 years, and 112 females, ages 42.3 ± 13.3 years, was recruited to the study of additional chest leads.

The upper limit of normal ST in males was found to be age-dependent and clearly lead-dependent, particularly in the precordial leads. Figure 1 illustrates the findings for V3. By contrast, the upper limits for females were not age-related, as exemplified in Fig. 1, but they were lead-dependent. As a result, there are unique upper limits of normal for each age and gender. As an example, Table 2 shows the upper limits of normal STj in leads V1–V6 for males and females ages 40–49 years.

Age-related equations were therefore derived for the upper limits of normal for males but constant values were selected for females. The goal was to obtain a high specificity based on a 96% normal range. For example, the upper limits of normal ST amplitude in V2 are given by the following equations:

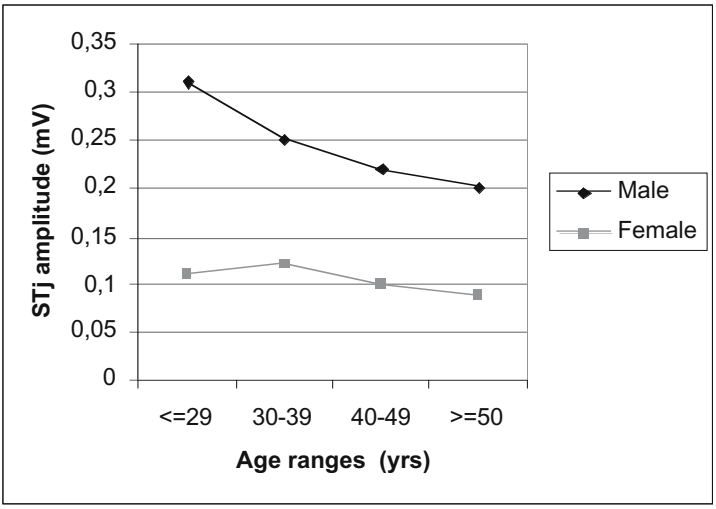


Fig. 1. The upper limits of normal ST amplitude for males and females in lead V3. The dependence on age for males is evident as is the lack of age dependence in females

Table 2. Upper-normal limits of ST amplitude V1–V6 for males and females ages 40–49 years. All data are in mV. Note how V1 is more aligned with V4–V6 than V2, V3, and that particularly for V2–V4 the limits for males are effectively double those for females.

	V1	V2	V3	V4	V5	V6
Males	0.11	0.27	0.22	0.13	0.09	0.07
Females	0.08	0.14	0.10	0.07	0.06	0.06

Upper limit ST_j in V2 (male) = -5 × age (years) + 450 μV
Upper limit ST_j V2 (females) = 140 μV

The study of additional chest leads showed that there was no age and gender difference except in V3R, where the upper limit of normal was 75 μV in males and 50 μV in females. Otherwise, 50 μV was found to be the upper limit of normal in all other additional chest leads for males and females.

Discussion

In short, the upper limits of normal ST amplitude are lead-dependent as well as age- and sex-dependent. It can be seen from Table 2 that it is completely incorrect to group V1 together with V2 and V3, as was the case with the initial ESC/ACC publication [1] containing the criteria listed in Table 1. This author strongly recommends that V1 be grouped with other chest and limb leads and not with V2 and V3.

With respect to age dependence and gender, leads V2 and V3 again illustrate very clearly how the upper limit of normal in males is very much greater than in females. This author suggests that the upper limit of normal in these leads should be 0.15 mV for females but 0.2 mV in males ≥ 40 years of age and indeed above 0.25 mV for males < 40 years of age. To facilitate the application of these criteria, it is suggested that 0.1 mV be regarded as the upper limit of normal in all other leads. However, for automated ECG interpretation, much more complex criteria are employed in the author's laboratory.

While this article has concentrated on ST elevation, the lower limits of normal ST junction can be regarded as -0.05 mV in V2 and V3 and -0.1 mV in the other leads. These criteria should be applied in conjunction with a horizontal or downward-sloping ST segment. There is no doubt that lesser degrees of ST depression will give an abnormal appearance to the ECG but, for the sake of specificity in dealing with acute ischemic changes, the foregoing thresholds are suggested.

Other work in this laboratory has shown that the revised criteria, when applied to a group of individuals with chest pain as well as to normal controls, resulted in improved sensitivity and indeed specificity in the diagnosis of acute ST elevation myocardial infarction [7].

The AHA is expected to issue guidelines in late 2007 on setting criteria for the diagnosis of acute ST change, and it is hoped that the above suggestions will be incorporated. Similarly, updated guidelines from an international group supported by the ESC and ACC will be issued late this year, and it is expected that there will be some revision to the previously reported criteria of 2000.

In conclusion, there is no question that the criteria for abnormal ST elevation should be age- and sex-dependent. Moreover, further revision of the lead dependency of criteria is merited when these are compared to the suggested criteria published in 2000 by the ESC/ACC [1]. It is expected that the revised guidelines to be published in the near future will make use, at least in part, of the suggestions outlined here.

References

1. The Joint European Society of Cardiology/American College of Cardiology Committee (2000) Myocardial infarction redefined – A consensus document. Eur Heart J 21:1502–1513
2. Macfarlane PW, Lawrie TDV (1989) The normal electrocardiogram and vectorcardiogram. In: Macfarlane PW, Lawrie TDV (eds) Comprehensive electrocardiology. Pergamon Press, Oxford, p 445
3. Macfarlane PW (2001) Age, sex and the ST amplitude in health and disease. J Electrocardiol 34(Suppl):235–241
4. Andersen HR, Nielsen D, Hansen LG (1987) The normal right chest electrocardiogram. J Electrocardiol 20:27–32
5. Pipberger HV, Arzbaecher RC, Berson AS et al; Committee on Electrocardiography of the AHA (1975) Recommendations for standardization of leads and of specifications for instruments in electrocardiography and vectorcardiography. Circulation 52(Aug Suppl):11–31
6. Macfarlane PW, Devine B, Latif S et al (1990) Methodology of ECG interpretation in the Glasgow program. Meth Inform Med 29:354–361
7. Macfarlane PW, Browne D, Devine B et al (2004) Modification of ACC/ESC criteria for acute myocardial infarction. J Electrocardiol 37(Suppl):98–103

ECG-MRI based Localization of Myocardial Infarction

Henrik Engblom, Olle Pahlm

Introduction

Magnetic resonance imaging (MRI) has emerged in the last decade as an important method for characterizing various aspects of cardiac anatomy, patho-anatomy, pathophysiology, and function. Measurements of flow parameters, left ventricular function, and grade of valvular regurgitation have been validated and proved to serve as excellent gold standards compared to simpler, established techniques, such as echocardiography, thermodilution measurements, and electrocardiography [1].

Introduction of the delayed contrast-enhanced MRI (DE-MRI) technique for visualization of myocardial necrosis and scar has made MRI the method of choice for myocardial infarct quantification in vivo [2]. Based on patterns of hyperenhancement, DE-MRI has proved useful for predicting functional recovery in patient with acute myocardial infarction [3, 4] and in patients suffering from ischemic heart disease who have undergone elective revascularization therapy [5].

In electrocardiography, the conventional 12-lead electrocardiogram (ECG) is still the dominating mode of registration, though it has at times been challenged by vectorcardiography and other lead systems with alternative electrode placement. Some of these systems employ fewer electrodes, while other employ several more electrodes than the 10 that are required for the 12-lead ECG [6].

Department of Clinical Physiology, University Hospital, Lund, Sweden

DE-MRI for Infarct Quantification

Pathophysiological Basis and Principles

When a coronary artery is occluded, the myocardium supplied by the occluded vessel is subject to ischemia, in the absence of extensive collateral circulation. What determines the reversibility of the impending injury is the duration and severity of the ischemia. If the ischemia is severe enough and its duration long enough to cause rupture of myocyte cell membranes, the myocardium becomes irreversibly injured, or infarcted. The loss of cell membrane integrity provides a useful indicator when acute myocardial infarction is visualized by DE-MRI.

Acquisition of DE-MR images is preceded by the intravenous injection of a gadolinium-based extracellular contrast agent. This agent distributes into the extracellular space of the myocardium. Since a myocyte with ruptured cell membrane is unable to prevent the extracellular contrast agent from entering its interior, the distribution volume for the contrast agent is increased in necrotic myocardium compared to viable myocardium [7, 8]. During the infarct-healing process, the acutely necrotic myocardium is replaced by fibrous scar tissue, which also has a larger distribution volume than viable myocardium. Thus, old myocardial infarction can also be visualized and quantified using DE-MRI [9]. Different wash-in/wash-out profiles have also been proposed to explain part of the difference in the amount of contrast agent present in infarcted vs viable myocardium [7, 10]. The difference in gadolinium concentration between areas with different distribution volumes enables distinction between viable and non-viable myocardium.

Validation Experiments

The hyperenhanced myocardium has been shown in animal models to closely resemble regions of infarction as assessed with triphenyltetrazolium chloride (TTC) [11, 12].

In order to correctly delineate the region of infarction, it is important to consider the so-called partial volume effects that arise in the infarct borders [12, 13]. The spatial resolution of a typical clinically acquired short-axis image of the heart is 1.5 x 1.5 x 8 mm. Thus, the thickness of each image slice is 8 mm. Within each slice, the infarct pattern might vary, especially at the infarct border; thus, a partial volume effect might cause an overestimation of the actual infarct size [14]. In a study including computer phantom experiments, animal experiments and validation in patients with acute and chronic ischemic heart disease, Heiberg et al. [13] showed that this problem can be

overcome using a computer algorithm developed to compensate for partial volume effects. The need for a common standard in the quantification of infarcted myocardium has recently been addressed [15].

Presence of Q Waves Indicates Large Extent Rather than Transmurality

The DE-MRI technique has also been used to explore the pathologic basis of infarct-related QRS changes. Several studies have shown that Q wave myocardial infarction should not be equated with transmural infarction, using DE-MRI as reference method for infarct transmurality [16–18]. Furthermore, the endocardial extent of infarction has been shown to be more predictive of infarct-related Q waves than is infarct transmurality [19]. This is illustrated in Fig. 1a, b. Figure 1c demonstrates that myocardial infarction limited to the lateral left ventricular wall does not generate pathological Q waves but rather prominent R waves and small S waves in lead sV1 and V2.

Recent Initiatives Regarding ECG Designation of Cardiac Walls

Recently, a group of international experts published a consensus document proposing a new terminology for left ventricular walls and the location of myocardial infarcts based on the 12-lead ECG (Fig. 2) [20]. This work became possible through the study of multiple patients who had undergone ECG and MRI studies that were performed in close temporal proximity. The focus of the consensus group's work was to adapt the ECG nomenclature to the established 17-segment model of the left ventricular myocardium agreed upon in 2002 by experts on various modalities for tomographic imaging of the heart [21].

Validation of Infarct-Size Measures Based on the 12-Lead ECG

Based on the description of the human myocardial activation published by Durrer et al. [22], Selvester and co-workers designed a computer simulation of the human activation sequence. Using this computer model they obtained different patterns of QRS changes on a fictitious torso surface by simulating infarcts of different sizes at various locations in the left ventricle. The results from the computer simulations were used to develop the Selvester QRS scoring system. However, in order to assess its diagnostic ability, the system had to be validated in humans. The scoring system was systematically evaluated

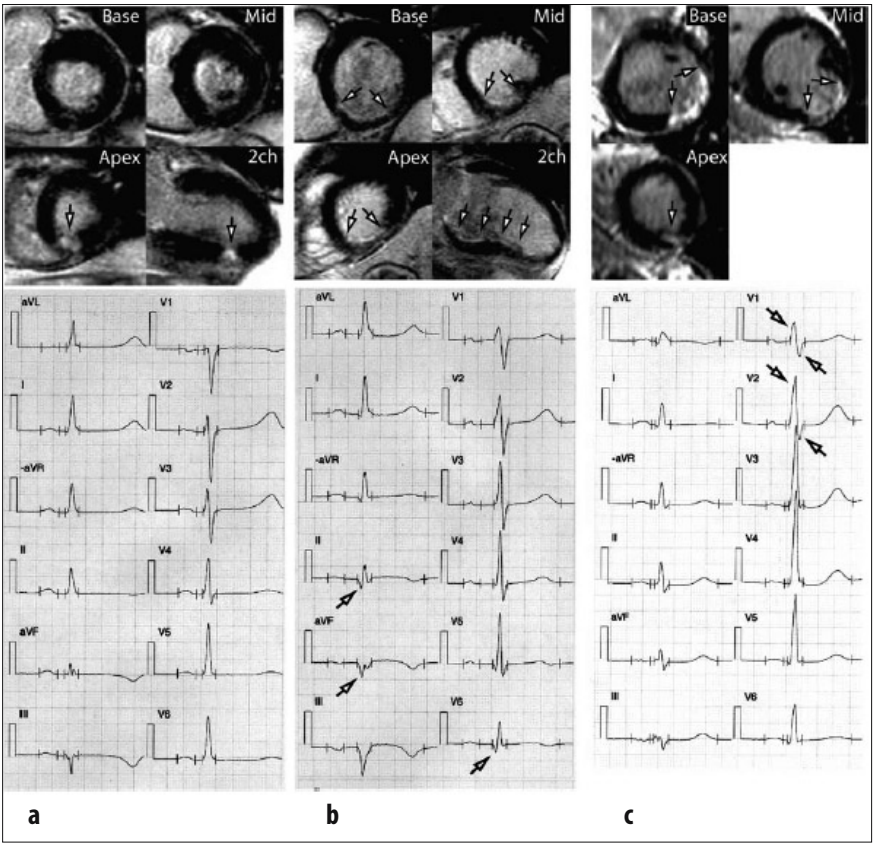


Fig. 1a–c. Three cases illustrating the importance of considering not only Q waves for myocardial infarction (MI) detection and quantification by electrocardiography (ECG). **a** Small transmural, non-Q wave MI in the inferior left ventricular (LV) wall. **b** Non-transmural, Q wave MI in the inferior LV wall. **c** Transmural, non-Q wave MI in the posterolateral LV wall. This patient had prominent R waves and small S waves in V1 and V2, suggestive of posterolateral MI. Magnetic resonance (MR) imaging was aborted before long-axis images were acquired. Arrows indicate either MI by delayed contrast-enhanced (DE)-MRI or QRS changes generating QRS points. *2ch*, Two chamber long-axis view. (From [18], with permission)

in human postmortem histopathology studies of single infarcts located in the anterior [23], inferior [24], and posterolateral [25] parts of the left ventricular wall.

More recently, the Selvester QRS scoring system was evaluated using DE-MRI as the reference method for infarct size. In a study of patients suffering from chronic ischemic heart disease accompanied by old myocardial infarc-

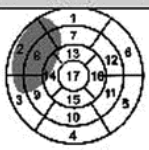
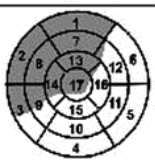
NAME	ECG PATTERN	INFARCTION AREA (CMR)
SEPTAL	Q in V1-V2	
MID-ANTERIOR	Q (qs or qr) in aVL and sometimes in I and/or V2-V3	
APICAL - ANTERIOR	Q in V1-V2 to V3-V6	
EXTENSIVE ANTERIOR	Q in V1-V2 to V4-V6, aVL and sometimes I	
LATERAL	RS in V1-V2 and/or Q wave in leads I, aVL, V6 and/or diminished R wave in V6	
INFERIOR	Q in II, III, aVF	

Fig. 2. The ECG patterns of Q wave MI or Q wave equivalents with the names given to MI and related infarction area documented by cardiovascular MR imaging. (From [20], with permission)

tion in the anterior left ventricular wall, the Selvester QRS scoring system significantly underestimated the amount of infarction at the left ventricular apex [26]. In patients with reperfused first-time myocardial infarction, the scoring system was shown to correlate strongly with infarct size assessed by DE-MRI [18].

Since MRI is not associated with ionizing radiation, this imaging modality is feasible for serial follow-up examination. Recently, DE-MRI was used to explore the pathologic correlate to resorption of infarct-related QRS changes by following patients with first-time myocardial infarction after primary percutaneous coronary intervention [4].

MRI as the Gold Standard for Refining Diagnostic ECG Criteria

Several databases are being developed that contain 12-lead ECGs and MRI studies carried out within minutes or hours of each other. These databases will allow elaboration of enhanced diagnostic ECG criteria for implementation in digital interpretation programs or for manual application by physicians responsible for the care of patients with suspected heart disease.

References

1. Bellenger NG, Davies LC, Francis JM et al (2000) Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2:271–278
2. Pennell DJ, Sechtem UP, Higgins CB et al (2004) Clinical indications for cardiovascular magnetic resonance (CMR): Consensus Panel report. Eur Heart J 25:1940–1965
3. Choi KM, Kim RJ, Gubernikoff G et al (2001) Transmural extent of acute myocardial infarction predicts long-term improvement in contractile function. Circulation 104:1101–1107
4. Engblom H, Hedstrom E, Heiberg E et al (2007) Time course and magnitude of infarct involution, functional recovery, and electrocardiographic changes in patients with reperfused first myocardial infarction. (submitted)
5. Kim RJ, Wu E, Rafael A et al (2000) The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 343:1445–1453
6. Tragardh E, Engblom H, Pahlm O (2006) How many ECG leads do we need? Cardiol Clin 24:317–330, vii
7. Tong CY, Prato FS, Wisenberg G et al (1993) Measurement of the extraction efficiency and distribution volume for Gd-DTPA in normal and diseased canine myocardium. Magn Reson Med 30:337–346
8. Arheden H, Saeed M, Higgins CB et al (1999) Measurement of the distribution volume of gadopentetate dimeglumine at echo-planar MR imaging to quantify myocardial infarction: comparison with 99mTc-DTPA autoradiography in rats. Radiology 211:698–708
9. Rehwald WG, Fieno DS, Chen EL et al (2002) Myocardial magnetic resonance imaging contrast agent concentrations after reversible and irreversible ischemic injury. Circulation 105:224–229

10. Klein C, Nekolla SG, Balbach T et al (2004) The influence of myocardial blood flow and volume of distribution on late Gd-DTPA kinetics in ischemic heart failure. J Magn Reson Imaging 20:588–593
11. Nishimura T, Yamada Y, Hayashi M et al (1989) Determination of infarct size of acute myocardial infarction in dogs by magnetic resonance imaging and gadolinium-DTPA: comparison with indium-111 antimyosin imaging. Am J Physiol Imaging 4:83–88
12. Kim RJ, Fieno DS, Parrish TB et al (1999) Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 100:1992–2002
13. Heiberg E, Ugander M, Engblom H et al (2007) Accounting for partial volume effects in the automated quantification of myocardial infarction from delayed enhancement MRI. Radiology (in press)
14. Hsu LY, Natanzon A, Kellman P et al (2006) Quantitative myocardial infarction on delayed enhancement MRI. Part I: Animal validation of an automated feature analysis and combined thresholding infarct sizing algorithm. J Magn Reson Imaging 23:298–308
15. Foster JE, Arheden H, Engblom H (2007) Myocardial infarct quantification: is MR imaging ready to serve as gold standard for ECG? J Electrocardiol (in press)
16. Moon JC, De Arenaza DP, Elkington AG et al (2004) The pathologic basis of Q wave and non-Q wave myocardial infarction: a cardiovascular magnetic resonance study. J Am Coll Cardiol 44:554–560
17. Kaandorp TA, Bax JJ, Lamb HJ et al (2005) Which parameters on magnetic resonance imaging determine Q waves on the electrocardiogram? Am J Cardiol 95:925–929
18. Engblom H, Hedstrom E, Heiberg E et al (2005) Size and transmural extent of first-time reperfused myocardial infarction assessed by cardiac magnetic resonance can be estimated by 12-lead electrocardiogram. Am Heart J 150:920
19. Engblom H, Carlsson MB, Hedström E et al (2007) The endocardial extent of reperfused myocardial infarction is a stronger determinant of pathological Q waves than is infarct transmurality. Clin Physiol Funct Imag 27:101–108
20. Bayes de Luna A, Wagner G, Birnbaum Y et al (2006) A new terminology for left ventricular walls and location of myocardial infarcts that present Q wave based on the standard of cardiac magnetic resonance imaging: a statement for healthcare professionals from a committee appointed by the International Society for Holter and Noninvasive Electrocardiography. Circulation 114:1755–1760
21. Cerqueira MD, Weissman NJ, Dilsizian V et al (2002) Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. Circulation 105:539–542
22. Durrer D, van Dam RT, Freud GE et al (1970) Total excitation of the isolated human heart. Circulation 41:899–912
23. Ideker RE, Wagner GS, Ruth WK et al (1982) Evaluation of a QRS scoring system for estimating myocardial infarct size. II. Correlation with quantitative anatomic findings for anterior infarcts. Am J Cardiol 49:1604–1614
24. Roark SF, Ideker RE, Wagner GS et al (1983) Evaluation of a QRS scoring system for estimating myocardial infarct size. III. Correlation with quantitative anatomic findings for inferior infarcts. Am J Cardiol 51:382–389

25. Ward RM, White RD, Ideker RE et al (1984) Evaluation of a QRS scoring system for estimating myocardial infarct size. IV. Correlation with quantitative anatomic findings for posterolateral infarcts. Am J Cardiol 53:706–714
26. Engblom H, Wagner GS, Setser RM et al (2003) Quantitative clinical assessment of chronic anterior myocardial infarction with delayed enhancement magnetic resonance imaging and QRS scoring. Am Heart J 146:359–366

Electrocardiographic Predictors of Arrhythmias In CCU Patients

Afshin Parspour, Alparslan Birdane, Bulent Gorenek

Introduction

Patients hospitalized in the coronary care unit (CCU) are vulnerable to many kinds of arrhythmias, including ventricular and supraventricular arrhythmias, especially in the setting of acute coronary syndrome. Some of these arrhythmias can be predicted electrocardiographically. This chapter discusses the arrhythmias commonly afflicting CCU patients and their electrocardiographic predictors.

Ventricular Arrythmias

Death from a ventricular tachyarrhythmia in the setting of an acute myocardial infarction (MI) has historically been one of the most frequent causes of sudden cardiac death [1, 2]. In a 1985 report, for example, 60% of deaths associated with acute MI occurred within the first hour after the event and were attributable to a ventricular arrhythmia, in particular ventricular fibrillation (VF) [3]. Subsequent improvements in arrhythmia detection and treatment have had a major impact on the outcome of ventricular arrhythmias associated with acute MI. As a result, arrhythmic and overall in-hospital mortalities have fallen significantly [4, 5]. Ventricular arrhythmias, ranging from isolated ventricular premature beats to ventricular fibrillation, are common in the immediate post-infarction period. Observations in the prethrombolytic era led to the identification of several types of ventricular arrhythmias [6, 7]:

Department of Cardiology, Eskisehir Osmangazi University Medical Faculty, Eskisehir, Turkey

- Ventricular premature beats (VPBs), which are typically asymptomatic, are common after acute MI and their reported incidence is as high as 93% [6]. Early VPBs do not predict short-or long-term mortality, but frequent and/or multiform VPBs that persist more than 48–72 h after an MI may be associated with an increased long-term risk of arrhythmia [6].
- Ventricular tachycardia (VT) can be further classified as nonsustained or sustained.
  - Nonsustained VT (NSVT) terminates spontaneously in less than 30 s. The incidence of NSVT is 1–7% [7, 8]. In the first 24–48 h after an infarction, NSVT is usually due to abnormal automaticity or to triggered activity in the region of ischemia or infarction. NSVT that occurs later is more often due to reentry. Thus, the probable mechanism and prognostic significance of NSVT depend upon the time at which it occurs [8].
  - Sustained VT is defined as three or more consecutive beats originating below the atrioventricular node, with a heart rate greater than 100 or 120 beats/min. There is some disagreement as to whether 100 or 120 beats/min represents the upper limit for an accelerated idioventricular rhythm. VT is considered sustained if it lasts more than 30 s or if it causes instability that requires termination (e.g., cardioversion) within 30 s [9]. Sustained monomorphic VT (SMVT) in the perinfarction period (i.e., within the first 48 h after the infarct) occurs in approximately 2–3% of patients with an ST-elevation MI [9, 10] and in less than 1% of patients with a non-ST elevation MI or unstable angina [9]. SMVT is associated with larger MIs [10]. The factors responsible for SMVT differ in the very early (30 min) and later (6–48 h) phases of the early post-MI period.
- Accelerated idioventricular rhythm occurs in up to 50% of patients with acute MI. Some studies have suggested an association with reperfusion following thrombolytic therapy [11].
- Ventricular fibrillation is the most frequent mechanism of sudden cardiac death. It is a rapid, disorganized ventricular arrhythmia, resulting in non-uniform ventricular contraction, no cardiac output, and no recordable blood pressure. The electrocardiogram (ECG) in VF shows rapid (300–400 beats/min), irregular, shapeless QRST undulations of variable amplitude, morphology, and interval. Over time, these wave forms decrease in amplitude until, ultimately, asystole occurs. VF is often further classified as primary or non-primary. Primary VF occurs early after MI (usually < 48 h) and is not associated with recurrent ischemia or heart failure. This category comprises patients who experience VF despite

a relatively uncomplicated MI (i.e., as a primary electrical event). Non-primary VF refers to all other episodes. VF is more common in patients with MIs that are complicated by heart failure or recurrent ischemia [12]. The incidence appears to be higher with ST elevation (Q wave) MI than with non-ST elevation (non-Q wave) MI [9].

Several predictors of ventricular arrhythmias after MI have been identified:

- The clinical usefulness of measuring changes in the duration of the QT interval in the standard 12-lead ECG is the focus of growing interest. Day et al. [13] proposed using the QT dispersion (QTd) as an index of inhomogeneous myocardial repolarization. This measurement may provide a prognostic tool in the detection of future ventricular tachyarrhythmic events that may cause death [14].
- In a study by Kudaiberdieva et al. [15], reduced left ventricular ejection fraction (LVEF) and late potentials (LPs) were used in post-MI risk stratification. The authors noted that the QT clinical variability index (QTVI) is a predictor of sudden death in patients with structural heart disease. They showed that patients with both LPs and increased QTVI after MI had a high likelihood of developing sustained arrhythmias. Consequently, a simple bedside ECG recording with further analysis of LPs and the QTVI may be the first step in a strategy to identify patients at risk for arrhythmia after MI [15].
- Since the first report by Wolf et al. [16], in1978, on the association between decreased heart rate variability (HRV) and increased mortality after MI, numerous studies have used HRV, either alone or in combination with other variables, to establish post-infarction risk [17–19]. The predictive value of HRV was found to be independent of other factors, such as depressed LVEF, increased ventricular ectopic activity, and presence of LPs [20]. For prediction of all-cause mortality, the value of HRV is similar to that of LVEF, but in predicting arrhythmic events (sudden cardiac death and ventricular tachycardia) HRV is superior [20].
- T-wave or repolarization alternans (TWA) refers to variability in the timing or morphology of repolarization occurring in alternate beats on the surface ECG [21]. TWA is indicative of repolarization heterogeneity, which increases susceptibility to ventricular tachyarrhythmias [22]. The presence of TWA has high sensitivity and specificity for predicting inducible ventricular arrhythmias on electrophysiologic study (EPS). The value of TWA vs LPs on signal-averaged ECG (SAECG) in predicting clinical events was evaluated in a prospective study of 102 patients with a

recent MI; 49% had TWA and 21% had LPs [23]. After a follow-up of 15 months, the sensitivity and negative predictive value of TWA for predicting arrhythmic events were 93 and 98%, respectively, while the positive predictive value was 28%. When TWA and LPs were combined, the positive predictive value increased to 50%. Thus, TWA is a promising ECG-detectable risk factor that indicates alternate-beat changes in the shape or amplitude of the T wave and reflects repolarization dispersion [24]. In a decade of contemporary clinical use [25], TWA has shown a negative predictive accuracy for sudden cardiac arrest above 90% in an accumulative population of thousands of cardiomyopathy patients, both ischemic and non-ischemic [26, 27]. Sanjav et al. showed that TWA is a promising ECG-based index of sudden cardiac arrest and is linked with repolarization dispersion as well as ventricular arrhythmias.

- Evidence for slowed conduction after MI, assessed indirectly by SAECG [28], successfully predicted sudden cardiac arrest in the *Multicenter Unsustained Tachycardia Trial* (MUSTT) [29]. Elevated sympathetic nervous activity increases the dispersion of repolarization and, when detected by cardiac nuclear imaging [30], reduced HRV [31], or heart rate turbulence [32], predicts events after MI. SAECG often demonstrates LPs in patients with SMVT and ischemic heart disease [33–35]. The presence of LPs on SAECG provides only indirect data that are suggestive, but not diagnostic of SMVT. Although the SAECG has a role in predicting the risk of SMVT in patients with ischemic heart disease, it is of limited use in the evaluation of patients who have already experienced SMVT [36, 37]. The Task Force of the American College of Cardiology published recommendations for the use of SAECG [38]. Also, in a study by Haghjoo et al., the importance of HRV, LVEF < 40%, and SAECG in predicting ventricular arrhythmias in post-MI patients was noted [39].
- Heart-rate turbulence (HRT) consists of a fluctuation in the sinus rate due to a ventricular premature beat [40]. HRV after ventricular premature beats was recently introduced as a noninvasive tool for arrhythmic risk stratification after MI. The absence of HRT is abnormal and has been associated with increased cardiac mortality [41, 42] and sudden cardiac death in patients with prior MI [41].
- A short-long (S-L) cardiac cycle is another predictor of ventricular arrhythmias in CCU patients. One or more S-L cardiac cycles, usually the result of a ventricular bigeminal rhythm, frequently precedes the onset of malignant ventricular tachyarrhythmias [43]. El Sharif et al. proposed that electrophysiologic mechanisms underlie the relationship between the S-L sequence and the onset of VT [44]. In a study by Gorenek et al.,

the clinical and electrophysiological features of monomorphic ventricular tachycardia (MVT) with different initiation patterns were investigated in patients with implantable cardioverter defibrillators. Non-sudden onset MVT was shown to be characterized by shorter cycle length, higher rate of different first-beat morphology, and the need for higher shock energy to achieve termination. Sudden-onset MVT was precipitated by shortening of the sinus cycle length before tachycardia [45].

Supraventricular Arrythmias

Supraventricular arrhythmias are relatively common in the peri-infarction period and their occurrence often heralds significant myocardial dysfunction. In addition, they may, in themselves, cause congestive heart failure and exacerbate ongoing myocardial ischemia [46].

Atrial Tachyarrhythmias

The overall incidence of atrial tachyarrhythmias in the peri-infarction period ranges from 6 to 20% and has not been altered by the use of thrombolytics [46–48]. These arrhythmias primarily occur within the first 72 h after infarction; however, only 3% were found to occur in the very early (less than 3 h) phase [48].

Atrial Fibrillation

Atrial fibrillation is the most common atrial arrhythmia. Inhomogeneous prolongations of sinus impulses may predict its recurrence [49]. The frequency with which atrial fibrillation occurs and its prognostic significance in the thrombolytic era were illustrated in the GUSTO-I and GUSTO-III trials [46, 50].

Atrial arrhythmias after MI can be predicted by a variety of ECG-based methods:

- P-wave dispersion (PWD) is a new electrocardiographic marker that reflects discontinuous and inhomogeneous propagation of sinus impulses, which in some cardiac conditions has been shown to be a useful predictor of paroxysmal atrial fibrillation (PAF) [51]. In a study by Dilaveris et al. that drew on previous studies, individuals with a clinical history of PAF had a P-wave of significantly increased duration in 12-lead surface ECG and SAECG recordings. Accordingly, the authors suggested that

PWD is a good predictor of PAF [52]. In another study, PWD was used to predict atrial fibrillation after percutaneous coronary intervention [53].

- The spontaneous onset of atrial fibrillation can also be predicted by HRV. This approach was used by Vikman and co-workers to evaluate the recurrence of atrial fibrillation after electrical cardioversion [54].
- SAECG of the P-wave is a useful predictor of idiopathic PAF among patients without atrial enlargement, especially the elderly [55]. It may also play a role in identifying patients at risk of developing PAF and those likely to undergo a change from PAF to chronic atrial fibrillation [56].
- In a study by Gorenek and co-workers, atrial ectopic beats with a long-short sequence were shown to be responsible for atrial-fibrillation relapse in about 70% of patients, and thus might predict early re-initiation of arrhythmia after electrical external cardioversion. This finding suggests that the ECG, recorded immediately after the external cardioversion, is a feasible approach in establishing patterns of atrial-fibrillation relapse and may be useful in managing the recurrence of this condition [57].

Conclusions

Arrhythmias are important problems in CCU patients, especially those with acute coronary syndrome and acute MI. In addition to the many clinical risk factors that are predictive of these arrhythmias, such as LVEF, there are electrocardiographic predictors, as discussed herein. Although all electrocardiographic predictors are important, we recommend using a combination of methods for a more accurate prediction of arrhythmia.

References

1. Lown B (1979) Sudden cardiac death: the major challenge confronting contemporary cardiology. Am J Cardiol 43:313–238
2. Myerburg RJ, Kessler KM, Castellanos A (1992) Sudden cardiac death: structure, function and time-dependence of risk. Circulation 85(1 Suppl):I2-I10
3. Pell S, Fayerweather WE (1985) Trends in the incidence of myocardial infarction and in associated mortality and morbidity in a large employed population, 1957–1983. N Engl J Med 312:1005–1011
4. Guidry UC, Evans JC, Larson MG et al (1999) Temporal trends in event rates after Q-wave myocardial infarction: The Framingham Heart Study. Circulation 100:2054–2059
5. Furman MI, Dauerman HL, Goldberg RJ et al (2001) Twenty-two year (1975 to 1997) trends in the incidence, in-hospital and long-term case fatality rates from initial Q-wave and non-Q-wave myocardial infarction: a multi-hospital, community-wide perspective. J Am Coll Cardiol 37:1571–1580

6. Bigger JT Jr, Dresdale FJ, Heissenbuttel RH et al (1977) Ventricular arrhythmias in ischemic heart disease: mechanism, prevalence, significance, and management. Prog Cardiovasc Dis 19:255–300
7. Eldar M, Sievner Z, Goldbourt U et al (1992) Primary ventricular tachycardia in acute myocardial infarction: clinical characteristics and mortality. Ann Intern Med 117:31–36
8. Heidbuchel H, Tack J, Vanneste L et al (1994) Significance of arrhythmias during the first 24 hours of acute myocardial infarction treated with alteplase and effect of early administration of a b-blocker or a bradycardic agent on their incidence. Circulation 89:1051–1059
9. Mont L, Cinca J, Blanch P et al (1996) Predisposing factors and prognostic value of sustained monomorphic ventricular tachycardia in the early phase of acute myocardial infarction. J Am Coll Cardiol 28:1670–1676
10. Newby KH, Thompson T, Stebbins A et al (1998) for the GUSTO Investigators. Sustained ventricular arrhythmias in patients receiving thrombolytic therapy: Incidence and outcomes. Circulation 98:2567–2573
11. Gorgels AP, Vos MA, Letsch IS et al (1988) Usefulness of the accelerated idioventricular rhythm as a marker for myocardial necrosis and reperfusion during thrombolytic therapy in acute myocardial infarction. Am J Cardiol 61:231–235
12. Volpi A, Cavalli A, Santoro L et al on behalf of the GISSI-2 Investigators. (1998) Incidence and prognosis of early primary ventricular fibrillation in acute myocardial infarction – results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2) database. Am J Cardiol 82:265–271
13. Day CP, McComb JM, Campbell RW (1990) QT dispersion: an indication of arrhythmia risk in patients with long QT intervals.Br Heart J 63:342–344
14. Okin PM, Devereux RB, Howard BV et al (2000) Assessment of QT interval and QT dispersion for prediction of all-cause and cardiovascular mortality in American Indians. The Strong Heart Study. Circulation:101:61–66
15. Kudaiberdieva G, Gorenek B, Timuralp B et al (2002) Value of combination of QT variability and late potentials in identification of patients with ventricular tachycardia after myocardial infarction. Int J Cardiol 83:263 –265
16. Wolf MM, Varigos GA, Hunt D, Sloman JG (1978) Sinus arrhythmia in acute myocardial infarction. Med J Australia 2:52–53
17. Cripps TR, Malik M, Farrell FG, Camm AJ (1991) Prognostic values of reduced heart rate variability after myocardial infarction: clinical evaluation of a new analysis method. Br Heart J 5:14–19
18. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ (1987) The Multicenter Post-infarction Research Group. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. Am J Cardiol 59:256–262
19. La Rovere MT, Bigger JT Jr, Marcus FL et al (1998) Baroreflex sensitivity and heart rate variability in prediction of total cardiac mortality after myocardial infarction. ATRAMI (Autonomic Tone and Reflexes After Myocardial Infarction) Investigators. Lancet 351:478–484
20. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (1996) Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Eur Heart J 17(3):354–381
21. Armoundas AA, Tomaselli GF, Esperer HD (2002) Pathophysiological basis and clinical application of T-wave alternans. J Am Coll Cardiol 40:207–217
22. Rosenbaum DS, Jackson LE, Smith JM et al (1994) Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 330:235–241

23. Ikeda T, Sakata T, Takami M et al (2000) Combined assessment of T-wave alternans and late potentials to predict arrhythmic events after myocardial infarction. A prospective study. J Am Coll Cardiol 35:722–730
24. Sanjiv M, Narayan SM (2006) T-wave alternans and the susceptibility to ventricular arrhythmias. J Am Coll Cardiol 47:269–281
25. Rosenbaum DS, Jackson LE, Smith JM et al (1994) Electrical alternans and vulnerability to ventricular arrhythmias. N Engl J Med 330:235–241
26. Bloomfield DM, Bigger JT, Steinman RC et al (2006) Microvolt T-wave alternans and the risk of death or sustained ventricular arrhythmias in patients with left ventricular dysfunction. J Am Coll Cardiol 47:456–463
27. Chow T, Kereiakes D, Bartone C et al (2006) Prognostic utility of microvolt T-wave alternans in risk stratification of patients with ischemic cardiomyopathy. J Am Coll Cardiol 47:1820–1827
28. Hood MA, Pogwizd SM, Peirick J, Cain ME (1992) Contribution of myocardium responsible for ventricular tachycardia to abnormalities detected by analysis of signal-averaged ECGs. Circulation 86:1888–1901
29. Gomes JA, Cain ME, Buxton AE et al (2001) Prediction of long-term outcomes by signal-averaged electrocardiography in patients with unsustained ventricular tachycardia, coronary artery disease, and left ventricular dysfunction. Circulation 104:436–441
30. Arora R, Ferrick KJ, Nakata T et al (2003) I-123 MIBG imaging and heart rate variability analysis to predict the need for an implantable cardioverter defibrillator. J Nucl Cardiol 10:121–131
31. Farrell TG, Odemuyiwa O, Bashir Y et al (1992) Prognostic value of Baroreflex sensitivity testing after acute myocardial infarction. Br Heart J 67:129–137
32. Schmidt G, Malik M, Barthel P et al (1999) Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 353:1390–1396
33. Denniss AR, Richards DA, Cody DV et al (1986) Prognostic significance of ventricular tachycardia and fibrillation induced at programmed stimulation and delayed potentials detected on the signal-averaged electrocardiograms of survivors of acute myocardial infarction. Circulation 74:731–745
34. Vaitkus PT, Kindwall KE, Marchlinski FE et al (1991) Differences in electrophysiological substrate in patients with coronary artery disease and cardiac arrest or ventricular tachycardia. Insights from endocardial mapping and signal-averaged electrocardiography. Circulation 84:672–678
35. Martinez-Rubio A, Shenasa M, Borggrefe M et al (1993) Electrophysiologic variables characterizing the induction of ventricular tachycardia versus ventricular fibrillation after myocardial infarction: relation between ventricular late potentials and coupling intervals for the induction of sustained ventricular tachyarrhythmias. J Am Coll Cardiol 21:1624–1631
36. Ommen SR, Hammill SC, Bailey KR(1995) Failure of signal-averaged electrocardiography with use of time-domain variables to predict inducible ventricular tachycardia in patients with conduction defects. Mayo Clin Proc 70:132–136
37. Steinberg JS, Prystowsky E, Freedman RA et al (1994) Use of the signal-averaged electrocardiogram for predicting inducible ventricular tachycardia in patients with unexplained syncope: relation to clinical variables in a multivariate analysis. J Am Coll Cardiol 23:99–106
38. Anonymous (1996) Signal-averaged electrocardiography. J Am Coll Cardiol 27:238–249

39. Haghjoo M, Kaini R, Fazelifar AF et al (2007) Early Risk stratification for Arrhythmic death in Patients with ST-Elevation Myocardial Infarction. Indian Pacing Electrophysiol J 7:19–25
40. Watanabe MA, Schmidt G (2004) Heart rate turbulence: a 5 year review. Heart Rhythm 1:732–738
41. Schmidt G, Malik M, Barthel P et al (1999) Heart-rate turbulence after ventricular premature beats as a predictor of mortality after acute myocardial infarction. Lancet 353:1390–1396
42. Barthel P, Schneider R, Bauer A et al (2003) Risk stratification after acute myocardial infarction by heart rate turbulence. Circulation 108:1221–1226
43. Leclerq JF, Maison-Blanche P, Cauchemez B, Coumel P (1988) Respective role of sympathetic tone and cardiac pauses in the genesis of 62 cases of ventricular fibrillation recorded during Holter monitoring. Eur Heart J 9:1276–1283
44. El-Sherif N, Caref EB, Chinushi M, Restivo M (1999) Mechanism of arrhythmogenicity of the short–long cardiac sequence that precedes ventricular tachyarrhythmias in the long QT syndrome. J Am Coll Cardiol 3:1415–1423
45. Gorenek B, Kudaiberdieva G, Birdane A et al (2004) Clinical importance of the initiation pattern of monomorphic ventricular tachycardia. Int J Cardiol 93:325–327
46. Crenshaw BS, Ward SR, Granger CB et al for the GUSTO-1 Trial Investigators (1997) Atrial fibrillation in the setting of acute myocardial infarction: The GUSTO-1 experience. J Am Coll Cardiol 30:406–413
47. Pizzetti F, Turazza FM, Franzosi MG et al (2001) Incidence and prognostic significance of atrial fibrillation in acute myocardial infarction: the GISSI-3 data. Heart 86:527–532
48. James TN (1961) Myocardial infarction and atrial arrhythmias. Circulation 24:761–776
49. Gorenek B, Bakar S, Kudaiberdieva G et al (2003) Predicting atrial fibrillation after mitral valve replacement. Ann Noninvasive Electrocardiol 8:97
50. Wong CK, White HD, Wilcox RG et al (2000) New atrial fibrillation after acute myocardial infarction independently predicts death: the GUSTO-III experience. Am Heart J 140:878–885
51. Turhan H, Yetkin E, Sahin O et al (2003) Comparison of P-wave duration and dispersion in patients aged > or =65 years with those aged < or =45 years J Electrocardiol 36:321–326
52. Dilaveris PE, Gialafos JE (2001) P-wave dispersion: a novel predictor of paroxysmal atrial fibrillation. Ann Noninvasive Electrocardiol 6:159–165
53. Gorenek B, Parspur A, Timuralp B et al 2006) Atrial Fibrillation after percutaneous coronary intervention: predictive importance of clinical, angiographic features and P-wave dispersion. Cardiology 107:203–208
54. Vikman S, Makikallio TH, Yli-Mayry S et al (2003) Heart rate variability and recurrence of atrial fibrillation after electrical cardioversion. Ann Med 35:36–42
55. Ishimoto N, Ito M, Kinoshita M (2000) Signal-averaged P-wave abnormalities and atrial size in patients with and without idiopathic paroxysmal atrial fibrillation. Am Heart J 139:684–689
56. Darbar D, Jahangir A, Hammill SC, Gersh BJ (2002) P wave signal-averaged electrocardiography to identify risk for atrial fibrillation. Pacing Clin Electrophysiol 25:1447–1453
57. Gorenek B, Kudaiberdieva G, Goktekin O et al (2003) Long-short sequence may predict immediate recurrence of atrial fibrillation after external cardioversion. Europace 5:11–16

The Routine ECG as a Marker of Sudden Cardiac Death

Luigi De Ambroggi

Introduction

The incidence of sudden cardiac death (SCD) in industrialized countries is around 1 per 1,000 inhabitants per year, thus representing a major public health problem [1]. In the majority of cases, SCD occurs in the presence of coronary artery disease, and in about 10% of cases it is associated with arrhythmogenic cardiomyopathies or with primary electrical defect in the absence of cardiac structural abnormalities.

The identification of subjects prone to malignant ventricular arrhythmias and SCD is a difficult problem still unsolved. Different indices of vulnerability to arrhythmias, based on electrocardiographic recordings or hemodynamic data, have been studied but no marker has proved sufficiently sensitive in predicting high risk. In the last decade, various methods of analysis of short or long periods of electrocardiographic recordings have been proposed in order to detect information not deducible by traditional analysis of the standard 12-lead ECG, such as body surface potential mapping, signal averaging ECG, T wave alternans, heart-rate variability, and heart-rate turbulence. Nevertheless, the routine ECG still plays an important role in identifying subjects at risk for SCD. The ECG can reveal signs of heart diseases that are potentially arrhythmogenic and generic markers of susceptibility to arrhythmias.

The importance of the 12-lead ECG in the diagnosis of ischemic heart disease and in hypertrophic and dilated cardiomyopathies is well-recognized. This presentation focuses only on the diagnostic role of the ECG in primary arrhythmogenic heart diseases. Particular attention is given to pri-

Division of Cardiology, IRCCS Policlinico San Donato, University of Milan, San Donato Milanese (MI), Italy

mary electrical disorders that are not associated with structural heart disease. For such patients, no other imaging methods can provide relevant information.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a familial heart-muscle disease characterized by atrophy of the right ventricular myocardium with fibro-fatty replacement and by electric instability of the right ventricle. These changes predispose such patients to malignant ventricular arrhythmias and SCD [2, 3].

Several ECG features have been described in ARVC, but their sensitivity and specificity are far from satisfactory. The most frequent are negative T waves in lead V2–V3, and in the most severe forms in V4, V5; right ventricular conduction defect (QRS duration ≥ 110 ms in right precordial leads, incomplete or complete right bundle branch block); epsilon wave (in the most severe forms); prolonged PR interval; and the presence of premature ventricular beats with left bundle branch block morphology. In most patients, the ventricular tachycardia shows a left bundle branch block pattern on 12-lead ECG.

The predictive value for life-threatening arrhythmias and SCD of each abnormality is still not well established.

Ventricular Pre-excitation

Ventricular pre-excitation is due to the presence of an accessory atrioventricular (AV) pathway, which can be located anywhere along the AV annuli and constitutes the anatomic substrate of AV re-entry tachycardias (Wolff-Parkinson-White syndrome). When the refractory period of the accessory AV pathway is very short, the occurrence of atrial fibrillation can precipitate ventricular fibrillation and SCD even in young healthy individuals. Therefore, the electrocardiographic recognition of ventricular pre-excitation is quite important for preventing SCD in athletes.

The typical electrocardiographic findings of ventricular pre-excitation are a short P-Q interval and a delta wave. The approximate location of the accessory pathway can be deduced by the delta wave and the QRS morphology in the different leads. Actually, the pre-excited QRS complex represents a fusion between activation of the ventricles over the normal AV conduction system and the accessory AV pathway. In some subjects, accessory pathways

may be incapable of continuous anterograde conduction, giving rise to an intermittent pre-excitation. Such patients are at low risk for sudden death caused by rapid pre-excited ventricular rates, as can occur during atrial fibrillation [4].

Primary Electrical Heart Diseases

Long QT Syndrome

The long QT syndrome (LQTS) is a familial disease characterized by an abnormally prolonged QT interval and life-threatening ventricular arrhythmias. Different genes encoding subunits of cardiac ion channels have been associated with LQTS. The most frequent subtypes are LQT1 and LQT2, which involve two genes (*KCNQ1* and *ERG*) encoding major potassium currents (I_{Ks} and I_{Kr}), and LQT3, which involves *SCN5A*, the gene encoding the sodium current.

The diagnosis of LQTS is obviously based on prolongation of the QT interval. A value of QTc > 450-460 ms in the absence of drug or electrolyte abnormality is suggestive of the diagnosis. However, it is well known that the absence of a prolonged QT does not exclude the possibility that the subject may be genetically affected [5].

Characteristic features of the ECG in the three forms, LQT1, LQT2, and LQT3, have been described [6]. LQT1 is usually associated with the presence of broad-based T waves, LQT2 is characterized by low-amplitude T waves, and LQT3 shows late-peak T waves (long ST segment).

Priori et al. reported that all mutation carriers with a QTc > 500 ms are at high risk for syncope and SCD [5]. It was recently reported that the overall risk in 200 LQTS family members increased nearly exponentially by QTc interval deciles, i.e., the longer the QTc the greater the risk for cardiac events [7].

In some individuals, macroscopic T wave alternans have been observed on routine ECG, suggesting severe electrical instability [8], but this finding is exceptional.

Catecholaminergic Polymorphic Ventricular Tachycardia

This condition usually manifests in children older than 10 years in the form of exercise- or emotion-induced palpitations or syncope. CPVT is characterized by adrenergically induced polymorphic ventricular tachycardia in the

absence of structural cardiac abnormalities. The genetic defect consists of overactivity of the ryanodine receptor gene (*RYR2*), which regulates calcium exchange [9]. Other genes, such as calsequestrin 2, may also be involved.

The electrocardiographic pattern during tachycardia typically shows a bidirectional pattern of the QRS complex that can be reproduced by exercise or isoproterenol infusion. Unfortunately, the ECG at rest is usually normal.

Brugada Syndrome

Brugada syndrome (BS) is characterized by ST-segment elevation in the right precordial leads and a high incidence of SCD in patients with a structurally normal heart. BS is estimated to be responsible for about 4% of all SCDs and at least 20% of SCDs in patients with structurally normal hearts. Since the ECG pattern can be dynamic and is often concealed, it is difficult to evaluate the true prevalence of the disease in the general population, which should be approximately 5–10 per 10,000 inhabitants [10].

In BS, three ECG patterns of ventricular repolarization in the right precordial leads are recognized, and they are often associated with a QRS having incomplete or complete right bundle branch block morphology. Only type 1 is considered definitely diagnostic of BS; this type is characterized by a coved ST-segment elevation ≥ 0.2 mV followed by a negative T wave in leads V1–V3. In types 2 and 3, the ST-segment elevation has a saddleback aspect. These types are considered suspicious but not diagnostic of BS. Moreover, all three patterns can be observed in serial ECG tracings in the same patient.

Placement of the right precordial leads in a superior position (2nd, 3rd intercostal space) can increase the sensitivity of the ECG for detecting the typical aspects of BS.

The diagnosis of BS is considered positive when a type 2 or type 3 ST-segment elevation observed in more than one right precordial lead under baseline conditions converts to a type 1 pattern following the administration of a sodium-channel blocker.

The ECG manifestations of BS, when concealed, can be unmasked in particular situations, such as febrile state or increase vagal tone or, as noted above, by administration of sodium-channel blockers (flecainide, ajmaline, procainamide).

Approximately 20% of patients with BS develop supraventricular arrhythmias, mainly atrial fibrillation.

Short QT Syndrome

The association between a familiar history of SCD and short QT interval has only recently been recognized [11]. Subsequently, short QT syndrome (SQTS) was found to be related to various genetic disorders [12–14]. Up to now, the published data have included only a limited number of patients and little is known about the clinical presentation of SQTS [15].

The ECG obviously provides the main diagnostic clue, i.e., a short QTc value (ranging from 250 to 340 ms). Although it would be reasonable to suppose that a shorter QT interval could predispose to a higher risk of ventricular arrhythmias, at multivariate analysis the QTc value was not found to be a significant risk factor for cardiac arrest [15], probably due to the small number of patients studied.

Electrocardiographic Markers of Vulnerability to Arrhythmias

Many investigations have focused on the key role played by ventricular repolarization abnormalities in the genesis of cardiac arrhythmias. Schematically, vulnerability to arrhythmias can arise from two conditions of the repolarization process: (1) a state of heterogeneity of repolarization, i.e., a greater than normal dispersion of recovery times, and (2) a dynamic (beat to beat) variation of the repolarization sequence. This last condition can seldom be detected by visual inspection of a routine ECG, because the beat to beat variations are usually very subtle (in the order of microvolts); rather, sophisticated computerized analyses of multiple beats of an ECG tracing are required (analysis of T wave alternans, RR/QT relation variations). However, repolarization heterogeneity can be detected by analyzing even a single beat, using the 12-lead ECG. In recent years, various methods to quantify this condition from the standard 12-lead ECG have been proposed.

QT Interval

Ventricular repolarization was traditionally quantified by measuring the QT interval on the 12-lead ECG and correcting for the heart rate using the Bazett formula.

General population studies have shown that a QTc > 440 ms doubles the SCD risk. In particular, the QT duration has been found to predict all-cause and cardiovascular mortality in subjects at high cardiovascular risk, such as

those with previous myocardial infarction [16] and arterial hypertension [17]. As mentioned above, in congenital LQTS, the QTc duration showed a positive significant correlation with SCD risk [7].

QT Dispersion

The measurement of 12-lead QT-interval dispersion was at one time widely used as an index of repolarization heterogeneity, mainly because of its simplicity, but this approach has several limitations. The major limitation is that this measure cannot be related to the "true" spatial heterogeneity of repolarization, since each surface lead is influenced by the electrical activity of the entire heart. Moreover, there are other well-known methodological limitations (e.g., accuracy of measurements, inter-/intra-observer variability, number of leads used) that can partly explain the controversial results reported in the literature [18]. In summary, whereas initial results of small retrospective studies seemed to prove the predictive value of QTd as a risk stratifier, more recent prospective trials have not confirmed these data [19, 20]. Actually, QTd represents only a gross estimate of repolarization abnormalities and inconsistently shows a positive correlation with arrhythmic risk.

In order to identify more reliable ECG predictive markers, principal-component analysis of ST-T waves and a set of new descriptors of the 12-lead T wave morphology have been proposed. These measure the spatial and temporal variations of T-wave morphology, the difference in the mean wavefront direction between ventricular depolarization and repolarization, and the non-dipolar component of repolarization [21–25]. The advantage of these variables is that they are not critically dependent on time-domain measurements (for instance, identification of the end of the T wave) and show good reproducibility. Nevertheless, they cannot be deduced directly by visual analysis of the ECG, but instead require appropriate computer analysis. For these reasons, they have remained substantially confined to the clinical research setting.

References

1. Priori SG, Aliot E, Blomstrom-Lundqvist C et al (2001) Task force on sudden cardiac death of the European Society of Cardiology. Eur Heart J 22:1374–1450
2. McKenna WJ, Thiene G, Nava A et al (1994) Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. Br Heart J 71:215–218
3. Corrado D, Basso C, Thiene G et al (1997) Spectrum of clinico-pathologic manifestations of arrhythmogenic right ventricular cardiomyopathy/dysplasia: a multicenter study. J Am Coll Cardiol 30:1512–1520

4. Klein GJ, Gulamhusein SS (1983) Intermittent pre-excitation in the Wolff-Parkinson-White syndrome. Am J Cardiol 52:292–296
5. Priori SG, Schwartz PJ, Napolitani C et al (2003) Risk stratification in the long QT syndrome. N Engl J Med 348:1866–1874
6. Moss AJ, Zareba W, Benhorin J et al (1995) ECG T-wave patterns in genetically distinct forms of the hereditary long QT syndrome. Circulation 92:2929–2934
7. Monnig G, Eckardt L, Wedekind H et al (2006) Electrocardiographic risk stratification in families with congenital long QT syndrome. Eur Heart J 27:2074–2080
8. Schwartz PJ, Malliani A (1975) Electrical alternation of the T wave: clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long QT syndrome. Am Heart J 89:45–50
9. Priori SG, Napolitano C, Memmi M et al (2002) Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. Circulation 106:69–74
10. Antzelevitch C, Brugada P, Borggrefe M et al (2005) Brugada syndrome: report of the second consensus conference. Circulation 111:659–670
11. Gaita F, Giustetto C, Wolpert C et al (2003) Short QT syndrome. A familial cause of sudden death. Circulation 108:965–970
12. Brugada R, Hong K, DumaineR et al (2004) Sudden death associated with short QT syndrome linked to mutation in HERG. Circulation 109:30–35
13. Bellocq C, van Ginneken AC, BezzinaCR et al (2004) Mutation in the KCNQ1 gene leading to the short QT interval syndrome. Circulation 109:2394–2397
14. Priori GS, Pandit SV, Rivolta I et al (2005) A novel form of short QT syndrome (SQT3) is caused by mutation in the KCNJ2 gene. Circ Res 96:800–807
15. Giustetto C, Di Monte F, Wolpert C et al (2006) Short QT syndrome: clinical findings and diagnostic-therapeutic implications. Eur Heart J 27:2440–2447
16. Locati E, Schwartz PJ (1987) Prognostic value of QT interval prolongation in post myocardial infarction patients. Eur Heart J 8(Suppl A):121–126
17. Schillaci G, Pirro M, Ronti T et al (2006) Prognostic impact of prolonged ventricular repolarization in hypertension. Arch Intern Med 166:909–913
18. Malik M (2000) QT dispersion: time for an obituary? Eur Heart J 21:955–957
19. Zabel M, Klingenheben T, Franz MR, Hohnloser S (1998) Assessment of QT dispersion for prediction of mortality or arrhythmic events after myocardial infarction. Results of a prospective, long-term follow-up study. Circulation 97:2543–2550
20. Brendorp B, Elming H, Jun L et al (2001) QT dispersion has no prognostic information for patients with advanced congestive heart failure and reduced left ventricular systolic function. Circulation 103:831–835
21. De Ambroggi L, Aimè E, Ceriotti C et al (1997) Mapping of ventricular repolarization potentials in patients with arrhythmogenic right ventricular dysplasia. Principal component analysis of the ST-T waves. Circulation 96:4314–4318
22. Okin PM, Devereux RB, Fabsitz RR et al (2002) Principal component analysis of the T wave and prediction of cardiovascular mortality in American Indians. The Strong Heart Study. Circulation 105:714–719
23. Zabel M, Acar B, Klingenheben T et al (2000) Analysis of T wave morphology for risk stratification after myocardial infarction. Circulation 102:1252–1257
24. Kardys I, Kors JA, van der Meer IM et al (2003) Spatial QRS-T angle predicts cardiac death in a general population. Eur Heart J 24:1357–1364
25. Zabel M, Malik M, Hnatkova K et al (2002) Analysis of T wave morphology from the 12-lead electrocardiogram for prediction of long-term prognosis in male US veterans. Circulation 105:1066–1070

International Guidelines on Acute Coronary Syndrome: Practical Application and Current News in Cardiology

Giacomo Chiarandà, Giuseppa Strano, Angela Lazzaro, Marta Chiarandà

Introduction

For the last few years, the main scientific international societies have enacted guidelines regarding the treatment of acute coronary syndrome (ACS), with the aim of promoting the best diagnostic and therapeutic methods in cardiology. These guidelines have been frequently revised according to scientific evidence of randomized clinical studies [1, 2]. Among other issues, they have addressed the use of glycoprotein IIb/IIIa inhibitors, low-molecular-weight heparin, the prescription of clopidogrel, and criteria for the selection of patients for very aggressive or less aggressive early treatment.

Risk Stratification

Risk stratification is made up of a simple score [3, 4], such as the thrombolysis in myocardial infarction (TIMI) risk score or that of the European Society of Cardiology (ESC). Determination of risk is very important because it increases the advantages of very aggressive and expensive therapy in high-risk patient groups.

The TACTICS-TIMI 18 Study demonstrated an absolute reduction of risk (death, infarction, etc.) increases with increasing calculated individual risk (actual number of patients needed to be treated with interventionist therapy or glycoprotein IIb/IIIa inhibitors to save one life increases from 100 for TRS 0-2, to 25 for TRS 3-4, to 9 for high-risk patients with TRS 5-7) [5]. In addition, in patients with ACS with ST elevation (STE), Kent et al. showed the

Cardiology Operative Unit, Muscatello Hospital, AUSL 8 Syracuse, Augusta (SR), Italy

benefits of primary percutaneous transluminal coronary angioplasty (PTCA) over thrombolysis in high-risk patients [6].

Role of Guidelines in Clinical Practice

While guidelines in clinical practice are important in therapeutic decision-making, the use of a specific set of guidelines is limited. This is due to the fact that developments in the treatment of ACS occur very rapidly, such that the time needed to establish guidelines based on the consolidation of scientific findings and then review and implement them in clinical practice may soon make them obsolete [7].

Nonetheless, the main problem in daily clinical practice is a lack of awareness of existing guidelines or the failure to adhere to them. The use of guidelines in the clinical practice of Coronary Intensive Therapy Unit (CITU) is the main objective of several medical professional societies. A few, such as the ESC, have elaborated definite standards for the realization and development of guidelines in order to increase their scientific credibility and practitioners' awareness of them.

Observational studies carried out by many researchers, such as in the form of patient registers or surveys, ultimately means an improved daily clinical reality and better large-scale clinical trials. These have provided important data concerning the management of ACS and the therapeutic implications of patient outcome, but also about adhesion or non-adhesion to guidelines.

Registers

Information obtained from patient registers demonstrates the discrepancy between current guidelines and actual clinical/therapeutic management of ACS, in that an opposite relationship between a patient's individual risk factor and the degree of therapeutic aggressiveness has been demonstrated. Moreover, reports in the literature have shown that coronarography within 48 h of the beginning of symptoms is very important for correct management of patients with cardiovascular risk in ACS and non-ST-elevation (NSTE) [2–8].

In another recent study of patients at low risk and with TRS 0-2 who were treated conservatively, outcome, as measured by survival, was 11.8% vs 12.8% with invasive therapy; while in high-risk patients with TRS 5-7 who were treated conservatively, outcome was 30.6% vs 19.5% in patients treated

with invasive therapy [5]. While the literature confirms that early and invasive treatment is most effective in low-risk patients, this is often not applied in clinical practice.

The CRUSADE study demonstrated that early coronarography in ACS NSTE patients is frequently adopted in patients at low risk (young and few comorbidities) as in those at high risk (elderly, diabetes, high TRS) [9–13]. The Italian register BLITZ-2 confirmed that a large number of ACS in patients at high risk and with high TRS (female, diabetes, elderly) were seldom treated with coronarography, primary PTCA, or glycoprotein IIb/IIIa inhibitors [14]. Moreover, it also found that, in general, cardiologists do not take into consideration risk stratification; rather, the selection of invasive vs conservative treatment depends on the availability of equipment in the department. An invasive approach was practiced in 76% of patients hospitalized in departments with a hemodynamic laboratory but only in 36% of patients hospitalized in departments without one. Conservative treatment was practiced in 64% of patients hospitalized in departments with a hemodynamic laboratory. This study found that complications occurred in 2–3% of patients at low risk who were treated with PTCA. The implications of this value are adverse, because patients with low TRS 0-3 have a mortality of only 1–2% and ischemic complications occur in just 5% of patients after 30 days.

The Italian register ROSAI-2 (1,581 patients, 76 of CITU during 2002) demonstrated that patients admitted to a hospital with a hemodynamic laboratory were more often treated with invasive therapy (41 vs 19%; $p < 0.001$) than patients admitted to a hospital without one. Coronarography was most often used in patients at low risk: young (66 vs 77 years; $p < 0.001$), male (71 vs 65%; $p < 0.01$) and somewhat less frequently in patients with elevated ST (44 vs 49%; $p < 0.001$) [15].

Thus, it is evident that the presence of a hemodynamic laboratory in a hospital leads to a high number of invasive treatments in low-risk patient, without an overall improvement in prognosis (therapeutic paradox).

Is Prognosis Dependent on Hospital Complexity or Adhesion to Guidelines?

Several studies have found that the availability of a hemodynamic laboratory does not improve ACS patient prognosis, while adhesion to guidelines does positively influence survival. The American register CRUSADE found that mortality in patients with ACS NSTE during hospitalization was 5.9% if adhesion to guidelines was < 65%, 5.0 if 65–75%, 4.6 if 75–80%, and 3.6 if > 83%.

Moreover, this register found that an adhesion to guidelines of 10% reduced mortality by 11%, while the reduction in mortality during hospitalization for acute myocardial infarction was 40% in hospitals that nearly completely adhered to current guidelines [16, 17].

Drug Therapy

Poor adhesion to guidelines is also related to the use of drug therapy. According to the French register PREVENIR, the use of statins, ASA, and beta-blockers 6 months after admission is much greater in patients treated with PTCA during recovery than in patients not treated with PTCA [18].

The CRUSADE register also found that highly qualified centers use PTCA therapy, while poorly qualified ones often use anti-aggregating therapy combined with an anticoagulant [aspirin (95 vs 82%), beta-blocker (89 vs 69%), statins (81 vs 64%), clopidogrel (60 vs 36%)] [16]. In the BLITZ-2 register, more patients treated with PTCA also received anti-aggregating/anticoagulant therapy than patients treated with conservative drug therapy (60 vs 40%).

In the GRACE study, 30% of high-risk patients (elderly, diabetes, heart failure or aortocoronary bypass) were not treated with perfusion therapy [19].

The most up-to-date Canadian register (NRMI) consists of 200,000 patients with ACS STE myocardial infarction (MI) and NSTEMI (14.3 vs 12.5%). It was found that in this population, NSTEMI patients have a 20-40% reduced probability of being treated with ASA, beta-blocker; ACE-I, or statins than STEMI patients [20].

Optimal adhesion to guidelines, with subsequent improvement of therapies and prognosis, is obtained with an increased number of guidelines as well as feedback to researchers regarding their implementation, as demonstrated by CHAMP [21].

The German registers MITRA/MIR found that continuous improvement in adhesion to guidelines was associated with improved prognosis [22].

Is It Necessary To Shape Risk Stratification into Organizational Ability?

Eighty percent of patients with ACS NSTEMI in BLITZ- 2 and 75% of patients with ACS STEMI in BLITZ-1 were found to be at high risk and require invasive therapy. This percentage, however, was not compatible with the organized system for ACS treatment established by European “hub and spoke” centers. Moreover according to the TIMI risk score, 14% of patients at low risk, 50% at middle risk, and 36% at high risk received early invasive

therapy. Identification of patients at high risk should be based on the use of prognostic information, such as heart failure, ST shifts, ECG findings, and improvement of myocardial necrosis markers. When confronted with limited means, it is very important that hub and spoke centers for ACS treatment use a qualified classification risk, one that is consistent with the local availability of resources and technology. When resources are limited, it is important to reserve resources for patients at high risk [23].

What Difficulties Arise in the Application of Guidelines?

There are many reasons for non-adhesion to guidelines:

1. Few and poorly known or unknown guidelines.
2. Limitation acceptance of criticism; hurried acceptance of recent, non-definitive, and poorly confirmed trials.
3. Personal beliefs of clinicians based on randomized studies.
4. Local treatment preferred by departmental leaders.
5. Poor logistical technological conditions, since the recommended treatments sometimes are very expensive or not available.

The application of guidelines in clinical practice is complex and difficult, and their elaboration and publication in scientific reviews is not enough to guarantee their use. Therefore, in Europe and in the USA programs have been developed to improve the acceptance and use of clinical guidelines. These programs are based on information from physicians, non-physician clinical professionals, patients, and the public and make use of several strategies (protocols; algorithms; multimedia systems, outsourcing, pathology management, case histories) to provide continuous feedback to researchers as well as those involved in clinical practice [16–20]. The application of guidelines to the treatment of patients with acute or chronic ACS could save many lives, with annual costs that are lower than those arising from the development of new therapies [21].

What Can Be Expected from the Next Guidelines?

1. Increase loaded dose of clopidogrel from 300 mg to 600–900 mg in ACS NSTEMI treatment.
2. Combine the use of clopidogrel and aspirin in ACS STEMI treatment.
3. Revised statin dose (atorvastatine 80 mg) in ACS NSTEMI treatment (see PROVIT TIME, REVERSAL and ALLIANCE results).

4. ARB use in ACS NSTEMI in patients with FE< 40%.
5. Cholesterol LDL target < 70–80 mg in management of ACS STEMI and chronic ischemic cardiopathy.
6. Use low molecular heparin in ACS STEMI.
7. Clear definition of use of metallic stent or drug-releasing stents.

References

1. Van de Werf D, Ardissimo D, Betriu A et al (2003) Management of acute myocardial infarction in patients presenting with ST segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 24:28–66
2. Bertrand ME, Simoons MI, Fox KA et al, on behalf of the Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology (2002) Management of acute coronary syndromes in patients presenting without persistent – ST segment elevation. Eur Heart J 223:1809–1840
3. Antman EM, Cohen M, Bernink PJ et al (2000) The TIMI risk score for unstable angina/non ST elevation MI: a method for prognostication and therapeutic decision making. JAMA 284:835–842
4. Oltrona L, Ottani F, Galvani M, on behalf of the Working Group on Atherosclerosis, Thrombosis, and Vascular Biology and Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO) (2004) Clinical significance of a single measurement of troponin-I and C-reactive protein at admission in 1,773 consecutive patients with acute coronary syndromes. Am Heart J 148:405–415
5. Cannon CP, Weintraub WS, Demopoulos LA et al, for the TACTICS Investigators (2001) Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med 344:1879–1887
6. Kent DM, Schimd CH, Lau J et al (2002) Is primary angioplasty for some as good as primary angioplasty for all? J Gen Intern Med 17:887–894
7. Bassand JP (2000) Improving the quality and dissemination of guidelines: the quest for the Holy Grail. Eur Heart J 21:1289–1290
8. Braunwald E, Antman EM, Beasley JW et al (2002) ACC/AHA guideline update for the management of patients with unstable angina and non ST-segment elevation myocardial infarction – 2002: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the management of patients with unstable angina). Circulation 106:1893–1900
9. Peterson ED (2005) Management of patients with NSTE ACS: latest insights from CRUSADE, a National Quality Improvement Initiative. American College of Cardiology, Scientific Sessions
10. Alexander HP, Roe MP, Chen AY et al (2005) Evolution in cardiovascular care for elderly patients with non ST-segment elevation acute coronary sondromes: results fron the CRUSADE National Quality Improvement Initiative. J Am Coll Cardiol 46:14479–14487
11. Blomkalns AL, Chen AY, Hochman JS et al () Gender disparities in the diagnosis and treratment of non ST-segment elevation acute coronary syndromes: large-scale observations fron the CRUSADE National Quality Improvement Initiative. J

Am Coll Cardiol 2005 45:832–837
12. Tricoci P, Peterson EP, Mulgund J et al () Temporal trends in the use of early cardiac catheterization in patients with non ST-segment elevation acute coronary syndromes (results from CRUSADE). Am J Cardiol 2006 98:1172–1176
13. Bhatt DL, Roe MT, Peterson ED et al, for the CRUSADE Investigators (2004) Utilization of early invasive management strategies for high-risk patients with non ST-segment elevation acute coronary syndromes: results from CRUSADE Quality Improvement Initiative. JAMA 292:2096–2104
14. Di Chiara A, Fresco C, Savonitto S et al (2006) Epidemiology of non ST elevation acute coronary syndromes in the italian cardiology network: the BLITZ-2 study. Eur Heart J 27:393–405
15. The Registro Osservazionale Angina Instabile (ROSAI-2) Investigators (2003) Treatment modalities of non-ST elevation acute coronary syndromes in the real world. Results of the prospective ROSAI-2 registry. Ital Heart J 4:782–790
16. Ohman EM, Roe MT, Smith SC et al, for the CRUSADE Investigators (2004) Care of non ST-segment elevation patients: insights fron the CRUSADE national quality improvement initiative. Am Heart J 148(Suppl):S34-S39
17. Peterson E, Parsons L, Pollack C et al (2002) Variation of AMI care quality across 1,085 US hospital and its association with hospital mortality rates. Circulation 106:II722 (Abstract)
18. Danchin N, Grenier O, Ferrieres J et al (2002) Use of secondary preventive drugs in patients with acute coronary syndromes treated medically or with coronary angioplasty: results from the nationwide French PREVENIR survey. Heart 88:20–24
19. Eagle KA, Goodman SG, Avezum A et al (2002) Practice variations and missed opportunities for reperfusion in ST-segment elevation myocardial infarction: findings from the Global Registry of Acute Coronary Events (GRACE). Lancet 359:373–377
20. Roe MT, Parson LS, Pollack CV et al, for the National Registry of Myocardial Infarction Investigators (2005) Quality of care by classification of myocardial infarction. Treatment patterns for ST-segment elevation vs non ST-segment elevation myocardial infarction. Arch Intern Med 165:1630–1636
21. Mehta RH, Montoye CK, Gallogly M et al, for the GAP Steering Committee of the American College of Cardiology (2002) Improving quality of care for acute myocardial infarction: the Guidelines Applied in Practice (GAP) initiative. JAMA 287:1269–1276
22. Gottwik M, Zahn R, Schiele R et al, for the Myocardial Infarction Registry (MIR) Study Group (2001) Differences in the treatment and outcome of patients with acute myocardial infarction admitted to hospitals with compared to without departments of cardiology: results from the pooled data of the Maximal Individual Therapy in Acute Myocardial Infarction (MITRA 1-2) Registres and Myocardial Infarction Registry (MIR). Eur Heart J 22:1794–1801
23. Topol EJ, Kereiakes DJ (2003) Regionalization of care for acute ischemic heart disease: a call for specialized centers. Circulation 107:1463–1466

Is There a Limit to PTCA in Elderly Patients?

Francesco Bovenzi, Roberto Lorenzoni, Mauro Lazzari, Andrea Boni, Cristina Gemignani

Introduction

Life expectancy in the western world is steadily increasing; as result, ischemic cardiopathy has a higher incidence in the population. Moreover, highly effective therapies have become available for treating this disease, which has led to an increase in the number of chronically ill patients. It can therefore be presumed that within the next few years the number of patients in their 80s and 90s will be much greater than today.

Medical therapy has undoubtedly not only improved the quality of life of elderly patients with ischemic cardiopathy, but it has also prolonged survival [1]. Unfortunately, however, there are situations when medical therapy alone is not sufficient to keep the symptoms under control, and in these cases interventional procedures are necessary. It has been demonstrated that coronary-artery bypass grafting (CABG) is better able than medical therapy alone to prolong the life of patients in their eighties. However, the mortality rate during surgery is very high for these patients, as is the incidence of complications following surgery, such as stroke and renal failure [2].

Angioplasty is far less invasive than CABG in the elderly and is thus the preferred procedure for revascularization in these patients [3–5]. Nonetheless, despite supportive research findings, cardiologists prefer to avoid invasive procedures in patients over the age of 80, with the result that angioplasty is performed much less in this group than in younger patients [6].

There are, undoubtedly, a number of problems to be faced when considering angioplasty in an elderly patient, but very little research has been carried out in this particular area, including a lack of specific trials. Such stud-

Division of Cardiology, Campo di Marte Hospital, Lucca, Italy

ies as well as patient registries are needed to confirm the possibility of positive results, such as those obtained when angioplasty is performed on younger patients with acute coronary syndrome.

Invasive Strategy

There is a general widespread tendency in medical practice to reduce symptoms and offer good quality of life rather than intervene to prolong the same in very elderly patients. This approach persists in spite of the fact that side effects of drugs are more common in older patients and that elderly patients frequently have co-morbidities, such as diabetes mellitus and chronic renal failure. If an elderly patient is in good general health, CABG can be performed. However, the sternotomy is more traumatic in elderly patients, and chronic obstructive bronchopathy and renal failure are frequent factors that increase the risk of further complications. In addition, the extent of cognitive deterioration following extracorporal circulation should not be underestimated [7]. Furthermore, the administration of radiographic contrast agents (in invasive strategies) often causes renal damage in elderly patients [8]. Another risk is linked to bleeding caused by an aggressive use of antithrombotic therapy [9].

Despite these drawbacks, coronary revascularization with bypass surgery or angioplasty has been shown to prolong life by 4 years compared to the administration of medical therapy alone in patients over 80 [4].

Stable Angina

The latest guidelines for the management of patients with chronic stable angina do not take age into consideration [1]. The TIME trial demonstrated that coronary revascularization with bypass surgery or angioplasty is superior to medical therapy [5].

Non-ST-Segment-Elevation Acute Coronary Syndrome

In these patients an invasive strategy proved to be advantageous compared with medical therapy even in older patients. The ROSAI-2 registry demonstrated that the mortality rate after 30 days in the elderly – that is patients over 75 – is four times higher than in younger patients. Nonetheless, a conservative rather than an invasive strategy is usually preferred in the elderly [10]. The TACTICS-TIMI 18 trial demonstrated, in fact, that an aggressive

approach was advantageous above all in the elderly [11]. Furthermore, in that study, there were fewer strokes, but an increased number of hemorrhagic events.

In many risk scores (TIMI, GRACE, PURSUIT), age is considered an important factor that leads to the decision for a therapeutic invasive strategy [12]. Unfortunately, the choice often depends on the availability of a cardiac catheterization lab, rather than on the risk score or age of the patient [10].

Acute ST-Segment-Elevation Myocardial Infarction

Age is fundamental when calculating the TIMI risk score in acute ST-segment-elevation myocardial infarction, for which primary angioplasty, according to the latest guidelines, remains the best therapeutic choice even in elderly patients [13–16]. It is known, however, that the incidence of hemorrhagic stroke increases following thrombolytic therapy, thus reducing the positive effects of treatment on outcome [17]. Primary angioplasty can be carried out safely and effectively in the elderly [18] and above all in patients with shock [19], even if shock, such as induced by heart-muscle rupture, is a frequent complication with acute ST-segment-elevation myocardial infarction [20].

Antithrombotic Therapy

Studies have shown that combined antiplatelet and anticoagulant therapy is effective in patients during percutaneous coronary intervention. It is, however, necessary to pay attention to the risk of minor and major bleeding in elderly patients. The early administration of aspirin has proved to be effective for the prevention and treatment of acute coronary syndrome [21]. Clopidogrel has been shown to reduce complications during percutaneous coronary intervention in elderly patients and should therefore be administered upstream of the procedure [22].

The intravenous use of GP IIb/IIIa inhibitors, in addition to aspirin, clopidogrel, and unfractionated heparin, is also important as part of the initial medical management of patients with acute coronary syndrome who are at high risk. However, in elderly patients, the risk of bleeding increases with these drugs; consequently, their downstream use, when complications arise, is more opportune [23].

The REPLACE-2 study showed that, in non-ST-segment-elevation acute coronary syndrome, bivalirudin with provisional GP IIb/IIIa blockade during elective percutaneous transluminal coronary angiography (PTCA)

proved superior to heparin alone with respect to protection from ischemic events and bleeding complications. The therapy was not inferior to that of heparin plus a GP IIb/IIIa inhibitor and was associated with fewer bleeding complications, above all in elderly patients (over age 75). As a result, bivalirudin with provisional GP IIb/IIIa inhibitors was validated as an anticoagulant strategy during contemporary PTCA [24, 25].

Drug-Eluting Stents

Very few indications are available regarding the use of drug-eluting stents in patients over 80, since most of the studies were carried out on patients who were younger than 75 years. However, according to a report presented at the 2004 American Heart Association Scientific Sessions, elderly patients treated with the CYPHER Sirolimus-eluting coronary stent should expect the same benefit in repeat coronary procedures as seen with younger patients. The data were taken from the e-CYPHER Registry [26], which was designed to better understand the safety and clinical benefits of the CYPHER stent in the therapy of coronary artery disease in difficult-to-treat patient groups. In this octogenarian group, 505 patients age 80 years or older had a low target-lesion revascularization rate, which was similar to the rate in the patient group under the age of 80 (0.8 vs 1.3%). It is certain, however, that double prolonged antiplatelet therapy is not auspicious in those who are at high risk of bleeding and who undergo surgery frequently.

Technical Aspects

As far as percutaneous vascular access in the elderly patient is concerned, it is preferable to use a radial rather than a femoral approach. Radial access is often associated with fewer puncture-site bleeding complications, as the radial artery is smaller and more superficial and therefore much easier to compress. Consequently, it is preferable not only in elderly patients who need to undergo percutaneous coronary intervention [27], but also in obese patients.

Conclusions

The number of over 80-year-olds suffering from ischemic cardiopathy is increasing, and hospitals must shoulder the burden of care. However, these

patients are not always managed according to current guidelines. The need for clear clinical indications as to how to manage this population clashes with the difficulties encountered when random trials are carried out and with often-incomplete registry information. The effectiveness of therapeutic choices, on the one hand, and the iatrogenic risk (risk/benefit-damage/benefit), on the other, must be evaluated and adjusted according to the protocol in use (guidelines) and to the clinical and biohumoral checks carried out. The effectiveness of invasive therapy is indeed significant in high-risk cases and in particular in those involving acute coronary syndrome. However, as the clinical features of the individual elderly patient are extremely variable and as these patients often present with co-morbidities, a personalized evaluation is fundamental to effective and safe treatment.

References

1. Fox K, Garcia MA, Ardissino D et al (2006) Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology. Eur Heart J 27(11):1341–1381
2. MacDonald P, Johnstone D, Rockwood K (2000) Coronary artery bypass surgery for elderly patients: is our practice based on evidence or faith? Can Med Ass J 162(7):1005–1006
3. Graham MM, Norris CM, Galbraith PD et al (2006) Quality of life after coronary revascularization in the elderly. Eur Heart J 27(14):1690–1698
4. Graham MM, Ghali WA, Faris PD et al (2002) Survival after coronary revascularization in the elderly. Circulation 105(20):2378–2384
5. Anonymous (2001) Trial of invasive versus medical therapy in elderly patients with chronic symptomatic coronary-artery disease (TIME). A randomised trial. Lancet 358(9286):951–957
6. Di Chiara A, Chiarella F, Savonitto S et al (2003) Epidemiology of acute myocardial infarction in the Italian CCU network: the BLITZ study. Eur Heart J 24(18):1616–1629
7. Newman MF, Kirchner JL, Phillips-Bute B et al (2001) Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 344(6):395–402
8. Tepel M, Aspelin P, Lameire N (2006) Contrast-induced nephropathy: a clinical and evidence-based approach. Circulation 113(14):1799–1806
9. Shaw RE, Anderson HV, Brindis RG et al (2002) Development of a risk adjustment mortality model using the American College of Cardiology-National Cardiovascular Data Registry (ACC-NCDR) experience: 1998-2000. J Am Coll Cardiol 39(7):1104–1112
10. De Servi S, Cavallini C, Dellavalle A et al (2004) Non-ST-elevation acute coronary syndrome in the elderly: treatment strategies and 30-day outcome. Am Heart J 147(5):830–836

11. Bach RG, Cannon CP, Weintraub WS et al (2004) The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes. Ann Intern Med 2004 141(3):186–195
12. de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R (2005) TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J 26(9):865–872
13. Morrow DA, Antman EM, Charlesworth A et al (2000) TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation. An intravenous nPA for treatment of infarcting myocardium early II trial substudy. Circulation 102(17):2031–2037
14. Silber S, Albertsson P, Aviles FF et al (2005) Guidelines for percutaneous coronary interventions. The Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Eur Heart J 26(8):804–847
15. Van de Werf F, Ardissino D, Betriu A et al (2003) Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 24(1):28–66
16. Holmes DR Jr, White HD, Pieper KS et al (1999) Effect of age on outcome with primary angioplasty versus thrombolysis. J Am Coll Cardiol 33(2):412–419
17. Thiemann DR, Coresh J, Schulman SP et al (2000) Lack of benefit for intravenous thrombolysis in patients with myocardial infarction who are older than 75 years. Circulation 101(19):2239–2246
18. Antoniucci D, Valenti R, Santoro GM et al (1999) Systematic primary angioplasty in octogenarian and older patients. Am Heart J 138(4 Pt 1):670–674
19. Migliorini A, Moschi G, Valenti R et al (2006) Routine percutaneous coronary intervention in elderly patients with cardiogenic shock complicating acute myocardial infarction. Am Heart J 152(5):903–908
20. Wang YC, Hwang JJ, Hung CS et al (2006) Outcome of primary percutaneous coronary intervention in octogenarians with acute myocardial infarction. J Formos Med Assoc 105(6):451–458
21. Antiplatelet Trialists' Collaboration (1994) Collaborative overview of randomized trials of antiplatlet therapy. I: prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Br Med J 308:81–106
22. Cannon CP, Turpie AG (2003) Unstable angina and non-ST-elevation myocardial infarction: initial antithrombotic therapy and early invasive strategy. Circulation 107(21):2640–2645
23. Iakovou I, Dangas G, Mehran R et al (2003) Comparison of effect of glycoprotein IIb/IIIa inhibitors during percutaneous coronary interventions on risk of hemorrhagic stroke in patients ≥ 75 years of age versus those < 75 years of age. Am J Cardiol 92(9):1083–1086
24. Lincoff AM, Bittl JA, Harrington RA et al (2003) Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. JAMA 289(7):853–863
25. Lincoff AM, Kleiman NS, Kereiakes DJ et al (2004) Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. JAMA 292(6):696–703

26. Urban P, Gershlick AH, Guagliumi G et al; e-Cypher Investigators (2006) Safety of coronary sirolimus-eluting stents in daily clinical practice: one-year follow-up of the e-Cypher registry. Circulation 113:1434–1441
27. Archbold RA, Robinson NM, Schilling RJ (2004) Radial artery access for coronary angiography and percutaneous coronary intervention. Brit Med J 329(7463):443–446

When Should Patients with Ischemic Mitral Regurgitation Undergo Cardiac Surgery?

Scipione Carerj, Concetta Zito, Giuseppe Dattilo, Gianluca Di Bella, Carmelo Nipote, Annalisa Lamari, Rossella Garufi, Salvatore Micciulla, Francesco Arrigo

Introduction

Ischemic mitral regurgitation (MR) is a frequent entity that is often overlooked in the setting of acute or chronic coronary disease [1, 2]. The prevalence of this disorder varies between 10 and 30% of MR cases. The papillary muscles are particularly jeopardized by acute ischemia, and the posteromedial muscle (perfused by the posterior descending coronary artery) is more vulnerable than the anterolateral one (perfused by branches of the anterior and circumflex coronary arteries). The posteromedial muscle is perfused by one vessel in 63% of patients, whereas the anterolateral muscle receives blood from the two major coronary branches in 73% of patients [3]. MR following acute myocardial infarction (AMI) develops in 15% of patients suffering from an anterior insult as compared to 40% of those with an inferior infarction. Functional MR after the ischemic insult, or induced by myocardial ischemia and transient papillary-muscle-related myocardial wall dysfunction, is therefore characterized by preserved valve integrity.

The major determinant of functional MR is systolic valve tenting, which is directly caused by the local remodeling and, particularly, by the apical and posterior papillary muscle displacement. Previous studies have shown that posterior infarctions involving the posterior papillary muscle can produce severe MR, by asymmetric tethering, whereas large anterior myocardial infarctions with involvement of the anterior papillary muscle do not lead to this condition. Moreover, in almost half of the patients with chronic ischemic MR due to anterior infarction and symmetric tethering, the anterior papillary muscle is not involved, but the left ventricle is always markedly dilated [4–6]. Indeed, MR secondary to asymmetric tethering represents the conse-

Cardiology Department, University of Messina, Messina, Italy

quence of a limited posterior infarction and causes displacement of the posterior papillary muscle and prevalent posterior tethering of both leaflets. In symmetric tethering, MR generally represents progressive global left ventricular remodeling that is determined by a previous anterior myocardial infarction and which also involves remote zones.

Evaluation of Ischemic Mitral Regurgitation

Acute MR due to rupture of the papillary muscle should be considered in a patient presenting with shock during AMI. The murmur may even be inaudible, which stresses the importance of performing echocardiographic examination as soon is possible in this setting. It should be remembered that chronic ischemic MR is a dynamic condition and its severity may vary from time to time in relation to arrhythmias, ischemia, hypertension, or exercise.

In patients with coronary disease, echocardiographic examination is useful for establishing the diagnosis and for differentiating true ischemic MR, in which the valves are normal, from organic MR. The use of quantitative methods adds valuable information. In ischemic MR, lower thresholds of regurgitation severity, using quantitative methods, have been proposed (20 mm^2 for effective regurgitant orifice and 30 ml for regurgitant volume) [1, 7]. Preliminary studies have shown that quantitation of MR during exercise is feasible, provides a good evaluation of dynamic characteristics, and has prognostic importance [7]. Limited studies using low-dose dobutamine or positron emission tomography have explored preoperative myocardial viability as a predictor of outcome [8].

Indications for Cardiac Surgery

There has been progressive improvement in our understanding of the variable mechanisms of MR in relation to different etiologies. Better knowledge of mitral-valve anatomy and pathophysiology in different MR etiologies has been paralleled by substantial advances in surgical management and postoperative results [2, 9–11]. Enormous progress has been made in the surgical procedures for MR, with a trend towards tailored reconstructive operations according to the specific valvular pathology [9–11]. Indeed, conservative techniques, such as the treatment of MR by prosthetic valve replacement alone, have emerged as the gold standard and applied in MR to restore proper valve function and to improve postoperative outcome by maintaining the valve-ventricle relationship and avoiding the well-known complications associated with prosthetics [9–11].

Data concerning the results of surgery are far more limited in ischemic MR than in organic MR. Operative mortality is higher than in organic MR and the long-term prognosis is less satisfactory, with a higher recurrence rate of MR after valve repair [12]. These less favorable results are partially due to the more severe comorbidities in ischemic MR patients.

Acute MR secondary to papillary muscle rupture has a dismal short-term prognosis and requires urgent surgical treatment, after stabilization of the patient's hemodynamic status, using an intra-aortic balloon pump and vasodilators.

In patients with chronic ischemic MR, although coronary artery disease and left ventricular dysfunction have prognostic importance, the presence and severity of MR are independently associated with increased mortality [1]. The limited data in the field of chronic ischemic MR has resulted in less evidence-based management (Table 1). While chronic severe MR should be corrected at the time of bypass surgery, there is continuing debate on the management of moderate ischemic MR. In such patients, valve repair is preferable and the decision must be made pre-operatively, since intraoperative echocardiographic assessment underestimates the severity of ischemic MR. In patients with low ejection fraction, surgery is more likely to be considered if myocardial viability is present and if comorbidity is low.

There are no data to support surgically correcting mild MR due to ischemia when the patient is asymptomatic, from the point of view of MR, and, particularly, when coronary revascularization can be carried out by percutaneous coronary intervention. However, these patients should be carefully followed, by clinical and echocardiographic examination, to detect any change in the degree and the consequences of ischemic MR.

Table 1. Indications for surgery in patients with chronic ischemic mitral regurgitation (Modified from [13])

Clinical indications	Class
Patients with severe MI, LVEF > 30% undergoing CABG	IC
Patients with moderate MI undergoing CABG if repair is feasible	IIaC
Symptomatic patients with severe MI, LVEF < 30% and option for CABG	IIaC
Patients with severe MR, LVEF >30%, no option for CABG, refractory to medical therapy, and low comorbidity	IIbC

CABG, Coronary artery bypass grafting; *MR*, mitral regurgitation; *LV*, left ventricle; *EF*, ejection fraction

References

1. Grigioni F, Enriquez-Sarano M, Zehr KJ et al (2001) Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 103:1759–1764
2. Levine RA, Scwammenthal E (2005) Ischemic mitral regurgitation on the threshold of a solution: from paradoxes to unifying concepts. Circulation 112:745–758
3. Voci P, Bilotta F, Caretta O et al (1995) Papillary muscles perfusion pattern. A hypothesis for ischemic papillary muscle dysfunction. Circulation 91:1714–1718
4. Gorman 3rd JH, Gorman RC, Plappert T et al (1998) Infarct size and location determine development of mitral regurgitation in the sheep model. J Thorac Cardiovasc Surg 115:615–622
5. Gorman 3rd JH, Jackson BM, Gorman RC et al (1997) Papillary muscle discoordination rather than increased annular area facilitates mitral regurgitation after posterior myocardial infarction. Circulation 96(Suppl):II124-II127
6. Agricola E, Oppizzi M, Maisano F et al (2004) Echocardiographic classification of chronic mitral regurgitation caused by restricted motion according to tethering pattern. Eur J Echocardiogr 5:326–334
7. Lancellotti P, Lebois F, Simon M et al (2003) Prognostic importance of exercise-induced changes in mitral regurgitation in patients with chronic ischaemic left ventricular dysfunction. Circulation 108:1713–1717
8. Pu M, Thomas JD, Gillinov MA et al (2003) Importance of ischaemic and viable myocardium for patients with chronic ischaemic mitral regurgitation and left ventricular dysfunction. Am J Cardiol 92:862–864
9. Enrique-Sarano M, Schaff HV, Frye RL (2003) Mitral regurgitation: what causes the leakage is fundamental to the outcome of valve repair. Circulation 108:253–256
10. Yacoub MH, Cohn LH (2004) Novel approaches to cardiac valve repair: from structure to function. Part I. Circulation 109:942–950
11. Al-Radi OO, Austin PC, Tu JV et al (2005) Mitral repair versus replacement for ischemic mitral regurgitation. Ann Thorac Surg 79:1260–1267
12. Lung B (2003) Management of ischaemic mitral regurgitation. Heart 89:459–464
13. The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (2007) Guidelines on the management of valvular heart disease. Eur Heart J 28:230–268

Minimally Invasive Techniques in Cardiac Surgery: An Opportunity for All Patients?

Leonardo Patanè, Alfio Cavallaro

Introduction

Cardiac operations have traditionally been carried out through the median sternotomy approach and cardiopulmonary by-pass (CPB). However, the procedures are associated with complications, such as infection, dehiscence, mediastinitis, and neurological problems, some of which have an unacceptably high mortality rate. CPB, in particular, is responsible for diverse objective problems, such as hemolysis, heparin rebound phenomena, complement activation, and deterioration of the immune system, as well as subjective factors related to the degree of surgical invasiveness, such as poor appetite, insomnia, depression, visual, memory, intellectual deficits, and loss of sexual ability.

The experience gained through less invasive surgery in other specialties has influenced clinical thinking regarding minimally invasive cardiac surgery (MICS), a term initially used to describe small-incision approaches to the heart [1]. Limited access was initially used only in coronary artery bypass graft (CABG) surgery, but today minimally invasive approaches are being applied to a number of other cardiac procedures as an alternative to conventional median sternotomy. While the advantages of MICS have been well-documented, it remains clear that a successful outcome requires a close working relationship between surgeons, anaesthetists, and perfusionists. Supporters of minimally invasive techniques in cardiac surgery claim significant improvements in patient comfort, lower procedural costs, and decreased operative morbidity [2–5]. In this article, we review the current minimally invasive techniques that are available and discuss whether they represent an opportunity for all or only a select group of patients.

Centro Cuore Morgagni, ISCAS, Pedara (CT), Italy

Background

Cardiac surgery was the last of the surgical specialties to embrace the principles of minimal invasiveness. The complexity of the procedures presents both obstacles and opportunities to make them less invasive. However, since the mid-1990s, MICS has rapidly gained popularity through pioneers in the field, such as F.J. Benetti and H. Vanermen [6, 7]. The first Port-Access single CABG surgery procedure was done at Stanford University, California, in April 1995. In 1996, Colvin, Galloway, Ribakove, and Grossi, performed the world's first minimally invasive mitral-valve repair, at the NYU School of Medicine. The heart was accessed via small chest incisions, allowing the patient to recover more quickly than would have been the case with traditional open-heart surgery [8]. Robotic-surgery clinical trials of minimally invasive surgical procedures, particularly those involving repair of the mitral valve, began that same year.

MICS Procedures: Techniques and Results

There are benefits in avoiding both median sternotomy and CPB. While in MICS procedures this is not always possible, there is no question that they reduce the degree of invasiveness. Besides having different degrees of invasiveness, MICS procedures may also introduce additional risk, make the conversion to conventional surgery more or less difficult, and have different learning curves. The possibility of additional risk and the length of the learning curve are affected by changes in instrumentation, including stabilizers, special retractors, trocar ports, and smaller-shafted instruments, the change in visualization to partial or complete video assistance, and new ways to carry out CPB.

To compare the different ways to lessen the aggression in cardiac surgery, a definitive classification of this type of surgery is needed. We distinguish five different types of MICS procedures.

Direct CABG Surgery Without CPB (Off-Pump CABG or OPCAB)

Coronary-artery bypass graft (CABG) surgery through a complete sternotomy without CPB is, for the most part, conventional and can only be considered less invasive because the CPB complication is avoided. The heart keeps beating during the procedure and stabilizers are necessary to immobilize the

distal anastomotic site. Anastomoses are performed using conventional forceps and visualization. Hence, the learning curve is fairly short. This procedure carries the risk of partial revascularization but conversion to conventional surgery is not difficult. Specific indications for this type of surgery include single-vessel disease, such as disease of the left anterior descending artery (LAD) or right coronary artery; previous or current malignancy, hemodialysis, severe pulmonary insufficiency, advanced age, poor ejection fraction, calcified aortic root and arch, redo situations, recent history of cerebral hemorrhage, and a patient who is a Jehovah's Witness [9].

Several companies have developed technologies that "stabilize" the anastomotic site in the same way as the Cardiac Thoracic System (CTS) or the Octopus stabilizer. In many centers, both surgeons and anesthesiologists have elaborated techniques to work on the beating heart without compromising the patient's hemodynamic status. It remains to be seen whether full revascularization using the same number of arterial grafts and results as good as those obtained with CPB can be achieved.

As yet, there is no clear evidence of significant benefits for those patients undergoing OPCAB, except for in high-risk situations (for example, elderly patients, or patients with low ejection fraction, renal failure, etc.) [10].

Limited or Modified Approaches with CPB

An increasing array of surgical corrections have involved a limited or modified alternative approach, thus lessening the damage to the thoracic cavity. These include: hemisternotomy, partial T, J or L sternotomy through the 3rd or 4th intercostal space, reversed-T sternotomy, transverse sternotomy, parasternotomy with excision of two or more costal cartilages (as in the Dresden technique), and various types of anterolateral minithoracotomies [11, 12]. The surgical techniques are fairly conventional so the learning curve is short, but conversion to conventional surgery is more difficult. CPB can be done either in the conventional manner or with the EndoCPB System. Visualization is conventional, but special retractors are required.

Specific indications for such procedures include redo situations, previous sternitis and mediastinitis, severe pulmonary insufficiency, and disorders of the ventilatory muscles. These approaches reduce the injury to the thoracic cavity and the amount of pain. The thoracic cavity is more stable after hemisternotomy or J sternotomy, which will most certainly benefit some patients. Comfort and cosmesis may also be improved, and some patients will have a shorter rehabilitation period.

Minimally Invasive Direct CABG Surgery without CPB (MIDCAB)

This approach consists of the anastomosis of a pedicle of an arterial graft, most commonly the internal mammary artery (IMA), to a coronary branch (usually the LAD) on the beating heart via a parasternal or left anterior small thoracotomy (LAST operation). The value, even in the extended 18- to 20-year follow-up, of a bypass from an IMA to the LAD is well-documented in the literature, and in the off-pump and mini-thoracotomy setting the procedure is extremely cost-effective. Thus, it is a valid alternative for endovascular procedures. In two- or three-vessel disease, it may be a part of a well-designed hybrid therapy protocol. It is most definitely minimally invasive, and epidural anesthesia can provide additional comfort to the patient. However, the learning curve is difficult, and conversion to conventional surgery can be cumbersome. Special retractors and stabilizers are required, although visualization may be conventional or video-assisted, particularly in the take-down of the IMA to obtain a full-length view of the graft [13].

Keyhole Approaches with Endo-CPB System (True Port-Access or Heartport)

For some surgical procedures, an endoscopic or "keyhole" approach, also referred to as true Port-Access or Heartport surgery, or video-assisted surgery, may be performed [7, 8, 14–16]. In this approach, surgery is through one to four small (5–10 mm) incisions or "ports" and a 5–7 cm "working port" in the chest wall between the ribs. An endoscope or thoracoscope and surgical instruments are placed through the incisions. Since the large vessels are not easily accessible, new methods to install the CPB and to arrest the heart are necessary to allow surgery in a gold-standard setting. A CPB system that does not require a large access and that uses "endovascular" methods is called endo-CPB. The Seldinger technique is used to introduce Heartport's arterial and venous cannula in the femoral artery and femoral and internal jugular veins, respectively. Since endo-CPB is not appropriate for all patients, it is important to take into account the preoperative thresholds indicating the presence of good peripheral arteries. During surgery, it is essential to know exactly when to retreat and/or to convert in order to exclude additional risk. Transesophageal echocardiography (TEE) will clearly show the right lumen, the passage through the right vessel, and the exact positioning of, for example, the endo-aortic balloon. Safe cardiac arrest is a challenge in Port-Access surgery. The technology of the Heartport Endo-aortic clamp allows endo-aortic balloon inflation to occlude the lumen and the delivery of antegrade cardioplegia, under TEE positioning and monitoring.

In some centers, a large percentage of Port-Access mitral or tricuspid valve procedures have been carried out on the beating heart. This is an advanced technique that uses Endo-CPB and better preserves heart function than when the heart is stopped during surgery.

The types of MICSs that are possible using the innovative Port-Access or "keyhole" approach include: valve surgery, atrial-septal defects (ASD) and myxoma surgery, biventricular pacemaker lead placement on the surface of the left ventricle, and minimally invasive surgery for atrial fibrillation [8, 14–16]. The ability to perform an endoscopic anastomosis, if not robotically assisted, still remains the rate-limiting step for totally endoscopic CABG surgery [17].

Robotic-Assisted Cardiac Surgery

Robotic-assisted cardiac surgery may change the way certain heart surgeries, such as valve surgery and single-vessel or multi-vessel CABG surgery, are performed in the future [17]. In this type of MICS, the cardiac surgeon uses a computer to control surgical instruments on thin robotic arms. The technology allows surgeons to perform certain types of complex heart surgeries with smaller incisions and precise motion control. The surgeon's hands control the movement and placement of the endoscopic instruments. The robotic "arm and wrist" movements mimic those of the surgeon. The surgeon is always in control during the surgery, and there is no chance that the robotic arms will move on their own. In several centers, robotic-assisted surgical technique is used in select patients during CABG surgery (with single-vessel disease), biventricular pacemaker lead placement on the surface of the left ventricle, and catheter ablation for the treatment of paroxysmal atrial fibrillation. Robotic technology is a prerequisite in totally endoscopic CABG surgery. During the implementation phase, several surgeon-related technical difficulties may be encountered. Technical difficulties associated with this type of surgery translate into markedly increased operative time, moderately prolonged postoperative ventilation time, and slightly increased hospital stay. Short-term survival and freedom from angina, however, do not seem to be compromised.

Benefits of Minimally Invasive Surgery and Patient Selection

Several studies have demonstrated that the aforementioned techniques offer several patient benefits [2–5, 18]. The documented advantages of MICS

include a smaller incision and a smaller scar. Incisions are 3–4 inches instead of 6–8 inches, as required for traditional surgery. Other possible benefits of MICS, compared to open-chest surgery, are listed in Table 1.

According to Vaca et al. patients experience less pain and return to normal activities faster [19].

Hospital stays are shortened to 4–5 days or less, compared to 8–12 days for conventional heart surgery.

The recovery period is reduced to 2–4 weeks instead of 8–12 weeks. Other patient benefits in CABG surgery include the decreased incidence of atrial fibrillation (10–15% vs 35–50% post-conventional), therefore lowering morbidity. Although, on balance, the techniques require larger amounts of disposable items and have higher revenue costs, intensive care and hospital stay are shorter. This, along with more rapid rehabilitation, results in lower healthcare costs.

MICS is appropriate and effective for the treatment of many congenital or acquired cardiac conditions, including such complex and demanding clinical cases as mitral and tricuspid valvulopathies, single-vessel CABG surgery, myxomas, epicardial lead placement in cardiac resynchronization therapy, paroxysmal atrial fibrillation, and ASDs. Also, harvesting of the saphenous vein and radial artery may be performed using small-incision approaches.

At this early stage, not all patients are candidates for a minimally invasive approach [9, 16], as there are some relative contraindications. These include a previous right or left thoracotomy with an adherent lung, severe mitral valve annulus calcification, a dilated ascending aorta greater than 4.5 cm in

Table 1. Minimally invasive cardiac surgery: benefits

• Less damage to tissue and muscle
• Reduced risk of infection
• Less bleeding
• Elimination, in some patients, of the need for cardiopulmonary bypass
• Lower risk of complications
• Less pain and trauma
• Shorter hospital stay, quicker return home
• Quicker recovery
• Improved quality of life and heart function
• Easier mobility and walking
• Faster return to “normal life” (often in 2 weeks)
• Minimal assistance, once home
• Earlier, more consistent cardiac rehabilitation program

diameter, and severe pulmonary hypertension. Thus, each patient must be individually assessed prior to surgery.

Discussion

Unquestionably, MICS benefits both CABG and heart valve surgeries [2–5]. In all cases, the emerging data suggest that these less-invasive operative techniques provide measurable clinical and physiologic benefits.

CPB and the access represent the two sources of invasiveness. Whenever a revascularization is needed, it should be as least invasive as possible, and a complete armamentarium suited to the procedure must be at hand. Nonetheless, CPB must be avoided in several specific cases, such as renal, recent cerebrovascular accident, calcified aorta, malignant tumor, the patient being a Jehovah's Witness, and in elderly people in whom the number of targets is low.

Important advantages (such as less pain, less systemic stress response, and recovery in approximately half the time, based on the Duke activity index score) have been seen in patients who have undergone OPCAB and MIDCAB compared to those who had conventional surgery for multi-vessel CABG. Since these techniques avoid CPB, the risk of stroke and other bypass-related complications is diminished. At NYU School of Medicine, approximately 25–30% of patients requiring CABG are currently treated with a less-invasive operative approach. A study of high-risk patients with atheromatous disease of the aortic arch requiring CABG surgery demonstrated that patients who received OPCABG or MIDCABG had half the risk of stroke and death compared to those receiving conventional surgery.

MIDCAB is an excellent surgical procedure when LIMA to LAD is the only aspect to be considered, although the learning curve is probably the most important factor. In complete revascularization through a small access on- or off-pump, such as important lesions of the LAD and its tributaries, the alternative of leaving the rest to the cardiologists in a hybrid-therapy strategy, should also be considered. Whenever complete and/or arterial revascularization is "mandatory" and the patient would be at risk with either technique, opting for the conventional approach is the best option.

Small-access is the best choice for those patients in whom fast rehabilitation and/or cosmesis are important to return to work and/or sport, and the number of target is not impressive.

These strategies, which allow risk stratification based on anatomy and risk factors such as severe vascular disease or renal failure, have led to improved overall results and a reduced risk.

The impact of minimally invasive approaches on valvular surgery has been even more striking than those of coronary bypass surgery. Cohn et al. [11] recently reported results of 100 patients who underwent minimally invasive mitral valve repair or replacement using a right parasternal incision. The operation was successfully completed in all patients. Sixty percent of the patients did not require blood transfusion and the mean hospital stay was only 5 days. The authors observed that post-operative pain and return to "normality" were improved compared to sternotomy patients.

Cosgrove et al. [12] reported results from 115 patients who underwent isolated mitral or aortic valve surgery using a parasternal incision. The operative risk in this series was 1%. Seventy-seven percent of the patients did not receive blood and the mean hospital stay was 5 days. The authors concluded that the less invasive approach reduced surgical trauma, the need for blood transfusion, and length of hospital stay.

Although less invasive, MICS is still major heart surgery, with the potential for risks and complications, including stroke and death. A patient's particular anatomy, clinical circumstance, or tendency for excessive bleeding may cause the surgeon to switch to a conventional sternotomy approach to complete the operation safely and effectively.

Risks and complications of any type of heart surgery include damage to major blood vessels or adjacent structures, chest wound pain or infection, bleeding from the wound or internal organs, irregular heartbeat, stroke, or death. Risks associated with MICS include damage to major blood vessels, especially aortic dissection, and potential damage to the ribs.

Results of MICS have been extremely good, with a very low operative risk, less bleeding, less risk of infection, and shorter overall recovery. Follow-up studies have shown that valve repair durability is equivalent to that achieved with conventional surgery. Thus, the short-term risks are reduced with equivalent to long-term results.

The minimally invasive approach has become the standard of care for most patients requiring isolated valve repair or replacement, with the Port-Access approach being used for virtually all mitral-valve surgery.

In summary, the large and extremely favorable experience with MICS suggests that this form of less-traumatic surgery is now preferred for most patients requiring aortic- or mitral-valve surgery, for ASD repair, and for atrial myxoma excision. Patients requiring CABG surgery are risk-stratified for either conventional surgery, MIDCAB, or OPCAB, which has lowered the overall risk significantly. MICS patients require less blood, have fewer infections, and recover more quickly. Emerging new technologies are having a dramatic impact on patient care by lowering the overall morbidity, pain, and

suffering associated with heart surgery.

Costs can be phenomenal as instruments are disposable, with new instruments being required for each operation. Thus, the initial cost of setting up a theatre with the correct equipment must also be considered.

Long-term costs will be lower due to reduced hospitalization and improved recovery times.

Conclusions

Since 1996, the use of MICS has expanded dramatically, and this surgical strategy has become an accepted and established alternative to conventional surgery. Many groups are developing minimally invasive techniques for all types of heart surgery. In each of these procedures, every effort is made to limit the trauma to the patient. The experience to date has demonstrated that MICS is a safe and broadly applicable technique for performing a wide range of complex cardiac procedures with highly reproducible results and several benefits. CABGs and mitral-valve replacement are examples of the successful surgeries performed using minimally invasive techniques. However, risks and complications remain. Currently, not all patients are suitable for MICS. Technical, anatomical, and organizational aspects associated with the surgical learning curve and the high initial costs influence the indications for these approaches. Heartport's technology has the potential to change cardiac surgery in much the same way that laparoscopic techniques have revolutionized gall-bladder surgery. It is likely that over the next few years the term "minimally invasive" will be replaced with "minimally invasive and innovative" to encompass all forms of innovative cardiac surgery that carry less invasion of tissues, thus reflecting the true meaning of MICS.

References

1. Mack MJ (2006) Minimally invasive cardiac surgery. Surg Endosc Suppl 2:S488-492
2. King RC, Reece TB, Hurst JL et al (1997) Minimally invasive coronary artery bypass grafting decreases hospital stay and cost. Ann Surg Jun 225:805–811
3. Del Rizzo DF, Boyd WD, Novick RJ et al (1998) Safety and cost-effectiveness of MIDCABG in high-risk CABG patients. Ann Thorac Surg 66:1002–1007
4. Magovern JA, Benckart DH, Landreneau RJ et al (1998) Morbidity, cost, and six-month outcome of minimally invasive direct coronary artery bypass grafting. Ann Thorac Surg 66:1224–1229
5. Arom KV, Emery RW, Flavin TF et al (1999) Cost-effectiveness of minimally invasive coronary artery bypass surgery. Ann Thorac Surg 68:1562–1566
6. Benetti FJ, Ballester C, Sani G et al (1995) Video assisted coronary bypass surgery. J Card Surg 10:620–625

7. Vanermen H, Wellens F, De Geest R et al (1999) Video-assisted Port-Access mitral valve surgery: from debut to routine surgery. Will Trocar-Port-Access cardiac surgery ultimately lead to robotic cardiac surgery. Semin Thorac Cardiovasc Surg 11:223–234
8. Schwartz DS, Ribakove GH, Grossi EA et al (1997) Minimally invasive mitral valve replacement Port-Access technique, feasibility and miocardial functional preservation. J Thorac Cardiovasc Surg 113:1022–1031
9. Diegeler A, Matin M, Falk V et al (1999) Indication and patient selection in minimally invasive and off-pump coronary artery bypass grafting. Eur J Cardiothorac Surg Suppl 1:S79-S82
10. Acuff TE, Landreneau RJ, Griffith BP, Mack MJ (1996) Minimally invasive coronary artery bypass grafting. Ann Thorac Surg 61:135–137
11. Cohn LH, Adams DH, Couper GS et al (1997) Minimally invasive cardiac valve surgery improves patient satisfaction while reducing costs of cardiac valve replacement and repair. Ann Surg 226:421–426
12. Cosgrove DM 3rd, Sabik JF, Navia JL (1998) Minimally invasive valve operations. Ann Thorac Surg 65:1535–1539
13. Mack MJ, Acuff T, Osborne J (1998) Minimally invasive direct coronary artery bypass: technical considerations and instrumentation. J Card Surg 13:290–296
14. Chitwood R Jr (2000) Video-assisted mitral valve surgery using the Chitwood clamp. Oper Techn Thorac Cardiovasc Surg 5:176–189
15. Fann JI, Pompili MF, Stevens JH et al (1997) Port-Access cardiac operations with cardioplegic arrest. Ann Thorac Surg Jun 63(6 Suppl):S35-S39
16. Glower DD, Landolfo KP, Clements F et al (1998) Mitral valve operation via Port Access versus median sternotomy. Eur J Cardiothorac Surg 14:S143-S147
17. Bonatti J, Schachner T, Bonaros N et al (2006) Technical challenges in totally endoscopic robotic coronary artery bypass grafting. J Thorac Cardiovasc Surg 131:146–153
18. Schroeyers P, Wellens F, De Geest R et al (2001) Minimally invasive video-assisted mitral valve repair: short and mid-term results. J Heart Valve Dis 10:579–583
19. Vaca KJ, Daake C, Lambrecht DS (1997) Nursing care patients undergoing thoracoscopic minimally invasive bypass grafting. Am J Crit Care 6:281–286
20. Chitwood WR Jr, Nifong LW (2003) Minimally invasive and robotic valve surgery. In: Cohn LH, Edmunds LH Jr (eds) Cardiac surgery in the adult. McGraw-Hill, New York, pp 1075–1092

Cardiovascular Risk Management: An Overview

Andrea Boni, Roberto Lorenzoni, Mauro Lazzari, Cristina Gemignani, Francesco Bovenzi

Introduction

Cardiovascular disease (CVD) is a leading cause of mortality and is responsible for one-third of all global deaths annually. This translates into the deaths of 17 million people each year [1, 2]. Despite research-based gains in the treatment of CVDs, they remain the leading killer in the USA and in most developed areas of the world. Coronary heart disease (CHD) accounts for the majority of CVD deaths, disproportionately afflicts racial and ethnic minorities, and is a prime target for prevention. Hypertension is the most prevalent CVD, affecting at least 600 million people, and is an important contributor to cardiovascular mortality and morbidity [3]. Nearly 85% of the global mortality and disease burden from CVD is borne by low- and middle-income countries.

In India, for example, approximately 53% of CVD deaths are in people younger than 70 years of age; in China, the corresponding figure is 35%. The majority of the estimated 32 million heart attacks and strokes that occur every year are caused by one or more cardiovascular risk factors – hypertension, diabetes, smoking, high levels of blood lipids, and physical inactivity – and most of these CVD events are preventable if meaningful action is taken against these risk factors.

The Challenges of Effective Cardiovascular Risk Management

The prevention of CVDs too frequently focuses on single risk factors, rather than on comprehensive cardiovascular risk. For many years, individual car-

Division of Cardiology, Campo di Marte Hospital, Lucca, Italy

diovascular risk factors have been dealt with in isolation, often by specialists with an interest in one particular risk factor, for example hypertension or hypercholesterolemia. There has recently been a move to emphasize the importance of reducing global cardiovascular risk. This requires clinicians to address any one of a number of different risk factors. The interplay between these various factors is important in our understanding of development of CVD and, similarly, the synergistic effects of targeting different risk factors is important in risk reduction.

Evidence based, cost-effective interventions are available for addressing comprehensive cardiovascular risk, and the challenge now is to use what we know, particularly in low- and middle-income countries. Advances in cardiovascular epidemiology in developed countries provide the knowledge base necessary to understand the underlying biological processes that account for these emerging epidemics [4, 5]. This calls for resource-sensitive, innovative strategies.

Barriers to Comprehensive Cardiovascular Risk Assessment and Management

Health Policy

The overriding barrier to CVD risk-management programs in low- and middle-income countries is that there are no formal policies that target CVD as a major health issue. In 2001, a survey of 167 countries in the six WHO regions found that 57% of the countries lacked a non-communicable-disease policy, and 65% had no CVD plan [6]. Several factors explain the absence of formal policies in such settings: a paucity of epidemiological data documenting the scope of CVD; a focus on communicable diseases; a lack of knowledge about the cost-effectiveness of CVD prevention; and limited human and physical resources. The per capita health expenditures vary from US$ 4,055 in the USA, to US$ 34 in China and US$ 1 in Liberia.

Health-care Systems

The lack of a health policy for CVDs can have many downstream effects, most notably the inadequate allocation of resources to local health systems for CVD management. Other factors that limit CVD risk management at the system level include: under-equipped health facilities; a lack of continuity between primary health-care and the secondary- and tertiary-care sectors

[7]; poorly developed information systems; a lack of awareness of the potential health benefits and cost savings of CVD programs; and the influence of commercial interests on resource allocation.

This situation needs to be rectified, such that primary health facilities, which are most accessible to patients, are equipped to provide basic CVD care. This sector has been developed for treating acute, time-limited illnesses and thus does not have information systems to support the patient follow-up necessary for CVD risk management. Finally, the commercial interests that shape the purchase of pharmaceuticals and devices have a strong impact on the current provision of CVD care in under-resourced settings.

Hypertension: "A Gateway to Risk Factor Management"

Several studies have demonstrated that conventional management of hypertension leaves patients at an unacceptably high risk of cardiovascular and other complications, such as myocardial infarctions, strokes, cardiac failure, renal failure and death [7, 8]. This appears to be due mainly to suboptimal blood-pressure control and failure to address other coexistent risk factors that contribute to total cardiovascular risk [9]. People with high blood pressure frequently have other risk factors for CVD. These include the common occurrences of dyslipidemia, impaired glucose tolerance, and target organ damage. Thus, the identification of hypertension should prompt the physician to search for other risk factors and consider them as part of a comprehensive strategy to reduce a patient's cardiovascular risk. This concept is important because the simple measurement of blood pressure provides what has been described as "a gateway to risk factor management," i.e., a simple means of identifying people at risk for CVD prior to the onset of disease-associated symptomatology and events. These findings demand a paradigm shift from "treatment of hypertension" to "management of comprehensive cardiovascular risk." In addition, the cost-effectiveness of treating hypertension is also determined by the overall cardiovascular risk and not by blood pressure alone [10, 11].

The Way Forward

Guideline developers may continue to focus their guidelines around traditional "gateways" of CVD risk management, notably, the detection of high blood pressure, dyslipidemia, or diabetes. Nevertheless, whatever the gateway, the objective of treatment must be the same, to optimize CVD risk

reduction. The force of evidence from clinical trials has led to an evolution in thinking with regard to CVD prevention. It is rare to find an individual patient who has only a single risk factor for CVD; instead, the vast majority has multiple risk factors that conspire to increase their risk. The only effective strategy to optimize CVD risk reduction is to formally assess risk in each patient by using one of the many CVD risk calculators currently available. If risk is elevated, then optimal therapy must involve the use of multiple strategies aimed at reducing risk rather than focusing on individual risk factors. In the example of hypertension, an individual's risk is not determined solely by his or her blood pressure. Or, to benefit from a statin, all a hypertensive patient needs is an elevated risk, not necessarily an elevated cholesterol value. This is an important shift in thinking, but a shift that is consistent with long-established evidence from epidemiologic studies. Although the concept of applying evidence-based medicine to clinical practice seems simple, there are many issues to consider. Several studies, for example, have demonstrated low rates of compliance with evidence-based treatment guidelines for managing hypertension [12, 13]. Furthermore, conventional management of hypertension leaves patients at an unacceptably high risk of cardiovascular events, due to suboptimal blood pressure control and failure to address coexistent cardiovascular risk factors [8, 10]. In many settings, the management of hypertension is suboptimal, mainly due to barriers related to patients, health-care providers, and the health system [13]. Furthermore, the management of cardiovascular risk, compared to treating elevated blood pressure per se, demands more skills and better-maintained and better-equipped facilities. To meet these demands, flexible tools need to be developed that can be applied in many situations.

The Objective of CVD Prevention in Clinical Practice

The specific objective of CVD prevention for individuals at high risk is to reduce the risk of CVD and its complications, including the need for percutaneous or surgical revascularization procedures in any arterial territory, and to improve quality of life and life expectancy. The broader objective of CVD prevention is to reduce the risk of a non-fatal or fatal atherosclerotic cardiovascular event and to improve both quality and length of life. These broader goals can be achieved through lifestyle and risk-factor interventions and appropriate drug therapies to lower blood pressure, modify lipids, and reduce glycemia. For the high-risk population, a number of drugs from different classes will reduce the risk of recurrent disease and increase life expectancy. These drugs include: anti-thrombotics as well as blood-pressure-, lipid-,

and glucose-lowering therapies. CVD prevention should be provided in clinical practice and with equal access to: (1) people with any form of established atherosclerotic CVD; (2) asymptomatic people without established CVD but who have a combination of risk factors that put them at high total risk (estimated multifactorial CVD risk ≥ 20% over 10 years) of developing atherosclerotic CVD for the first time; (3) people with diabetes mellitus (type 1 or 2). Individuals in these three groups require professional lifestyle and multifactorial risk-factor management of defined lifestyle and risk factor targets. In addition, the elevation of a single risk factor is also an indication for CVD prevention because affected individuals are also at high cardiovascular risk, regardless of the presence of other risk factors. These single risk factors are: (1) elevated blood pressure ≥ 160 mmHg systolic or ≥ 100 mmHg diastolic, or lesser degrees of blood pressure elevation with target-organ damage; (2) elevated total cholesterol to high density lipoprotein (HDL) cholesterol ratio ≥ 6.0; (3) familial dyslipidemia, such as familial hypercholesterolemia or familial combined hyperlipidemia. Finally, anyone with a family history of premature CVD should be assessed for their cardiovascular risk and then managed appropriately.

Identifying Those at Risk

All adults from 40 years onwards who have no history of CVD or diabetes and who are not already on treatment for blood pressure or lipids should be considered for an opportunistic comprehensive CVD risk assessment in primary care. Younger adults (< 40 years) with a family history of premature atherosclerotic disease should also have their cardiovascular risk factors measured. Risk assessment should include ethnicity, smoking habit history, family history of CVD, and measurements of weight, waist circumference, blood pressure, non-fasting lipids (total cholesterol and HDL cholesterol), and non-fasting glucose. The new Joint British Societies' CVD risk prediction chart should be used to estimate total risk of developing CVD (CHD and stroke) over 10 years based on five risk factors: age, sex, smoking habit, systolic blood pressure, and the ratio of total cholesterol to HDL cholesterol. This is the estimated probability (percentage chance) of developing CVD over the next 10 years. Total CVD risk should be estimated for the person's current age group: < 50 years, 50–59 years, or 60 years. A total CVD risk of 20% over 10 years is defined as "high risk" and requires professional lifestyle intervention and, where appropriate, drug therapies to achieve the lifestyle and risk-factor targets. Numerous methods [14] to calculate a patient's absolute cardiovascular risk have been described (Table 1).

Table 1. Tools for determining cardiovascular prognosis in individual patients

Risk prediction model	Population derived in	Variables incorporated	Validated in other data sets?
Framingham (USA)	5,300 men and women age 30–74 (original and offspring Framingham studies)	Age; sex; systolic and diastolic blood pressure; total, LDL, and HDL cholesterol; diabetes mellitus; smoking	Yes
Cardiovascular disease life expectancy model (USA and Canada)	3,700 men and women age 35–74 (lipid research clinics follow-up cohort)	Age; sex; mean blood pressure; total and HDL cholesterol; diabetes mellitus; smoking; cardiovascular disease	Yes
Dundee coronary risk disk (UK)	5,203 men age 40–59 (UK heart disease prevention project)	Total cholesterol; systolic blood pressure; smoking	Not in women
PROCAM risk function (Germany)	4,400 men and women age 40–65 (workplace study)	Age; systolic blood pressure; total and HDL cholesterol; diabetes mellitus; smoking; family history; anginal symptoms	Not in women
British regional heart study risk function (UK)	735 men age 40–59 (from general 7practitioner practices)	Mean blood pressure; total cholesterol; diabetes mellitus; smoking; family history; anginal symptoms	No

LDL, Low density lipoprotein; *HDL*, high density lipoprotein

For people with established atherosclerotic CVD, hypertension with target-organ damage, familial dyslipidemias such as familial hypercholesterolemia, or diabetes, formal risk estimation is not necessary since all of them are at high total CVD risk.

The Targets in CVD Prevention

Lifestyle

Lifestyle intervention, i.e., to discontinue smoking, make healthier food choices, increase aerobic physical activity, and achieve optimal weight and weight distribution, is central to CVD prevention in all high-risk individuals. Involvement of the entire family may be helpful, together with community resources. Lifestyle measures consist of:

- Maintaining normal weight for adults (body mass index 20–25 kg/m^2)
- Reducing salt intake to < 100 mmol/day (< 6 g NaCl or < 2.4 g Na^+/day)
- Limiting alcohol consumption to 3 units/day for men and 2 units/day for women
- Engaging in regular aerobic physical exercise (brisk walking rather than weightlifting) for 30 min per day, ideally on most of days of the week but at least on 3 days of the week
- Consuming at least five portions/day of fresh fruit and vegetables
- Reducing the intake of total and saturated fat

Blood Pressure

The optimal blood pressure target is < 140 mmHg systolic and < 85mm Hg diastolic. In selected higher-risk people (established atherosclerotic disease, diabetes, and chronic renal failure) a lower blood-pressure target of < 130 mmHg and < 80mm Hg may be more appropriate. These targets can usually be achieved with antihypertensive drugs prescribed at doses (and in combinations) that were shown in clinical trials to be efficacious and safe. An "audit standard" of < 150 mmHg systolic and < 90 mmHg diastolic is also recommended. For higher-risk people with atherosclerotic disease, diabetes, or renal failure, the recommended audit standard is < 140 mmHg systolic and < 80 mmHg diastolic. However, these audit standards are considered to be the *minimum* standard of care for this population. Wherever possible, the optimal treatment targets should be achieved.

Blood Lipids and Dyslipidemia

The optimal total cholesterol target is < 4.0 mmol/l and low density lipoprotein (LDL) cholesterol < 2.0 mmol/l, or a 25% reduction in total cholesterol and a 30% reduction in LDL cholesterol, whatever results in the lowest absolute value. HDL cholesterol and triglyceride values should also be considered in overall lipid management. Total and LDL cholesterol targets are usually achieved with lipid-lowering drugs prescribed at doses shown to be efficacious and safe in trials. An "audit standard" for total cholesterol of < 5.0 mmol/l (or a 25% reduction in total cholesterol) *and* for LDL cholesterol of < 3.0 mmol/l (or a 30% reduction in LDL cholesterol), whatever results in the lowest absolute level, is also recommended. This audit standard is considered to be the minimum standard of care for all individuals at high risk. Whenever possible, the optimal treatment targets should be achieved.

Blood Glucose and Diabetes

In all those at high risk, optimal fasting glucose is 6.0 mmol/l. If the non-fasting glucose is < 6.1 mmol/l it does not need to be repeated. If it is 6.1 mmol/l then fasting glucose should be measured for evidence of impaired glucose regulation or new-onset diabetes. If this measurement is normal (6.0 mmol/l) there is no need to repeat it. If it is abnormal (6.1–6.9 mmol/l) but not indicative of diabetes (7.0 mmol/l), either it should be repeated on a separate occasion or an oral glucose tolerance test (OGTT) should be administered. If the second fasting glucose is still abnormal (6.1–6.9 mmol/l) the patient has impaired fasting glycemia (IFG). If fasting glucose values are 7.0 mmol/l on separate occasions, the diagnosis of diabetes is made regardless of symptoms. In the presence of diabetic symptoms (thirst, polyuria, and weight loss) a fasting glucose 7 mmol/l on one occasion is considered diagnostic of diabetes. An OGTT is the only way to diagnose impaired glucose tolerance (IGT) (2-h glucose 7.8 mmol/l but < 11.1 mmol/l) and is the conventional standard for the diagnosis of diabetes mellitus (2-h glucose 11.1 mmol/l).

For individuals with impaired glucose regulation (either IFG or IGT) the aim is to prevent progression to diabetes and CVD through lifestyle intervention and, where appropriate, drug therapy. These patients should be followed up annually to reassess glucose regulation and all other cardiovascular risk factors. With a diagnosis of type 1 and 2 diabetes mellitus, rigorous control of glycemia is recommended with treatment.

Conclusions

The enormous treatment opportunities available must be balanced against the magnitude of the health challenges. Although heart attacks and strokes are leading causes of death and disability, they represent only the tip of an iceberg. Indeed, all societies that adopt an industrialized lifestyle have seen the emergence of CVD risk factors on a mass scale. These modifiable risk factors (i.e., smoking, unhealthy diet, and lack of physical activity) are expressed as hypertension, diabetes, obesity, and high blood-lipid levels. Together they contribute to the total cardiovascular risk and are the root causes of the global CVD epidemic. Deaths mainly due to CVD and lung cancer are largely preventable. Although the relative importance of CVD risk factors may vary in different populations, they account for 75% of the CVD epidemic worldwide. Not only do we understand the causal pathways between these risk factors and CVD, we have extensive evidence that, when action is taken against the risk factors, the catastrophic consequences of this rapidly growing problem can be avoided.

References

1. Mathers CD, Stein C, Ma Fat DM et al (2002) Global burden of disease 2000. Version 2: methods and results. World Health Organization, Geneva
2. World Health Organization (2002) The World Health Report 2002 'Reducing risks and promoting healthy life'. World Health Organization, Geneva
3. Mensah GA (2002) The global burden of hypertension: good news and bad news. Cardiol Clin 20(2):181–185
4. Yusuf S, Reddy S, Ounpuu S, Anand S (2001) Global burden of cardiovascular diseases. Part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 104:2746–2753
5. Yusuf S, Reddy S, Ounpuu S, Anand S (2001) Global burden of cardiovascular diseases. Part II: variations in cardiovascular disease by specific ethnic groups and geographic regions and prevention strategies. Circulation 104:2855–2864
6. Alwan A, Maclean D, Mandil A (2001) Assessment of national capacity for noncommunicable disease prevention and control. The report of a global survey. World Health Organization, Geneva
7. World Health Organization (2001) Innovative care for chronic conditions. World Health Organization, Geneva
8. Klungel OH, de Boer A, Paes AH et al (1998) Undertreatment of hypertension in a population-based study in the Netherlands. J Hypertens 9:1371–1377
9. Hedner T (1998) Treating hypertension – effect of treatment and cost-effectiveness in respect to later cardiovascular diseases. Scand Cardiovasc J 47:S31-S35
10. Trilling JS, Froom J (2000) The urgent need to improve hypertension care. Arch Fam Med 9:794–801

11. Pocock SJ, McCormack V, Gueyffier F et al (2001) A score for predicting risk of death from cardiovascular disease in adults with raised blood pressure, based on individual patient data from randomised controlled trials. BMJ 2001 323:75–81
12. World Health Organization (2001) Adherence to long-term therapies: policy for action. World Health Organization, Geneva
13. Feldman R, Bacher M, Campbell N, Drover A, Chockalingam A (1998) Adherence to pharmacologic management of hypertension. Can J Public Health 89(5):116–118
14. Van Den Hoogen PCW, Feskens EJM, Nagelkerke NJD et al for the Seven Countries Study Research Group (2000) The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. N Engl J Med 342:1–8

Is Arterial Pressure Self-Measurement Better Than Ambulatory 24-Hour Pressure Monitoring?

Carlo Fernandez

Hypertension is an important risk factor for cardiovascular disease, which is the second leading cause of death in the world. The overall reduction of absolute risk factors for cardiovascular disease is the therapeutic goal, with blood pressure (BP) management being a key component. Thus, accurate diagnosis and treatment of hypertension are necessary to improve a patient's prognosis [1]. The bulk of our knowledge about the risks of hypertension and the benefits of treatment has been based on the traditional method of taking a small number of BP readings with the auscultatory technique in medical setting. However, such measurements, which are of enormous value on a population basis, often provide a poor estimate of risk in an individual patient for various reasons, such as poor technique of the observer, the "white-coat" effect (the transient but variable elevation of BP in a medical setting), and the inherent variability of BP [1, 2].

Any clinical measurement of BP may be regarded as a surrogate measure for the "true" BP of the patient, which may be defined as the mean level over prolonged periods. Two techniques have been developed to improve the estimate of true BP: ambulatory monitoring and home monitoring (or self-monitoring). In addition, the BP measurement techniques used to determine whether a patient has hypertension have undergone substantial changes in the past 30 years [3].

Self-measurement of BP at home can accomplish several of the advantages of ambulatory BP monitoring, such as a greater number of readings, an avoidance of the white-coat effect, and, when automated devices are used, an absence of observer bias. Furthermore, self-measurement of BP may also increase compliance with antihypertensive therapy and reduce the number

College of Practice Cardiology ANCE, Palermo, Italy

of visits required for the diagnosis and treatment of hypertension [4, 5]. Nonetheless, self-measurement of BP at home can only become a useful instrument in the management of hypertension if the technique is well-standardized and complies with defined quality criteria. Most national and international hypertension guidelines include recommendations for home BP measurement. In principle, these guidelines are not different from those of BP measurement in general, but some points deserve special attention [6].

Experts have not yet reached a general consensus about a standard protocol (how many measurements and on how many days) patients should follow to measure their BP at home. In a recent editorial in the *Journal of Hypertension*, Parati et al. [7] described two different methods to define the most suitable schedule for home BP measurement, namely, a statistical approach and a clinical approach. In the statistical approach, the reproducibility and stability over time of home BP values and their relation with ambulatory BP values are used as criteria for defining the best frequency of home BP measurement. The clinical approach is based on the power of home BP values to predict cardiovascular outcome, and the reproducibility of home BP depends on the number of measurements. However, Brook [8] reported that if the accuracy of the average home BP was determined by agreement with average ambulatory BP values, the total number of measurements and total duration of monitoring were not important and that most benefits of home BP monitoring could be achieved by obtaining as few as two home BP measurements on one day. The advantage of home BP monitoring thus does not seem only to lie in the statistical advantages associated with the availability of many measurements but also in obtaining information on BP levels away from the clinical setting [7].

Ambulatory BP monitoring was first described more than 40 years ago. The currently available ambulatory monitors are fully automatic and can record BP for 24 h or longer, while patients go about their normal daily activities. Most monitors use the oscillometric technique. They measure about 4 x 3 x 1 inches (10 x 8 x 3 cm) and weigh about 4 pounds (2 kg). They can be worn on a belt or in a pouch and are connected to a sphygmomanometer cuff on the upper arm by a plastic tube. Subjects are asked to keep their arm still while the cuff is inflating and to avoid excessive physical exertion during monitoring. The monitors are typically programmed to take readings every 15–30 min throughout the day and night. At the end of the recording period, the readings are downloaded into a computer. Standard protocols are used to evaluate the accuracy of the monitors, and approved devices are usually accurate within 5 mmHg of readings taken with a mercury sphygmomanometer.

Three types of clinically valuable information are provided by ambulatory BP monitoring: an estimate of the true, or mean, BP level; the diurnal rhythm of BP; and BP variability. Currently, clinical guidelines exist only for estimating true, or mean, BP levels [4–6, 9].

The correlation coefficient between ambulatory measurements and clinically based measurements of BP is usually about 0.5–0.7, but the relationship is such that at low clinical BP levels the ambulatory blood pressure is higher, and at high clinical BP levels the ambulatory blood pressure is lower [2]. The daytime level of ambulatory BP that is usually considered the upper limit of normal is 135/85 mmHg [6]. This cut-off is reasonable because it corresponds approximately to a clinical blood pressure of 140/90 mmHg; furthermore, it is the threshold above which cardiovascular risk appears to increase markedly [10]. Evaluation of the time course of BP over a 24-h period can be achieved only with the use of ambulatory BP monitoring.

Subjects with normotension have a pronounced diurnal rhythm of BP [11]. During the first few hours of sleep, BP falls to its lowest level while in the morning there is a marked surge that coincides with the transition from sleep to wakefulness. The average difference between waking and sleeping systolic and diastolic pressure is 10–20%. Patients with hypertension usually have the same pattern, but the diurnal profile of BP is set at a higher level [10]. In some subjects, whether they have normotension or hypertension, the normal nocturnal fall of BP is diminished (< 10%). This is referred to as a nondipping pattern, in contrast to the normal dipping pattern. In extreme cases (patients with autonomic insufficiency), BP rises during the night. The nondipping pattern is common in blacks but also has multiple causes, such as a high level of activity during the day, poor quality of sleep, highly active sympathetic nervous system, use of glucocorticoids, and the presence of renal disease. Nondipping has been proposed as one reason why blacks are at higher risk for cardiovascular disease than are members of other races or ethnic groups.

There are many different ways of measuring BP, ranging from beat-to-beat changes to changes over periods of weeks or months [12]. Since the readings are taken intermittently, ambulatory BP monitoring can yield only a crude estimate of the true variations of BP, rather than the changes related to sleep vs wakefulness. The clinical significance of BP variability remains uncertain.

One trial comparing ambulatory BP with conventional clinical BP included patients whose hypertension had been treated at the time of the initial measurements [13]. Most such studies, however, have included patients whose hypertension was untreated at the time of the initial measurements

but was treated according to the clinical BP during the follow-up period, which ranged from 2 to 8 years. The general finding has been that cardiovascular events are more accurately predicted with ambulatory BP than with clinical blood pressure [14, 15].

In addition, the majority of the studies used some measure of the mean level of ambulatory BP as the predictor variable, but it remains uncertain which component of the 24-h BP profile gives the best prediction of risk. The most widely used has been the mean 24-h BP. Many studies have compared the predictive value of daytime BP with that of night-time pressure; some have shown no difference, whereas others have reported that the best prediction of risk comes from night-time BP.

The main clinical indications for ambulatory blood-pressure monitoring (ABPM) is the diagnosis of white-coat hypertension. This requires the demonstration that the patient's BP is normal outside the clinic, which can be established using self blood-pressure monitoring (SBPM) and confirmed by ABPM. Even though ABPM may save drug costs in patients with white-coat hypertension, its use may also lead to increased drug expenditure in others in whom it demonstrates suboptimal BP control. SBPM has the potential to reduce the number of clinical visits and also to improve BP control. The ultimate validation of these two procedures will depend on whether either one can prevent cardiovascular morbidity. There have been suggestions that a nondipping pattern of nocturnal BP may carry a poor prognosis, but this may apply only to certain disease end-points. The greater recognitions of the relevance of dipping status should provide an additional stimulus to the use of ABPM and SBPM. Moreover, it is anticipated that hypertension will eventually be managed by the "virtual hypertension clinic," in which ABPM is used for the initial diagnosis and SBPM, through electronic linkage between the patient and the health-care provider, for maintenance and follow-up [16].

Twenty-four-hour ABPM has emerged as an important tool supporting physicians in the diagnosis and management of arterial hypertension compared with office measurements and self-measurements; however, it shows the lowest patient acceptance. Nonetheless, a number of interacting factors have resulted in the increased clinical use of ABPM and SBPM. These include the phasing out of mercury, evidence of the unreliability of clinically based measurements, technical advances in automated BP measurement, increasing evidence that out-of-office measurements give the best risk assessment, and gradual recognition by insurance providers of the clinical utility of ABPM and SBPM. Both techniques have been endorsed by the two major guidelines for managing hypertensive patients (World Health Organization,

International Society of Hypertension and Join National Committee VI). The use of SBPM has grown enormously over the past few years, mostly because of direct sales to patients. Although SBPM may give a better estimate of the true BP than obtained with clinical readings, there are concerns about the accuracy of the monitors in individual patients.

The following situations are considered to indicate the use of ABPM:

1. Labile hypertension. This is something of a misnomer because all hypertension is labile. However, ABPM may prove helpful in some patients with a history of paroxysmal hypertension.

2. Resistant hypertension. An exaggerated white-coat effect may be suspected in some patients whose clinic BP remains high even though they are taking three or more antihypertensive drugs.

3. Masked hypertension. Recently, interest has increased in the phenomenon of masked hypertension, defined as a normal clinical BP and a high ambulatory BP. This condition is the reverse of white-coat hypertension. The clinical BP levels of patients with masked hypertension may underestimate the risk of cardiovascular events. A study of patients with treated hypertension showed that about one-third of those seen in a hypertension clinic had masked hypertension, and over a 5-year follow-up period their relative risk of cardiovascular events was 2.28 times higher than that of patients whose BP was adequately controlled according to the criteria for both clinically based and ambulatory BP measurements [17].

4. Postural hypotension. This is a not uncommon finding in older patients who become dizzy when standing for long periods and who may also have syncopal episodes. The BP of patients with postural hypotension is unusually labile and depends on their body position. When such patients are supine, their BP may be quite high, particularly during the night [18]. Treatment with vasopressor drugs and antigravity stockings is a compromise between permitting the BP to go too low and making it go too high. Therefore, in these patients, ABPM is essential for evaluating optimal BP control.

Conclusions

Currently, ABPM is used only in the minority of patients with hypertension, but its use is gradually increasing. Compared with isolated clinically based measurements, ABPM provides insight into BP changes in everyday life.

Cross-sectional evidence suggests a direct and significant relationship between ambulatory BP and organ damage. There is also longitudinal evidence for a superior predictive value of 24-h ambulatory BP in relation to the

risk for cardiovascular morbidity and mortality as opposed to clinical BP.

Ambulatory monitors are reliable, reasonably convenient to wear, and generally accurate. Ambulatory monitoring can be regarded as the gold standard for the prediction of risk related to BP, since prognostic studies have shown that it predicts clinical outcome better than conventional BP measurements. Therefore, a good case can be made for using this technique in all patients in whom hypertension has been newly diagnosed by means of clinical BP measurements. The role of ABPM for diagnosing masked hypertension is uncertain.

The usefulness of ABPM in pharmacologic studies aimed at evaluating the 24-h antihypertensive efficacy of different drugs and drug combinations is now acknowledged. Among the mathematical indices available to explore 24-h BP coverage by treatment, the ABPM-derived smoothness index provides a superior measure of the homogeneity of BP control compared with episodic peak ratios. The main applications of this technique in clinical practice should be: (1) in identifying patients with isolated office hypertension and those who are nonresponders to treatment, (2) in assessing coverage of the 24-h BP profile in high-risk patients, and (3) in diagnosing suspected treatment-related hypotension.

Although ambulatory monitoring is relatively expensive compared with other methods of measuring BP, its ability to diagnose white-coat hypertension may reduce health-care costs. ABPM is also invaluable for assessing the efficacy of antihypertensive treatments and should be included in studies designed to compare the effects of various drugs.

Night-time blood pressure can be assessed only with ABPM, and evidence suggests that a failure of BP to decrease at night is associated with an adverse prognosis. Also unresolved is the extent to which ABPM can be supplanted by home monitoring – an aspect that was not included in most of the studies documenting the superiority of ambulatory monitoring over traditional clinical BP measurements.

In some hypertensive patients on adequate antihypertensive treatment there is a significant difference between clinical and ambulatory BP measurements. This difference (white-coat effect) is greater in elderly patients and in men. Although clinical BP values in these patients are significantly increased, the majority have controlled BP on ambulatory monitoring. In this population, ABPM has been of great value to identify a misdiagnosis of refractory hypertension, which could lead to improper decisions in the therapeutic management of elderly patients (increasing treatment) and compromise cerebrovascular or coronary circulation.

References

1. Pickering TG, Phil D, Shimbo D, Haa SD (2006) Ambulatory blood-pressure monitoring. N Engl J Med 354:2368–2374
2. Armitage P, Rose GA (1966) The variability of measurements of causal blood pressure. I.A. Laboratory study. Clin Sci 30:325–335
3. Wite WB (2003) Ambulatory blood-pressure monitoring in clinical practice. N Engl J Med 348:2377–2378
4. Staessen JA, Wang J, Bianca G (2003) Essential hypertension. Lancet 361:1269–1641
5. Staessen JA, Dean Hond E, Celis H et al (2004) Antihypertensive treatment based on blood pressure measurement at home or in the physician's office: a randomized controlled trial. Treatment of Hypertension Based on Home or Office Blood Pressure (THOP) Trial Investigators. JAMA 291:995–964
6. O'Brien E, Asnear R, Beilin L et al (2003) European Society of Hypertension recommendation for conventional, ambulatory and home blood pressure measurement. J Hypertens 21:821–848
7. Parati G, Stergiou G (2004) Self blood pressure measurement at home: how many times. J Hypertens 22:1075–1079
8. Brook RK (2000) Home blood pressure: accuracy is independent of monitoring schedules. Am J Hypertens 13:625–631
9. Little P, Barnet J, Barnsley L et al (2002) Comparison of agreement between different measures of blood pressure in primary care and daytime ambulatory blood pressure. BMJ 325:254–254
10. Verdecchia P (2000) Prognostic value of ambulatory blood pressure: current evidence and clinical implications. Hypertension 35:844–851
11. Pickering TG, Harshfield GA, Kleinert HD et al (1982) Blood pressure during normal daily activities, sleep, and exercise: comparison of values in normal and hypertension subjects. JAMA 247:992–996
12. Parati G, Valentini M (2006) Prognostic relevance of blood pressure variability. Hypertension 47:138–138
13. Clement DL, De Buyzere ML, De Bacquere DA et al (2003) Prognostic value of ambulatory blood-pressure recordings in patients with treated hypertension. N Engl J Med 348:2407-2415
14. Sega R, Facchetti R, Bombelli M et al (2005) Prognostic value of ambulatory and home blood pressure compared with office blood pressure in the general population: follow-up results from the Pression Arteriose Monitorate e Loro Associazioni (PAMELA) study. Circulation 111:1777–1783
15. Dolan E, Stanton A, Thijs L et al (2005) Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. Hypertension 46:156–161
16. Pickering T (2005) Future developments in ambulatory blood pressure monitoring and self-blood pressure monitoring in clinical practice. Blood Press Monit 7:21–25
17. Pierdomenico SD, Lapenna D, Bucci A et al (2005) Cardiovascular outcome in treated hypertensive patients with responders, masked, false resistant, and true resistant hypertension. Am J Hypertens18:1422–1428
18. Man S, Altman DG, Raftery EB, Bannister R (1983) Circadian variation of blood pressure in autonomic failure. Circulation 68:477–483

Role of Angiotensin-Receptor Blockers in the Prevention of Cardiovascular Risk: Clinical Guidelines

Pasquale Perrone-Filardi, Pierluigi Costanzo, Antonio Marzano, Paolo Cesarano, Paola Gargiulo, Enrico Vassallo, Caterina Marciano, Teresa Losco, Massimo Chiariello

Introduction

The development and progression of cardiovascular disease can be regarded as a continuum (Fig. 1) [1]. Targeting different points within this continuum is therefore of major importance for reducing cardiovascular morbidity and mortality. Inhibition of the renin-angiotensin-aldosterone system (RAAS) has become a key target in this regard, given that angiotensin II (Ang II) has been implicated as a pathogenic factor at many steps in the development and progression of cardiovascular disease [2, 3].

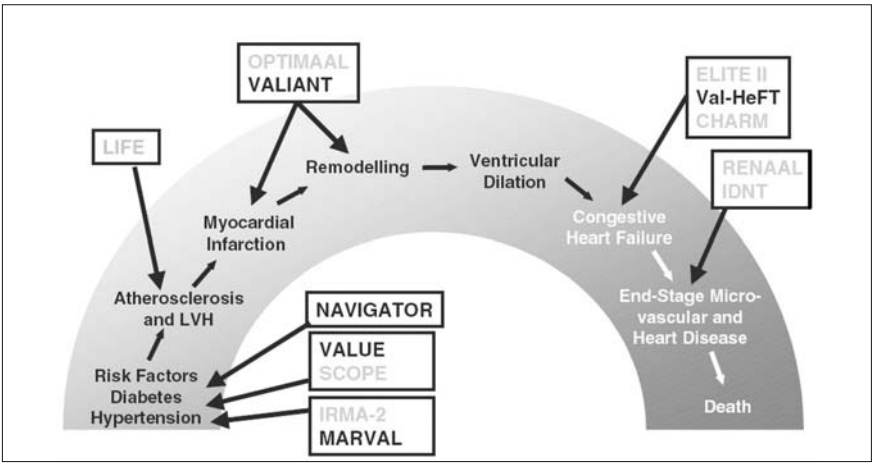


Fig. 1. The cardiovascular continuum showing key clinical trials with angiotensin receptor. Reproduced from [2], with permission

Department of Internal Medicine, Cardiovascular & Immunological Sciences, Federico II University, Naples, Italy

Current Evidence for the Prevention of Cardiovascular Risk with Angiotensin-Receptor Blockers

Patients with Hypertension

Three clinical trials have investigated the cardioprotective effects of angiotensin-receptor blockers (ARBs) in patients with hypertension. The *Valsartan Antihypertensive Long-Term Use Evaluation* (VALUE) trial compared valsartan (80–160 mg ± diuretic) with amlodipine (5–10 mg ± diuretic) in more than 15,000 patients with hypertension who were at high risk for a cardiac event. Even though amlodipine-based treatment resulted in a greater reduction in blood pressure (BP) in the early stages of the trial, the primary endpoint (a composite of cardiac mortality and morbidity) was not significantly different between the treatment groups at 66 months of follow-up [4]. The *Losartan Intervention For Endpoint reduction in hypertension* (LIFE) trial demonstrated the advantage of losartan, titrated to 100 mg once daily, compared with atenolol for reducing the composite endpoint (most notably stroke), despite similar BP reductions. Moreover, losartan induced a greater reduction of left ventricular mass than atenolol [5]. Similar findings have been observed for other ARBs, including valsartan and irbesartan [5]. These results indicate that the cardioprotective benefits of ARBs extend beyond BP reduction alone [6]. In addition, a subgroup analysis of hypertensive patients with left ventricular hypertrophy (LVH) who did not have clinically evident vascular disease showed that losartan was more effective than atenolol in preventing cardiovascular morbidity and death, with no difference between treatment groups regarding the lowering of BP. Similar to the reduction in stroke among the entire LIFE study sample, losartan reduced the rate of fatal and nonfatal stroke by 34% in this analysis [7]. Another recently published study compared the effectiveness of losartan vs atenolol for regression of LVH in patients enrolled in the LIFE study [8]. After a 6-month follow-up, losartan resulted in greater regression of LVH according to electrocardiographic criteria than did atenolol [9].

Prevention of Diabetes

As with the ACE inhibitors, the ARBs are known to exert positive metabolic effects. Also like the ACE inhibitors, initial evidence of the effects of ARBs on new-onset diabetes came from studies in which these drugs were compared with conventional therapies. At the end of the LIFE study, there was a 25% risk reduction in new-onset diabetes in patients in the ARB arm compared

with those in the beta-blocker arm [10]. In the *Antihypertensive Treatment and Lipid Profile, a North of Sweden Evaluation* (ALPINE), patients were randomized to receive either candesartan (16 mg) or hydrochlorothiazide (HCTZ; 25 mg), and both regimens reduced blood pressure effectively. However, fasting levels of both serum insulin and plasma glucose increased in HTCZ-treated patients but remained unchanged in the candesartan-treated group, and significantly more patients in the HCTZ group were diagnosed with diabetes during follow-up [11]. Additional evidence of the anti-diabetic effects of ARB therapy came from the VALUE study, in which, after a mean of 4.2 years, new-onset diabetes was diagnosed in significantly fewer patients in the valsartan group than in the amlodipine group [12]. Similar to ALLHAT, which compared an ACE inhibitor with amlodipine, the results from VALUE suggested that the reduced incidence of diabetes associated with ARB was due to a positive effect on metabolic control rather than a negative effect of the comparator amlodipine, as this drug is considered metabolically neutral. More recently, the *Candesartan in Heart Failure-Assessment of Reduction in Mortality and Morbidity* (CHARM) program included the reduction of new-onset diabetes in heart failure (HF) patients treated with candesartan compared with placebo as a prespecified secondary endpoint. After 3.5 years, patients who received candesartan had a significant reduction in relative risk of developing diabetes compared to placebo. The reduction in new-onset diabetes was even greater among patients in the CHARM-Preserved trial [13]. The *Study on Cognition and Prognosis in the Elderly* (SCOPE) also reported a 25% relative risk reduction in new-onset diabetes with candesartan compared with placebo [14]. Although this finding did not achieve statistical significance, it does, nevertheless, provide further support that ARBs can help to reduce the risk of diabetes in high-risk patients, such as those with hypertension. However, the recent disappointing results of the DREAM trial, which was specifically designed to test the anti-diabetic hypothesis of ACE-inhibitor therapy, raised caution about a significant anti-diabetic action of these drugs [15].

Renoprotective Activity of ARBs

Agents that delay the progression of renal disease are likely to be cardioprotective by lessening the systemic consequences of renal dysfunction [16]. A number of recent clinical studies with ARBs reported renal benefits in patients with type 2 diabetic nephropathy. The beneficial effects on microalbuminuria and renal function went beyond those attributed to the decrease in BP alone. The *Irbesartan in Patients with Type 2 Diabetes and*

Microalbuminuria 2 (IRMA-2) trial, which compared irbesartan to placebo, demonstrated a reduction in relative risk of diabetic nephropathy in the irbesartan group. The *Irbesartan Diabetic Nephropathy Trial* (IDNT), in which patients were randomized to receive either irbesartan or amlodipine or placebo, reported a reduced lower risk with irbesartan therapy of doubling serum creatinine concentration and developing end-stage renal disease (ESRD) [17]. In the *Microalbuminuria Reduction with Valsartan* (MARVAL) trial, there was a greater reduction in baseline urinary albumin excretion rate with valsartan than with amlodipine [18]. The *Reduction of Endpoints in Non-Insulin-Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan* (RENAAL) trial, in which patients were randomized to receive either losartan or placebo, demonstrated a reduction in the doubling of serum creatinine concentration, onset of ESRD, and in risk of primary composite endpoint by losartan. The trial also reported a significant reduction in the pre-specified secondary endpoint of new HF development in diabetic nephropathic patients [19]. The COOPERATE trial tested trandolapril, losartan, or both and demonstrated that an ARB in addition to ACE-inhibitor therapy is more renoprotective than either ARBs or ACE inhibitors alone in patients with non-diabetic renal disease [20].

ARBs and Heart Failure

Recent clinical studies have evidenced improvements in morbidity and mortality by treating HF with ARBs in addition to conventional therapy. The *Valsartan Heart Failure Trial* (Val-HeFT), with primary endpoints of all-cause mortality and cardiovascular morbidity, compared valsartan to placebo [21]. This was the first study demonstrating a significant benefit of combination therapy, mostly driven by a reduced number of hospitalizations.

Most recently, in the CHARM trials, candesartan reduced both all-cause mortality and composite endpoint of cardiovascular mortality and hospitalization for HF. The trial consisted of three separate studies with the same protocol conducted in different but complementary populations. All patients recruited to the study had symptomatic HF, but those in the CHARM-Alternative had a LVEF $\leq$ 40% and were ACE-inhibitor intolerant, those in CHARM-Added also had LVEF $\leq$ 40% but were treated with ACE inhibitors, and patients recruited to CHARM-Preserved had LVEF $>$ 40% [13]. Above all, these last two studies demonstrated the clinical efficacy of ARBs in decreasing morbidity and mortality in patients with HF and led to the introduction of ARB therapy indication in recently released HF guidelines [22].

ARBs in Patients After Myocardial Infarction

Left ventricular dysfunction and HF are common complications of myocardial infarction (MI) and place patients at high risk for cardiovascular mortality. The VALIANT results demonstrated the statistical non-inferiority of valsartan vs captopril in these high-risk patients, but also – unlike in patients with chronic HF – no advantage of combination therapy [23]. In contrast, the *Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan* (OPTIMAAL) trial demonstrated a non-significant difference in total mortality in favor of captopril, although losartan was better tolerated [24]. Current guidelines recommend the use of ARBs, specifically valsartan and candesartan, as an alternative to ACE inhibitors in high-risk, post-MI patients [25].

ARBs and Atrial Fibrillation

Secondary analysis of the findings of the LIFE and CHARM trials evidenced that losartan and candesartan reduced the incidence of atrial fibrillation (AF) in hypertensive patients with LVH and symptomatic HF, respectively [26–28]. These results, together with the favorable safety profiles of these two drugs compared with anti-arrhythmic agents, suggest a role for ACE inhibitors or ARBs in the primary prevention of initial or recurrent episodes of AF associated with hypertension, MI, HF, or diabetes mellitus. An overview of 11 clinical trials involving more than 56,000 patients with different underlying cardiovascular diseases suggested that ACE inhibitors or ARBs can reduce the occurrence and recurrence of AF [28]. Additional prospective research is ongoing to determine the impact of ACE inhibitors or ARBs in reducing AF occurrence.

Cardiovascular Risk and ARBs: Future Perspectives

Prevention of new-onset diabetes is currently under further investigation in the *Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research* (NAVIGATOR) trial. This study compares valsartan to nateglinide with the aim of evaluating the development of type 2 diabetes and cardiovascular disease in people with impaired glucose tolerance who are at high cardiovascular risk [29].

Two ongoing studies are examining the use of ARBs in patients at high risk of cardiovascular disease. The *Ongoing Telmisartan Alone and in*

Combination with Ramipril Global Endpoint Trial (ONTARGET) compares telmisartan monotherapy, ramipril monotherapy, and combination therapy with telmisartan plus ramipril. In a parallel study, patients who are unable to tolerate an ACE inhibitor will be randomized to receive either telmisartan or placebo (the *Telmisartan Randomized Assessment Study in ACE-Intolerant Patients with Cardiovascular Disease*, TRANSCEND). The primary endpoint in each trial is a composite of cardiovascular death, MI, stroke, and hospitalization for HF [30, 31].

Other ongoing trials include *Irbesartan in Heart Failure with Preserved Systolic Function* (I-PRESERVE) and the *Diabetic Retinopathy Candesartan Trials* (DIRECT) [32, 33]. In particular, the I-PRESERVE study is currently enrolling patients with chronic HF and preserved systolic function (ejection fraction ≥ 45%), a patient population for which fewer data are available. The primary aim of the study is to evaluate whether irbesartan is superior to placebo (i.e., existing therapy) for reducing mortality and morbidity. In contrast, DIRECT has been designed to examine the efficacy of candesartan for primary and secondary prevention of diabetic retinopathy in normoalbuminuric, normotensive patients with type 1 diabetes. This trial will also examine secondary prevention in normoalbuminuric, normotensive or treated patients with type 2 diabetes and hypertension [33].

Ongoing trials will determine the impact of the use of ACE inhibitors or ARBs in patients with AF. The irbesartan arm of the *Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events* (ACTIVE-I) trial will randomize 9,000 patients with a history of AF, with or without a history of hypertension, to receive an ARB, irbesartan, or placebo. A substudy of this trial will examine the effects of irbesartan on the recurrence of paroxysmal AF [34]. Finally, the *Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Atrial Fibrillation* (GISSI-AF) will evaluate the addition of valsartan to standard therapy or placebo (i.e., standard therapy) in reducing the recurrence of AF [35].

References

1. Dzau V, Braunwald E (1991) Resolved and unresolved issues in the prevention and treatment of coronary artery disease: a workshop consensus statement. Am Heart J 121:1244–1263
2. Weber MA (2003) Angiotensin receptor blockers and the cardiovascular continuum: what future is indicated by recent successes? Eur Heart J Supplements 5(Suppl C):C1-C4
3. Burnier M, Brunner HR (2000) Angiotensin II receptor antagonists. Lancet 355:637–645

4. Julius S, Kjeldsen SE, Weber M et al (2004) Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 363:2022–2031
5. Dahlöf B, Devereux RB, Kjeldsen SE et al (2002) Cardiovascular morbidity and mortality in the Losartan Intervention For End point reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 359:995–1003
6. Thurmann PA, Kenedi P, Schmidt A et al (1998) Influence of the angiotensin II antagonist valsartan on left ventricular hypertrophy in patients with essential hypertension. Circulation 98:2037–2042
7. Malmquist K, Kahan T, Edner M et al (2001) Regression of left ventricular hypertrophy in human hypertension with irbesartan. J Hypertens 19:1167–1176
8. Devereux RB, Dahlöf B, Kjeldsen SE et al (2003) Effects of losartan or atenolol in hypertensive patients without clinically evident vascular disease: a substudy of the LIFE randomized trial. Ann Intern Med 139:169–177
9. Okin PM, Devereux RB, Jern S et al (2003) Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol: the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study. Circulation 108:684–690
10. Lindholm LH, Ibsen H, Borsch-Johnsen K et al (2002) Risk of new-onset diabetes in the Losartan Intervention For Endpoint reduction in hypertension study. J Hypertens 20:1879–1886
11. Lindholm LH, Persson M, Alaupovic P et al (2003) Metabolic outcome during 1 year in newly detected hypertensives: results of the Antihypertensive Treatment and Lipid Profile in a North of Sweden Evaluation (ALPINE study). J Hypertens 21:1563–1574
12. Montalescot G, Collet JP (2005) Preserving cardiac function in the hypertensive patient: why renal parameters hold the key. Eur Heart J 26:2616–2622
13. Pfeffer MA, Swedberg K, Granger CB et al (2003) Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 362:759–766
14. Lithell H, Hansson L, Skoog I et al (2003) The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. J Hypertens 21:875–886
15. DREAM Trial Investigators (2006) Effect of ramipril on the incidence of diabetes. N Engl J Med 355:1551–1562
16. Lewis EJ, Hunsicker LG, Clarke WR et al (2001) Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 345:851–860
17. Parving HH, Lehnert H, Brochner-Mortensen J et al (2001) The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 345:870–878
18. Viberti G, Wheeldon NM for the Microalbuminuria Reduction with Valsartan (MARVAL) Study Investigators (2002) Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus. Circulation 106:672–678
19. Keane WF, Lyle PA (2003) Recent advances in management of type 2 diabetes and nephropathy: lessons from the RENAAL study. Am J Kidney Dis 41(Suppl 3):S22-S25
20. Nakao N, Yoshimura A, Morita H et al (2003) Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. Lancet 361:117–124

21. Krum H, Carson P, Farsang C et al (2004) Effect of valsartan added to background ACE inhibitor therapy in patients with heart failure: results from Val-HeFT. Eur J Heart Fail 6:937–945
22. ESC Task Force (2005) Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005). Eur Heart J 26:1115–1140
23. Pfeffer MA, McMurray JJ, Velazquez EJ et al (2003) Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 349:1893–1906
24. Dickstein K, Kjekshus J, and the OPTIMAAL Steering Committee, for the OPTIMAAL Study Group (2002) Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Lancet 360:752–760
25. ACC/AHA Task Force (2004) ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction – executive summary. J Am Coll Cardiol 44:671–719
26. Wachtell K, Lehto M, Gerdts E et al (2005) Angiotensin II receptor blockade reduces new-onset atrial fibrillation and subsequent stroke compared to atenolol: the Losartan Intervention For End Point Reduction in Hypertension (LIFE) study. J Am Coll Cardiol 45:712–719
27. Maggioni AP, Latini R, Carson PE et al (2005) Valsartan reduces the incidence of atrial fibrillation in patients with heart failure: results from the Valsartan Heart Failure Trial (Val-HeFT). Am Heart J 149:548–557
28. Healey JS, Baranchuk A, Crystal E et al (2005) Prevention of atrial fibrillation with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis. J Am Coll Cardiol 45:1832–1839
29. McMurray JJ, Califf R, Holman R et al (2004) Cardiologists should care about glucose: most people with cardiovascular disease or risk factors have diabetes or significant glycaemic abnormalities. Results of screening over 39,000 subjects for NAVIGATOR. Eur Heart J 25(Suppl):239 (abs)
30. Yusuf S (2002) From the HOPE to the ONTARGET and the TRANSCEND studies: challenges in improving prognosis. Am J Cardiol 89:18A-26A
31. Teo K, Yusuf S, Anderson C et al (2004) Rationale, design, and baseline characteristics of 2 large, simple randomized trials evaluating telmisartan, ramipril and their combination in high-risk patients: the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND). Am Heart J 148:52– 61
32. Carson P, Massie BM, McKelvie R et al (2005) The irbesartan in heart failure with preserved systolic function (I-PRESERVE) trial: rationale and design. J Cardiol Fail 11:576–585
33. Chaturvedi N, Sjoelie AK, Svensson A for the DIRECT Programme Study Group (2002) The DIabetic Retinopathy Candesartan Trials (DIRECT) Programme, rationale and study design. J Renin Angiotensin Aldosterone Syst 3:255–261
34. The Active Steering Committee; ACTIVE Investigators (2006) Rationale and design of ACTIVE: the atrial fibrillation clopidogrel trial with irbesartan for prevention of vascular events. Am Heart J 151:1187–1193
35. Disertori M, Latini R, Maggioni AP, Delise P (2006) Rationale and design of the GISSI-Atrial Fibrillation Trial: a randomized, prospective, multicentre study on the use of valsartan, an angiotensin II AT1-receptor blocker, in the prevention of atrial fibrillation recurrence. J Cardiovasc Med 7:29–38

New Evidence about the Beneficial Effects of Angiotensin-Receptor Blockers on the Heart and the Kidney

Claudio Borghi[1], Marco Manca[2]

Introduction

Historically, renal dysfunction has been considered separately from the cardiovascular risk profile, and has been treated as such. In particular, cardiologists, concerned with treating the heart and vasculature, did not routinely consider the impact of disturbed renal function on the progression toward cardiac events. However, the landscape of cardiovascular disease has changed dramatically in recent years, most notably with the publication in 2003 of a joint statement by a panel of cardiologists and nephrologists illustrating the importance of kidney disease as a risk factor for the development of cardiovascular disease [1]. Recent evidence clearly showed that both microalbuminuria and glomerular filtration rate (GFR), even in the very earliest and otherwise asymptomatic stages of renal disease, are risk factors for cardiovascular disease, and there are numerous links between renal dysfunction and other common risk factors.

Microalbuminuria is surprisingly prevalent, even in patients without common comorbidities that are conventionally thought to cause nephropathy, and is strictly linked to many important cardiovascular end points. For instance, of the 1,499 participants without diabetes or hypertension in the Framingham Heart Study, 15% developed hypertension and 33% progressed to a high blood pressure category over the 2.9-year follow-up period. After adjusting for other risk factors, patients in the highest quartile of baseline urinary albumin-to-creatinine ratio had a 2.2-fold higher risk of developing new hypertension and a 1.5-fold higher risk of hypertension progression than those in the lowest quartile.

[1]Unit of Internal Medicine, Department of Clinical Medicine and Applied Biotechnology, University Hospital St. Orsola, Bologna; [2]Descovich Atherosclerosis and Metabolic Disease Study Centre, Department of Clinical Medicine and Applied Biotechnology, University Hospital St. Orsola, Bologna, Italy

One of the most important studies of the natural course of microalbuminuria and its relation to renal and cardiovascular disease is the *Prevention of Renal and Vascular End-Stage Disease* (PREVEND) study, which collected postal questionnaires and morning urine samples from > 40,000 residents of the Dutch city of Groningen [2]. Although 7.2% of residents had microalbuminuria (20–200 mg/l) and 0.2% had macroproteinuria (> 200 mg/l), a further 16.6% had high-normal albuminuria (10–20 mg/l). In other words, nearly 25% of the population had increased urinary albumin excretion rates, despite the fact that in this population the prevalence of diabetes was only 2.6% and that of hypertension was 11.2%. The high prevalence of high-normal albuminuria is a concern because it has been shown that the cardiovascular risk due to albuminuria is continuous.

Inhibition of the renin-angiotensin system (RAS) by administration of an angiotensin-receptor blocker (ARB) reduces blood pressure (BP) in hypertensive patients [3]. ARBs also slow the progressive decline in renal function that marks renal injury, particularly in patients with diabetic nephropathy [4, 5]. The renoprotective effects of these drugs relate, in part, to their capacity to moderate protein excretion [6]. ARB therapy has been shown to decrease the cardiovascular event rate in high-risk cardiac patients [7, 8]. Moreover, ARBs are of proven benefit in systolic forms of heart failure (HF) [9].

Effects on the Kidneys

Angiotensin-II-receptor blockers have been repeatedly shown to reduce microalbuminuria and proteinuria to a greater degree than expected from their effect on blood pressure alone. This has been well-documented for patients with diabetes [4, 5, 10] (although not so well-documented in nondiabetic individuals); thus, ARBs are an established first-line treatment for diabetic kidney disease or kidney disease with significant proteinuria [11]. However, several issues demand further investigation, one of the most important being establishment of the optimal dose. Data from animal models have suggested that the doses of ARBs required for full renal protection are greater than those required for maximal lowering of blood pressure. In Sprague–Dawley rats subjected to subtotal surgical renal ablation, subsequent treatment with high-dose enalapril (48 mg/kg, equivalent to a dose of approximately 3 g in humans) significantly reduced the resultant glomerulosclerosis and tubulointerstitial and vascular damage [12]. Not only was renal damage reduced compared with untreated controls, but it was also reduced compared with baseline (i.e., 4 weeks after renal ablation), suggesting that appropriately high doses of ARBs may even have the potential to reverse preexisting glomerulosclerosis.

Some evidence of the renoprotective effects of high-dose ARB treatment has come from clinical studies. The *Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria* (IRMA-2) trial compared irbesartan (150 or 300 mg daily) with placebo in 590 patients over a 2-year period [13]. Both irbesartan doses significantly reduced the progression to overt proteinuria compared with placebo. However, the percentage of patients who progressed to proteinuria with the higher dose (5.2%) was almost 50% of that in the lower-dose arm (9.7%), despite the fact that mean arterial BP reductions were almost identical in the two groups. Similar effects were seen in the mean urinary albumin excretion rate (UAER), which was reduced by 34% in the low-dose arm and 60% in the high-dose arm.

Higher doses of ARBs may have a progressive effect that takes months to be fully manifested. In one study, 78 patients with nondiabetic hypertensive and proteinuric chronic nephropathy received telmisartan (80 mg) either once daily (which is the dose that produces maximal reduction in BP) or twice daily for 18 months, with all patients remaining in the study for ≥ 12 months [14]. At 6 months, both groups had a similar reduction in proteinuria. However, there were further reductions in the high-dose group by month 12, with the result that total reduction was significantly greater than in the lower-dose group. BP control was similar in the two groups.

If ARBs truly do reduce the progression of kidney disease independently of their hemodynamic effects, then treatment withdrawal should be accompanied by at least partial maintenance of the effects. Such an analysis was conducted in IRMA-2, in which patients were followed for 1 month after withdrawal of treatment [13]. In the placebo and irbesartan 150-mg and 300-mg groups, BP returned to baseline values during this follow-up period, and albuminuria in the placebo and irbesartan 150-mg arms increased to approximately 10% greater than baseline [15]. In the 300-mg arm, however, albuminuria was still 47% lower than baseline 1 month after treatment discontinuation, strongly suggestive of prolonged, non-hemodynamic effects.

In patients with diabetes, blockade of the RAS reduced not only the level of microalbuminuria but also the risk of developing new-onset microalbuminuria compared with other antihypertensives. In the subset of 1,195 patients with type 2 diabetes in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, new-onset albuminuria (identified as albuminuria reported as an adverse event during the study period) occurred in 7% of patients in the losartan arm compared with 13% of patients in the atenolol arm [7]. More recently, in the *Bergamo Nephrologic Diabetes Complications Trial* (BENEDICT) of patients with hypertension, type 2 diabetes, and normalbuminuria, 6% of the trandolapril arm pro-

gressed to persistent microalbuminuria, compared with 10% of patients in the placebo arm and 11% of patients in the verapamil arm [16].

Effects on the Heart

Persistent morbidity and mortality benefits of chronic angiotensin-converting enzyme (ACE) inhibition have established ACE inhibitors as the first-line therapy for patients with reduced left ventricular function and symptoms of HF in both acute infarction and chronic HF patients. The concept that more complete inhibition of the RAS system by blocking angiotensin II receptors might lead to similar or further benefits provided the rationale for clinical trials with ARBs, such as OPTIMAAL [17], ELITE II [18], Val-HEFT [19], CHARM [20], and VALIANT [21].

The first trial to directly compare an ARB with an ACE inhibitor in HF patients was the *Evaluation of Losartan in the Elderly* (ELITE) trial [22], which compared the potential renal benefits of an ARB with an ACE inhibitor in elderly patients with HF. Approximately 700 patients were randomized to losartan (50 mg daily) or to captopril (50 mg three times daily). While no benefit in terms of renal function was observed in either arm, there was a statistically significant and unexpected mortality benefit in patients receiving losartan, albeit with a small number of events in each group. Despite the initial enthusiasm regarding these findings, this study was clearly underpowered to assess mortality. The subsequent and properly powered *Evaluation of Losartan in the Elderly* (ELITE) II study failed to show a benefit of losartan in reducing mortality or morbidity in HF patients, with a slight non-significant benefit to patients in the captopril group. While these findings provided no support for the notion that angiotensin-receptor blockade was superior to ACE inhibition in the treatment of HF, many clinicians criticized this study for using too low a dosage (50 mg daily) of losartan.

In contrast to ELITE II, the Val-HeFT study compared the ARB valsartan with standard therapy in HF patients. The majority of patients enrolled in Val-HeFT (92%) were already on ACE inhibitors. Val-HeFT demonstrated no mortality benefit, but a reduction in a combined endpoint of morbidity and mortality that was primarily driven by a reduction in HF-related hospitalization.

In the subset of patients not receiving ACE inhibitors in VALIANT, there was a substantial mortality benefit associated with valsartan. Val-HeFT, however, raised concerns about an increase in adverse outcomes in those patients receiving the combination of an ARB, an ACE inhibitor, and a beta-blocker simultaneously. This is a concern that would linger until the results of CHARM and VALIANT.

The CHARM program studied the benefits of candesartan in a broad range of chronic HF patients. The study consisted of three component trials: CHARM-Alternative [9], which enrolled patients with symptomatic HF and left ventricular dysfunction who were intolerant to ACE inhibitors; CHARM-Added [23], which enrolled symptomatic HF and left ventricular dysfunction patients who were already taking optimal doses of ACE inhibitors; and CHARM-Preserved [24], which enrolled patients with symptomatic HF but with preserved (LVEF > 40%) systolic function.

In CHARM-Alternative, candesartan reduced the primary endpoint of cardiovascular mortality and HF-related hospitalizations by 23% ($p < 0.0001$) in patients with left ventricular systolic dysfunction and intolerance to ACE inhibitors. In CHARM-Added, which enrolled patients already on optimal doses of ACE inhibitors, the composite endpoint was reduced by 14% ($p < 0.01$).

CHARM-Preserved demonstrated a non-significant trend towards improved outcome in patients with symptomatic HF and preserved systolic function. Importantly, patients enrolled in CHARM-Added who received the combination of ARB, ACE inhibitor, and beta-blockers had better outcomes than patients receiving ARB and ACE inhibitors but without beta-blockers.

These findings, along with similar lack of concern regarding "triple" therapy in VALIANT, helped to allay many of the fears raised by the VAL-HeFT results. Thus, the CHARM studies suggested a benefit of ARB therapy both in HF patients who are intolerant to ACE inhibitors and in patients already receiving optimal doses of ACE inhibitors.

In myocardial infarction patients, ARBs have been tested in two large outcome studies. The *Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan* (OPTIMAAL) was designed similarly to ELITE II, and compared losartan (50 mg daily) with captopril (50 mg three times daily) in patients with high-risk myocardial infarction. Similarly to the findings of ELITE II, OPTIMAAL failed to show a benefit of losartan over the ACE inhibitor at that dose. Patients treated with losartan (50 mg) had a borderline increase in mortality (odds ratio [OR] 1.13, 95% confidence interval [CI] 0.99–1.28, $p < 0.069$) and significant increase in cardiovascular death (OR 1.17, 95% CI 1.10–1.34, $p < 0.032$). As was the case with ELITE II, this study was criticized because of the low dose of losartan administered.

In contrast to the head-to-head approach of OPTIMAAL, the *Valsartan in Acute Myocardial Infarction Trial* (VALIANT) tested the hypothesis that the ARB valsartan, either alone or in combination with captopril, would be better than captopril alone at reducing mortality following myocardial infarction. In addition, VALIANT was designed as a non-inferiority trial, and was

powered to determine whether valsartan, if not superior to captopril, would be non-inferior to captopril in reducing morbidity and mortality after myocardial infarction. VALIANT enrolled 14,703 patients who were randomized to valsartan (160 mg twice daily), captopril (50 mg three times daily) or a combination of captopril (50 mg three times daily) and valsartan (80 mg twice daily). VALIANT showed no differences among the three treatment arms, with virtually superimposable mortality curves. Nevertheless, VALIANT was able to effectively test the non-inferiority hypothesis and demonstrated that valsartan was as effective as captopril in reducing mortality.

Conclusions

The studies discussed above demonstrated clearly that microalbuminuria is an important cardiovascular and renal risk factor. In patients with microalbuminuria, RAS blockade is an effective tool to reduce cardiovascular risk. For these reasons, estimation of albuminuria will certainly become an important component of cardiovascular risk profiling.

Common pathologic mechanisms underlie the progression of cardiovascular and renal damage. This fact, coupled with evidence that renal damage can precipitate cardiovascular damage, reinforces the importance of targeting early renal disease with appropriate therapy in order to reduce the prevalence of cardiovascular disease. As succinctly summarized by de Zeeuw et al., we should "treat the kidney to protect the heart" [25] or, better, we should treat them both at once, as a logical and clinical unit. Clinical studies demonstrating sustained efficacy and tolerability identify ARBs as a rational choice of antihypertensive therapy for the prevention of stroke, chronic heart disease, and target-organ damage in a wide range of patients. Furthermore, several large-scale, prospective controlled trials revealed that ARBs simultaneously confer both cardiovascular and renal protective effects, beyond their ability to lower BP. By utilizing the large body of accumulated evidence, practitioners can deliver meaningful benefits to their patients in terms of survival, prognosis, and quality of life.

References

1. Sarnak MJ, Levey AS, Schoolwerth AC et al (2003) Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation 108:2154–2169

2. Hillege HL, Janssen WM, Bak AA et al (2001) Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. J Intern Med 249:519–526
3. Elliott WJ (2000) Therapeutic trials comparing angiotensin converting enzyme inhibitors and angiotensin II receptor blockers. Curr Hypertens Rep 2:402–411
4. Brenner BM, Cooper ME, Zeeuw D (2001) Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 345:861–869
5. Lewis EJ, Hunsicker LG, Clarke WR (2001) Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 345:851–860
6. Keane WF, Brenner BM, Zeeuw D (2003) The risk of developing end-stage renal disease in patients with type 2 diabetes and nephropathy: the RENAAL study. Kidney Int 63:1499–1507
7. Lindholm LH, Ibsen H, Dahlof B (2002) Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet 359:1004–1010
8. Julius S, Kjeldsen SE, Weber M (2004) Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 363:2022–2031
9. Granger CB, McMurray JJ, Yusuf S et al (2003) Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. Lancet 362:772–776
10. Viberti G, Wheeldon NM (2002) Microalbuminuria reduction with valsartan in patients with type 2 diabetes mellitus: a blood pressure-independent effect. Circulation 106:672–678
11. Kidney Disease Outcomes Quality Initiative (K/DOQI) (2004) K-DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. Am J Kidney Dis 43(Suppl 1):S1-S290
12. Adamczak M, Gross ML, Krtil J et al (2003) Reversal of glomerulosclerosis after high-dose enalapril treatment in subtotally nephrectomized rats. J Am Soc Nephrol 14:2833–2842
13. Parving HH, Lehnert H, Bröchner-Mortensen J et al (2001) The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. N Engl J Med 345:870–878
14. Aranda P, Aranda FJ, Frutos MA et al (2004) Comparative long-term renoprotective effects of usual versus high dose of telmisartan in nondiabetic nephropathies. J Hypertens 22(Suppl 2):S81-S82
15. Andersen S, Brochner-Mortensen J, Parving HH (2003) Kidney function during and after withdrawal of long-term irbesartan treatment in patients with type 2 diabetes and microalbuminuria. Diabetes Care 26:3296–3302
16. Ruggenenti P, Fassi A, Ilieva AP et al (2004) Preventing microalbuminuria in type 2 diabetes. N Engl J Med 351:1944–1951
17. Dickstein K, Kjekshus J (2002) Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial – Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet 360:752–760
18. Pitt B, Poole-Wilson PA, Segal R et al (2000) Effect of losartan compared with cap-

topril on mortality in patients with symptomatic heart failure: randomised trial – the Losartan Heart Failure Survival Study ELITE II. Lancet 355:1582–1587
19. Cohn JN, Tognoni G (2001) A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. N Engl J Med 345:1667–1675
20. Pfeffer MA, Swedberg K, Granger CB et al (2003) Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. Lancet 362:759–766
21. Pfeffer MA, McMurray JJ, Velazquez EJ et al (2003) Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med 349:1893–1906
22. Pitt B, Segal R, Martinez FA et al (1997) Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). Lancet 349:747–752
23. McMurray JJ, Ostergren J, Swedberg K et al (2003) Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 362:767–771
24. Yusuf S, Pfeffer MA, Swedberg K et al; CHARM Investigators and Committees (2003) Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet 362:777–781
25. de Zeeuw D, El Nahas AM (2005) Albuminuria, a new target for therapy: treat the kidney to protect the heart. In: El Nahas AM (ed) Kidney Diseases in the Developing World and Ethnic Minorities. Marcel Dekker, New York

Lercanidipine, Enalapril, and Their Combination in the Treatment of Elderly Hypertensive Patients

Juan Garcia Puig[1], Carlos Calvo[2], Olavi Luurila[3], Harri Luurila[3], Sakari Sulosaari[4], Arto Strandberg[4], Cristina Ghezzi[5]

Introduction

Several trials have shown that hypertensive patients whose blood pressure (BP) is brought under control (< 140/90 mmHg) have significantly fewer cardiovascular events than patients whose BP remains uncontrolled [1]. However, despite the availability of multiple antihypertensive drugs, BP is difficult to control, especially systolic BP and in elderly patients [2]. In most clinical trials aimed at controlling BP, more than two antihypertensive drugs are almost always required. The importance of combination therapy has been emphasized in current guidelines [3]. Adding a second antihypertensive drug may be a better option in non-controlled patients than switching to a different drug or increasing the dose of the first compound.

Aim

In this study, we tested the hypothesis that combination therapy with lercanidipine [4], a lipophilic dihydropyridine calcium antagonist with long duration of action, and enalapril [5] is more effective than either drug alone in reducing 24-h systolic BP in hypertensive elderly patients.

Methods

Patients aged 60–85 years with an office systolic BP (SBP) of 160–179 mmHg, an office diastolic BP (DBP) < 110 mmHg and a mean daytime SBP > 135 mmHg

[1]La Paz University Hospital, Madrid; [2]Hospital Clinico Universitario, Santiago de Compostela, Spain; [3]Kaisaniemen Lääkariasema Oy, Helsinki; [4]Keravan Lääkärikeskus, Kerava, Finland; [5]Medical Department, Recordati S.p.A., Milan, Italy

were included in the study. Patients with severe hypertension, diabetes mellitus, or prior cardiovascular events were excluded because the study design involved the administration of placebo for 4 weeks.

This was a randomized, double-blind, placebo-controlled, four-way crossover study, balanced for first-order carry-over. Four centers participated, two in Finland and two in Spain. After a 2-week run-in period, eligible patients were randomly assigned to receive a 4-week treatment with placebo (P); lercanidipine 10 mg (L); enalapril 20 mg (E); and a combination of the two drugs (L/E). All patients were scheduled to receive one of the four treatments. Double-blind medications were taken once-daily in the morning. At the end of each treatment period, office trough (24 ± 2 h post-dose) sitting blood pressure was measured. A 24-h ambulatory blood pressure monitoring (ABPM) was obtained on the last day of drug intake.

The primary efficacy parameter was the mean reduction in 24-h SBP of active treatment vs placebo. The 24-h SBP was chosen as the primary efficacy variable since the mean 24-h BP is the most solid information provided by ABPM.

Results

Of the 103 patients who were screened, 75 patients (40 males, 54%) with a mean age of 66 years were randomized to the study. Of these 75 patients, 71 received P, 69 L, 70 E and 72 L/E. The intention to treat (ITT) population consisted of 72 patients of which 62 patients completed the four ABPMs foreseen after randomization. Mean seated office BP was 168/92 mmHg. Mean baseline 24-h SBP was 151 mmHg. The administration of P, L, E and L/E was associated with a mean 24-h SBP of 144, 137, 133, and 127 mmHg, respectively (Fig. 1). Compared to the mean 24-h SBP reduction observed with P, active antihypertensive therapy significantly decreased the mean 24-h SBP by a mean of 8.2 (L), 12.9 (E), and 17.9 (L/E) mmHg ($p < 0.0001$ compared to 24-h SBP with P). Office BP values were similarly reduced. A seated SBP < 140 mmHg was recorded in 11% (P), 18% (L), 23% (E), and 48% (L/E) of the patients, and a seated BP < 140/90 mmHg in 8% (P), 18% (L), 19% (E), and 45% (L/E) of the patients.

Two patients on P and two on L/E were withdrawn from the study. Adverse events were recorded in 9% (P), 12% (L), 16% (E), and 14% (L/E) of the patients.

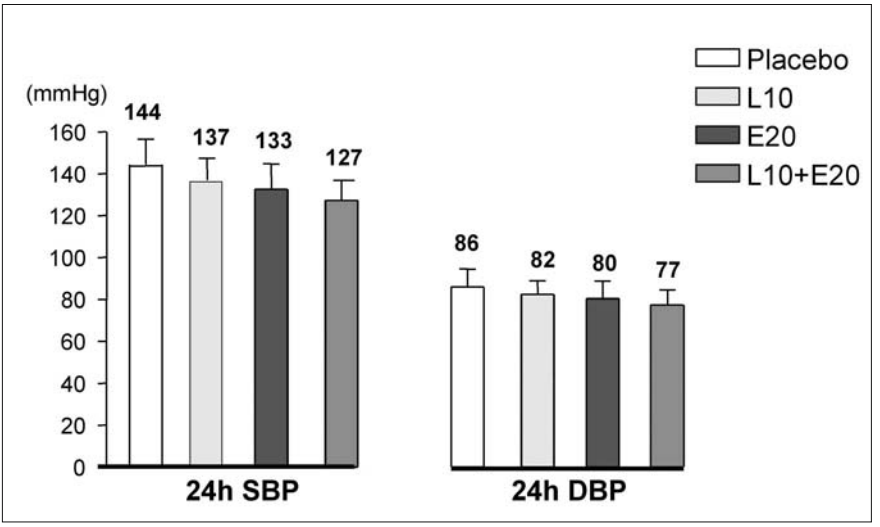


Fig. 1. Mean 24-h blood pressure. *SBP*, Office systolic blood pressure; *DBP*, office diastolic blood pressure; *L*, Lercanidipine (10 mg); *E*, enalapril (20 mg)

Conclusions

This study showed that in elderly hypertensive patients combination therapy with L/E is significantly more effective than either placebo or the two monotherapies in reducing ambulatory and clinic systolic and diastolic BP. The finding that combination therapy with enalapril and lercanidipine decreased 24-h BP by a mean of 17.9/9.2 mmHg supports the JNC 7 recommendation to initiate therapy with two agents in patients whose BP is > 20 mmHg above the SBP goal or > 10 mmHg above the DBP goal [3]. In fact, combination therapy with L and E was associated with a BP < 140/90 mmHg in 45% of the patients and monotherapy with L or E in < 20% of the patients. Since a prompt reduction of BP values is associated with a significant reduction in the number of cardiovascular events [6], the achievement of BP values < 140/90 mmHg within a 4-week period may be of substantial benefit.

Acknowledgements
The study was presented in abstract form at the XVI European Meeting on Hypertension (J Hypertension 2006, 24(Suppl 4):S420). The study was supported by a grant from Recordati S.p.A. Milan, Italy

References

1. Benetos A, Thomas F, Bean KE, Guize L (2003) Why cardiovascular mortality is higher in treated hypertensives versus subjects of the same age, in the general population. J Hypertens 21:1635–1640
2. Mancia G, Grassi G (2002) Systolic and diastolic blood pressure control in antihypertensive drug trials. J Hypertens 20:1461–1464
3. Chobanian AV, Bakris GL, Black HR et al (2003) The seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure. JAMA 289:2560–2572
4. Borghi C (2005) Lercanidipine in hypertension. Vasc Health Risk Manag 1:173–182
5. Todd PA, Goa LG (1992) Enalapril: a reappraisal of its pharmacology and therapeutic use in hypertension. Drugs 43:346–381
6. Julius S, Kjeldsen E, Weber M et al (2004) Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. Lancet 363:2022–2031

Subject Index

Ablation 8, 20, 23–25, 29–31, 33, 34, 41, 43–47, 49–53, 57–61, 63, 66, 68, 69, 76–78, 82, 83, 94–95, 111, 326, 328, 399, 434
Acute coronary syndrome 355, 360, 375, 384, 385, 387
Acute heart failure 125–127
Age and sex dependency 342
Ambulatory monitoring 159, 417, 422
Angioplasty 58, 206, 376, 383–385
Antiarrhythmic drugs 4, 5, 8, 13, 18–21, 23, 24, 43, 76, 87, 227, 229, 257, 260, 265
Anti-interference protection 319, 320
Application 46, 61, 76, 129, 160, 218, 299, 311, 344, 352, 375, 379
ARBs 106, 246, 426–430, 434–438
Arrhythmias 18, 19, 23, 24, 45, 46, 67, 93, 94, 109, 111, 160, 161, 173, 179, 180, 182–184, 186, 201, 206–208, 216, 218, 223, 240–242, 245, 247, 255, 257–258, 260, 261, 265, 266, 270, 355, 357–360, 365–369, 392
Arrhythmogenic heart diseases 365
Atrial arrhythmias 67, 241, 359
Atrial fibrillation 3, 11, 17, 19–21, 23, 24, 33, 41, 43, 44, 49, 54, 57, 63, 64, 75, 78, 79, 82, 83, 87, 93, 107, 108, 113, 122, 127, 138, 147, 169, 172, 191, 240–242, 247, 250, 297, 310, 317, 326, 327, 332, 359, 360, 366–368, 399, 400, 429, 430
Atrial flutter 11–13, 19, 23, 29, 41, 93, 240
Atypical atrial flutter 41
AV block 64, 106, 119, 161, 250, 280, 281, 288, 290, 291, 295, 310, 311, 322, 325, 328
AV node ablation 69, 326, 328

Blood pressure management 417
Brugada syndrome 94, 217, 255, 257, 368

Capture surveillance 320
Cardiac function 33, 281, 294, 328
Cardiac resynchronization therapy patients 125
Cardiac surgery 25, 32, 41, 42, 296, 391, 392, 395, 396, 399, 403
Cardiomyopathy 25, 29, 94, 111, 169, 173, 175, 180–182, 184–186, 191, 197, 199–201, 206, 215–217, 227, 258, 263, 358, 366
Cardiovascular disease 4, 89, 407, 417, 419, 425, 429, 430, 433, 434, 438
Cardiovascular risk 210, 369, 376, 407–411 414, 415, 419, 425, 426, 429, 433, 434, 438
Carotid sinus syndrome 145, 148, 153, 155
Catecholaminergic polymorphic ventricular tachycardia 255, 257, 367
Catheter ablation 3, 7, 11, 23–26, 30–33, 41, 42, 44, 45, 76, 94, 95, 111, 399
Cavotricuspid isthmus 23, 24, 26, 30, 41
Competitive athletes 93–95
Continuous monitoring 126, 283
Contractility 120–123, 132, 134, 135, 288, 289, 295, 298, 299, 304, 305, 311, 317, 318
Coronary care unit 355
Cost-effectiveness 30, 38, 263–271, 408, 409
Cryoablation 45, 46

Delay optimisation 120
Diabetes 172, 207, 333, 377, 378, 384, 407, 409, 411, 413–415, 426–430, 433–435, 442
Diagnosis 30, 58, 60, 61, 102, 103, 114, 126, 133, 146, 148–150, 153, 159–162, 202, 258, 288, 345, 365, 367, 368, 392, 414, 417, 418, 420
Drug eluting stent 386
Dual cardioverter defibrillator 79, 80
Dual chamber device 239–241

Dyslipidemia 409, 411, 413, 414

Echocardiographic examination 392, 393
Echocardiography 58, 60, 117, 120, 121, 123, 138, 296, 297, 310, 311, 398
Elderly patients 89, 146, 331, 332, 334–336, 383–386, 397, 422, 436, 441
Electrocardiogram (ECG) 29, 145, 347, 356
Electrocardiographic monitoring 12
Electrocardiographic risk stratifiers 370
Epidemiology 205, 408

Flecainide 5, 8, 11–13, 19–21, 368
Forensic pathology 199
Functional status 111, 113, 132, 182, 216, 218, 328, 333

Guidelines 3, 7, 14, 20, 24, 25, 81, 101–104, 108, 110–114, 147, 153, 157, 182, 192, 205, 207, 211, 215–218, 250, 260, 263, 271, 341, 345, 375–379, 381, 385, 387, 409, 410, 418–420, 425, 428, 429, 441

Heart failure 5, 25, 43, 63, 66, 69, 75, 76, 88, 101–104, 109, 111, 113, 117, 119, 125–127, 129, 137, 140, 167, 173, 181, 185, 187, 191, 200, 206, 218, 227, 234, 241, 245, 247, 261, 266, 267, 272, 279, 282, 294, 295, 297, 298, 303, 309, 310, 326, 332, 356, 357, 359, 378, 379, 427, 428, 430, 434
Heart rate turbolence 167, 358
Heart rate variability 130, 167, 207, 357
Hemodynamics 240, 293–294, 296, 298, 300, 304, 309, 310, 313, 325–326
Hypertension 14, 89, 333, 370, 392, 401, 407–410, 413, 415, 417–422, 426, 427, 429, 430, 433–435, 442, 443

Implantable cardioverter defibrillator 79, 109, 179, 192, 201, 239, 245, 263
Inappropriate therapies 240, 247
Indications 24–26, 80, 89, 90, 129, 147, 148, 192, 215, 217, 218, 234, 240, 241, 246, 250–252, 263, 279, 294, 303, 306, 326, 331, 386, 387, 392, 397, 403, 420
Intrathoracic impedance 126, 132, 137, 138, 141, 303
Ischemic mitral regurgitation 391, 392

Long QT syndrome 183, 317, 255, 367

Loop recorder 149, 153, 155, 159–162

Magnetic resonance imaging 44, 58, 347
Mapping systems 44, 59
Midcab 398, 401, 402
Middle-aged 95
Minimally invasive cardiac surgery 397
Mitral valve 122, 134, 295, 396, 400, 402
Monitoring 12, 25, 120–123, 125–127, 131, 135, 137–140, 145, 147, 159–162, 172, 173, 175, 194, 223, 226, 240, 258, 283, 303, 306, 307, 313, 335, 398, 417–420, 422, 442
Mortality 4, 20, 43, 75, 79, 82, 87, 88, 101, 109–111, 113, 114, 125, 126, 131, 137, 140, 169, 172–173, 179–181, 184–186, 191, 197–201, 206–209, 215, 216, 218, 235, 241, 245–247, 252, 263–269, 272, 297, 298, 325, 334, 335, 356–358, 269, 377, 378, 383, 384, 393, 395, 407, 422, 425–430, 436–438
Myocardial infarction 75, 89, 106, 107, 111, 168, 172, 179, 180, 216, 247, 266, 269, 296, 333, 334, 341, 342, 345, 247–352, 355, 370, 375, 378, 385, 391, 392, 429, 437, 438

3D Navigation 44
Neuromediated syncope 145
New developments 3, 44, 376
Normal limits 342, 343

Off-pump 396, 398, 401

Pacemaker 41, 63, 64, 66, 77, 78, 82, 106, 131, 132, 147, 149, 150, 155–157, 159, 167, 281, 283, 288–291, 294, 295, 299, 307, 309–311, 313
Pacing 20, 61, 63, 64, 66–69, 77–79, 82, 83, 95, 109, 112, 113, 119–122, 138, 148, 150, 155, 174, 181, 183, 192, 218, 222, 240–252, 245–247, 248–252, 279–284, 286, 288, 290, 291, 293–300, 303, 304, 306, 307, 309–311, 313, 317–322, 325–328, 331–336
Peak endocardial acceleration 121, 134
Port–Access 396, 398, 399, 402
Predictors 89, 118, 172, 173, 185, 193, 227, 232, 327, 333–334, 355, 357, 360
Preload 295, 298, 299, 304–306, 311, 318
Prevention 24, 58–60, 63, 66–68, 75, 78, 79, 82, 109–111, 113, 157, 192, 193, 201, 205–211, 215–218, 232, 234, 241, 247,

255, 260, 261, 263, 266–269, 271, 272, 309, 385, 407, 408, 410, 411, 413, 425, 426, 429, 430, 434, 438
Propafenone 5, 8, 11–13, 19–21
Pulmonary vein ablation 76, 77, 82, 83

QT dinamicity 167, 173

Right ventricular pacing 66, 68, 69, 77, 78, 241, 249, 251, 252, 279, 281, 284, 286, 288, 290, 291, 295, 297, 326–328, 336
Risk stratification 167, 169, 174, 179, 182, 184–186, 191–193, 201, 211, 259, 269, 357, 358, 375, 377, 378, 401

Self-measurement 417, 418
Sensors 121, 123, 127, 129, 130, 132, 134, 135, 280, 281, 294, 298, 310, 317
Short QT syndrome 94, 217, 255, 257, 369
ST amplitude 342–344
Stereotaxis 46, 47
Substrate–based ablation 50
Sudden cardiac death 109, 111, 169, 179, 181, 191, 205, 217, 245, 259, 263, 267, 355–358, 365
Sudden death 18, 173, 179, 181, 183, 186, 191, 193, 197, 205–207, 209–211, 217, 235, 255, 257–260, 263, 266–268, 270, 298, 357, 367
Syncope 12, 14, 110, 145–150, 153–157, 159–132, 191, 193, 194, 200, 217, 258–261, 367

Transvalvular impedance 132, 283, 286, 288, 298, 304, 317
Trigger–based ablation 49, 50

Ventricular desynchronization 310, 311
Ventricular fibrillation 18, 109, 179, 191, 200, 201, 206, 216, 221, 222, 227, 231, 257, 264, 322, 355–356, 366
Ventricular tachycardia 45, 109, 162, 173, 179, 194, 200, 207, 216, 217, 229, 239, 255, 257, 264, 356, 357, 359, 366, 367

Printed in May 2007