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Psychological Factors and Cardiovascular Disorders

The Role of Stress and Psychosocial Influences

Leo Sher
Editor

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Preface

Psychological factors significantly affect the cardiovascular system and play an important role in the etiopathogenesis of cardiovascular disorders. For the past several decades attention to the psychosocial and behavioral factors in cardiovascular disease has increased significantly. Multiple lines of evidence suggest that psychosocial factors contribute significantly to coronary heart disease as evidenced by data relating risk to depression, anxiety, personality factors and character traits, social isolation, and chronic life stress. When psychosocial stresses tend to cluster together, risk for cardiac events is often substantially elevated, equaling or exceeding that associated with standard biomedical risk factors for coronary disease such as hypertension and hypercholesterolemia. Understanding the integration of the interactions among multiple psychological and biological factors in the regulation of the cardiovascular system and the development of cardiovascular disorders is an important challenge for future research. I hope that this book will contribute to this goal. The contributors to this book are the leading international experts in the field of the relation between psychological processes and cardiovascular disorders. I would like to acknowledge and thank all the contributors. My task as the editor was greatly facilitated by their swift and positive response to my initial inquiry, and thereafter by producing their manuscripts diligently. I believe that this book will be of interest to clinicians, researchers, and the general public. This book is dedicated to the Memory of my Parents, Ivetta Sher (1927-2007) and Aleksandr Sher (1926-2008).

Leo Sher
May 2008

Chapter 1 - The relationship between the heart and brain has been a topic of interest since the earliest stages of psychological inquiry. As neuropsychological and cardiovascular assessment techniques have improved over the past century, so too has our understanding of the interconnections between cardiovascular health and neurobehavioral function. Cardiovascular health has a robust effect on cognitive function among adults, with associations at subclinical levels preceding the development of manifest cardiac disease. A graded relationship exists between increasing levels of cerebrovascular risk factors, markers of subclinical atherosclerosis, and cognitive performance. Although a multitude of pharmacological and surgical interventions are available to individuals at greater vascular risk, various vascular interventions may be associated with subtle cognitive decrements. The relationship between cardiovascular health and cognition may have important implications for the protection of neurocognitive function and the prevention of cognitive impairment and vascular dementia.

Chapter 2 - A body of evidence suggests that acute psychological stress can trigger acute cardiac events such as myocardial ischemia, acute coronary syndrome, apical ballooning syndrome, cardiac arrhythmias and sudden cardiac death. Psychological stress may provoke endogenous changes including biomechanical, prothrombotic, vasoconstrictive and proarrhythmic forces referred to as internal triggering mechanisms. These mechanisms may initiate the cardiac incident and/or favor its progression to a more severe clinical disease. Psychological factors also likely contribute to the increase in cardiac events associated with war, terrorist attacks, and natural disasters and may play a role in the major chronobiologic phenomena that affect cardiovascular diseases such as circadian, weekly and seasonal pattern. Complete elimination of psychosocial factors as potential triggers of cardiac events is not realistic. Successful management will probably include individually adjusted combination of medicamentous and other measures. Additional understanding of association between cardiovascular diseases and psychological factors may help in improving both prevention of triggering and treatment of acute cardiac diseases.

Chapter 3 - Both acute and chronic stress can be harmful for the cardiovascular system. Depression is also a risk factor for stroke. The positive effects of spiritual influences are outlined for their possible preventing effects. Religious attendance and prayer have been shown to reduce the mortality rate of cardiac diseases. Psychosocial factors should be considered in the delivery of care and the outcome.

Chapter 4 - Hypertension is a potent cardiovascular risk factor, thus the prevention and treatment of this condition is of major importance. Acute stress can induce transient increases in blood pressure and other psychosocial factors have been implicated in the development of hypertension. However, the effects of stress reduction interventions on cardiovascular outcomes have been inconsistent, thus the importance of psychosocial factors remains a matter of debate. One intriguing question that remains partly unanswered is why a similar level of stress exposure might lead to the development sustained hypertension in some individuals but not in others. Emerging evidence is beginning to demonstrate that the specific nature of the stressor, genetic factors, and behaviors such as sleep and physical activity may be important when considering psychological risk factors for hypertension.

Chapter 5 - Many clinical, epidemiological as well as animal studies bear out the participation of stress in the present proliferation of the cardiovascular diseases. In human

pathology the interaction with the environmental psycho-emotional or psychosocial stimuli represents the main part of the chronic stress origin. Activation of the sympathetic system plays a significant role in the cascade triggering the cardiovascular (CV) component of physiological reactions to different stimuli and situations, including stress response. On the other side sympathetic influences are associated with the alterations of function and structure of the heart and vessels including endothelial dysfunction and impairment of the local vasoregulatory mechanisms. There is a considerable variability in the CV stress responses due to genetic predisposition, postnatal development, different reactivity of the CV tissues, environmental risk factors, life style, pathophysiological processes, etc. Some contributions to this topic are reviewed in this paper.

Chapter 6 - The cardiovascular system is influenced by cognitive and emotional factors. Significant and novel stimulation promote bodily changes related to orienting and attention that in the cardiovascular system manifest themselves as heart rate decelerations. However, a more complex response appears when the stimuli are threatening. An intense noise elicits a heart rate response characterized by a pattern of short and long-latency accelerations and decelerations in alternating order, with the first, short-latency acceleration related to vigilance and orienting, and the second, long-latency acceleration, related to defence. This cardiac pattern quickly habituates and is modulated by the emotional context. Complex stimuli, like pictures, promote a triphasic wave response, with an initial deceleration followed by acceleration, and a final long deceleration. However, when phobic subjects are exposed to pictures related to their fear, the pattern changes to acceleration, reflecting the defence response promoted by these stimuli. Data coming from animal and human research on the neural bases of fear have identified the cerebral amygdala as a key structure that detects and responds to threatening stimuli. This structure modulates the behavioural and motor responses, as well as the cardiac and other physiological reactions to those stimuli.

Chapter 7 – The authors primary objective in this chapter was to review work regarding the association between stressors and cardiovascular disease (CVD) and examine scientific rationale behind this proposed link. Stress is a heuristic term often overused to describe many psychological anomalies. They attempt to narrow this definition of stress to one of biosocial synergy, encompassing various types of chronic and traumatic stressors, individual perception, and physiological responses. Given this conceptual basis, the authors describe relevant physiological pathways associated with stress and subsequent disease, focusing on the hypothalamic-pituitary-adrenal axis (HPA) and cortisol. A further specific discussion of stress, trauma stress (e.g., posttraumatic stress disorder), and CVD is provided. Lastly, they provide a discussion of the cardiovascular consequences of exposure to stressors in populations considered at high risk: caregivers, medical professionals, air traffic controllers, firefighters, and police officers.

Chapter 8 - The relation between stress and coronary diseases is controversial. Positive and null or negative results are almost equally obtained. An explanation of this can be that the most widely used stress questionnaires are not able to collect all the factors that constitute stress perception in different socio-cultural contexts. Indeed, from a clinical and experimental perspective the relation between breakdown in adaptation and cardiovascular disorder is a fact. More consistent results on the social, cultural and psychological determinants of an increased cardiovascular risk are obtained when stress is studied in relation to the socio-

economic condition of groups and individuals. To better embrace and describe the social factors, a new theoretical contribution has been introduced: social capital. This is a more sophisticated version of social cohesion, social integration and social support. For the future, an interdisciplinary approach is recommended in health surveillance of life and work environmnent.

Chapter 9 - Elaborating the reactivity hypothesis about the development of cardiovascular disease we posit that performance conditions having strong consequences for individuals' self-definitions and self-esteem can provide a severe health risk. Based on a recent application of motivational intensity theory to self-relevant performance conditions the authors argue that such performance conditions justify the mobilization of high resources for active coping. The result is high effort when self-relevant demands are difficult or individuals try to do their best in active coping. Given the systematic link between resource mobilization and cardiovascular reactivity, this leads to strong cardiovascular reactivity under these conditions, which in turn promotes the development of hypertension and cardiovascular disease. The results of a recent series of studies are discussed.

Chapter 10 - A long-standing research program in my laboratory has concerned the determinants and cardiovascular (CV) consequences of task engagement in people confronted with performance challenges. One focus has been on the manner in which ability perceptions impact engagement and CV response outcomes and this has evolved recently into an interest in how fatigue impacts these outcomes. The authors ability reasoning implies that fatigue should have potential for augmenting engagement and CV responses, retarding them, or leaving them unchanged, depending on the difficulty of the challenge at hand. The implication is supported by data from a variety of studies and suggests that chronic fatigue may increase health risk under some performance conditions.

Chapter 11 - Cardiovascular diseases are strongly linked to adverse lifestyle behaviors, psychosocial stress, and some mental disorders associated with modern Westernized societies. These diseases are accompanied by obesity, diabetes, and cancer in developing societies and among indigenous peoples "transitioning" into modern urban centers. This chapter explores pathogenic cultural influences which engender psychosocial dysfunction (e.g., chronic stress, constant time pressure, anxiety, depression, hopelessness) and increase cardiovascular disease and coronary artery disease risk factors (e.g., inactivity, unhealthy diet, tobacco use). Because overt signs of cardiovascular disease show up late—in advanced stages—and since research indicates that such degenerative disease first begins developing in adolescence, comprehensive prevention programs aimed at children and implemented at the national level are strongly advocated by the World Health Organization. To implement such programs at the national level is to engage in cultural change: therefore solid prevention planning can benefit from medical-anthropological and critical ethnographic investigation into the role of culture-syntonic (i.e., what seems normal but is pathogenic) influence on disease process in modern Western societies, bringing them into more explicit awareness and thereby rendering them culture-dystonic (i.e., perceived as pathogenic and needing to be changed).

Chapter 12 - Psychosocial stress experienced by Africans during urbanization is associated with socio-cultural disruption and concomitant increases in risk factors for non-communicable diseases. Social and psychological resources are necessary to successfully

cope with transitional changes or demands. An innate ability to resist or cope with psychosocial stress/urbanization may be seen in the negative effect of stress in the body, i.e. psychological distress, hypertension and the physiological dissociation/habituation of a specific coping style.

Chapter 13 - Central nervous system (CNS)/cardiac interactions in cardiac and epileptic patients are examined for sudden death risk factors, including arrhythmias, respiratory (hypoxia) and psychological (stress) factors. Possible overlapping risks of sudden unexpected death for epilepsy (SUDEP) and cardiac disease are examined. Interactions between the CNS, peripheral autonomic nervous and cardiopulmonary systems are explored. Potential interactions of subtle genetic arrhythmogenic risk factors predisposing to seizure related arrhythmias are discussed. We speculate about preventive measures to minimize the risk of SUDEP and sudden cardiac death. While cardiac and psychiatric patients, and certain ethnic groups, are at risk for stress related unexpected sudden death, stress as a risk factor for SUDEP is unexplored. The impact of emotional states on autonomic control of cardiac rhythm is an important factor in cardiac dysrhythmias. The association of epilepsy with neurogenic arrhythmias, microscopic perivascular and interstitial fibrosis, and with depression and anxiety indicates that emotional stress may be a potential risk factor for SUDEP. The role of emotion in increasing the risk of seizure occurrence indicates a need to study stress management intervention in helping to prevent seizures. Clarification of risk factors and the mechanisms will help to prevent SUDEP in patients unable to achieve seizure control. Patients with epilepsy should be encouraged to use life style modifying interventions that have preventive medical benefits even if there is as yet no consensus that these help prevent sudden death. Other animal and clinical studies are needed to address the roles of Omega-3 fatty acids, cold temperatures, exercise, and heart rate in cardiac arrhythmias and/or SUDEP.

Chapter 14 - The major risk factors for coronary heart disease (CHD) include smoking, hypertension, dyslipidemia, diabetes mellitus, a strong premature family history, as well as metabolic syndrome, and obesity. Sedentary lifestyle and poor physical fitness are generally considered to have adverse affects on many of these established CHD risk factors, but may also independently increase the odds of CHD. Although the importance of psychosocial risk factors in the development and expression of CHD and atherosclerosis has been debated for many decades, substantial evidence now exists that many components of psychological distress, especially depression, anxiety, and hostility, are also significant CHD risk factors that may also adversely affect recovery following major CHD events.

Chapter 15 - The implantable cardioverter defibrillator (ICD) has been shown in clinical trials to achieve significant mortality reduction for both primary and secondary prevention applications in patients at risk for potentially life threatening arrhythmias. Psychosocial challenges for patients and families may present themselves in the forms of specific device related apprehension, anxiety and depression, and/or quality of life concerns. The purpose of this chapter is to review common patient concerns and the assessment and treatment approaches for consulting clinicians to assist ICD patients. The empirical basis for device specific approaches continues to evolve and utilization of multi-disciplinary care teams appear warranted.

Chapter 16 - Psychological stress and depression have for some time been recognised as playing an important role in the etiology of coronary heart disease and for over thirty years the notion of risk factors has played an ever increasing role in estimating the probability of this disease and its sequela. There appears to be little debate as to stress being categorized as a risk factor. What appears to be at issue is the relative importance of stress and depression compared to both traditional and other risk factors for coronary heart disease, and whether new risk factors are even needed, given the current protocol for risk assessment which is periodically updated to reflect new study results and is currently undergoing recalibration outside North America.

This chapter will examine the current debate over the need for employing new risk factors, evidence that the currently used protocol for risk assessment appears less than ideal, and that the addition of new risk factors or an entirely different approach may have considerable merit, with psychological stress being a prime example. The discussion will include research that attempts to position psychological stress in the hierarchy of coronary heart disease risk factors and in addition, the role of stress in the development of atherosclerosis and as well as the apparent failure of the traditional risk factors to account this critical aspect of coronary heart disease.

Chapter 17 - Coronary heart disease (CHD) is the leading cause of death in the world. Women are as much at risk to suffer from CHD as men. Because treatment modalities have improved and lead to better survival of cardiac patients, the number of patients who need continuous care has increased substantially. Thus cardiac rehabilitation and secondary prevention have grown to be more and more important in healthcare.

Women are about ten years older at the onset of CHD and they display more coronary risk factors, a lower functional capacity, greater disease severity at first diagnosis, more concomitant diseases and higher psychological distress than men. Women also differ from men in their reactions and coping behaviors. After MI they do not cope as well as men both physically and psychosocially. They experience more depressive symptoms and have more problems to be compliant, to attend cardiac rehabilitation programs or to maintain exercise training. Depression, lack of social support, stress from work and family additionally worsen women’s outlook after an acute event of CHD. Women are at high risk because of their more common stressors, but also because the stressors convey a higher cardiac risk. In addition to the stressors which are relevant for men, the experience of stress from family ties is highly relevant in women. In fact in study groups, where women are gainfully employed to the same extent as men are, emotionally stressful marital relationships were found to worsen the prognosis and accelerate progression of CHD in women patients. However, women who experienced both work and family stress had the highest risk.

Cardiac rehabilitation has proved to be a useful tool in the treatment of coronary heart disease in women as in men. Given the beneficial effects it has even for women of higher age and with greater disease severity and functional limitations, women should be more strongly encouraged to take part in cardiac rehabilitation programs and the programs should be designed to meet their needs.

Chapter 18 - Background: Intracardiac catheterization is a routine physical examination. Due to psychological strains, several psychosocial interventions, including music therapy, have been proposed. The aim of the present study was to examine whether the preventive or

adjuvant use of music therapy results in a reduction in both subjective and objective anxiety and thus leads to a reduction in sedative medication. Methods of Assessment: N = 83 patients (48 male, 35 female, 66 ± 11 yrs) waiting for scheduled cardiac catheterization were randomly allocated to a control group (standard care), an exposure group (music stimulation during the procedure), or a coaching group (additional music therapeutic coaching in advance of the procedure). Target variables were subjective anxiety, physiological parameters and medication. Results: Music intervention did effectively reduce subjective anxiety. Physiological values and medication did not differ between groups. Conclusion: The use of music stimulation during the catheterization has a relaxing and calming effect on patients. It seems to be extra beneficial in a subgroup of patients with higher-than-average psychological strains. Physiological parameters and medication were not influenced by music therapy. Some limitations of the study and future prospects (e.g. use of music therapy in secondary prevention) are highlighted.

Chapter 19 - Researchers continue to report significant links between CVD and affective disorders. Recently, these links have been provided with plausible explanations in the context of psychosocial stress. Psychosocial stress is firmly identified as a factor contributing to CVD, and the same stress-response axes are engaged regardless of whether the stress arises from primarily physiological causes or from psychological causes such as depression and anxiety. Furthermore, an effective approach to stress reduction and psychological health, the Transcendental Meditation technique, is reported to reduce risk factors for CVD and to mitigate symptoms of established CVD. A thorough understanding of the nature and purpose of this technique and how it relates to psychosocial stress may shed light on the mechanisms underlying its CVD preventive and mitigating effects. The avowed purpose of the Transcendental Meditation technique is to facilitate the natural experience of a fourth state of consciousness, referred to as “transcendental” or “pure” consciousness, in which the thinking process is transcended and consciousness is left alone. Experience of this state is understood to have holistic normalizing effects on mind and body and to promote growth to yet higher states of consciousness. The normalization of adaptive systems distorted by chronic stress appears to be one of the transformative results of experiencing transcendental consciousness. These improvements in the functionality of critical adaptive systems may underlie the observed gains in physiological and psychological health, including the observed reductions in CVD risk and improvements in quality of life.

Chapter 20 - Hundreds years ago, people knew about the relation between emotions and the heart. Most ancient cultures felt the heart was the seat of emotions because it reacted via its heart rate depending on the emotional state of the person. The effect of emotions on the pulse is well documented in the writings of celebrated physicians such as Galen and Avicenna. During the Renaissance, there occurred a renewed interest in the cause and effect of natural phenomena. Important development in studies of the relation between psychological factors and cardiovascular disease took place in the first part of the 20^{th} century. For the past several decades attention to the psychosocial and behavioral factors in cardiovascular disease has increased significantly. As evidence has clarified how psychological factors affect the cardiovascular system, it is time now to focus on treatment interventions. It is to be hoped that the efforts of clinicians and researchers to prevent and to treat cardiovascular disorders related to psychological factors will be successful.

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Chapter 1

Neurobehavioral Functioning and Cardiovascular Disease

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Abstract

The relationship between the heart and brain has been a topic of interest since the earliest stages of psychological inquiry. As neuropsychological and cardiovascular assessment techniques have improved over the past century, so too has our understanding of the interconnections between cardiovascular health and neurobehavioral function. Cardiovascular health has a robust effect on cognitive function among adults, with associations at subclinical levels preceding the development of manifest cardiac disease. A graded relationship exists between increasing levels of cerebrovascular risk factors, markers of subclinical atherosclerosis, and cognitive performance. Although a multitude of pharmacological and surgical interventions are available to individuals at greater vascular risk, various vascular interventions may be associated with subtle cognitive decrements. The relationship between cardiovascular health and cognition may have important implications for the protection of neurocognitive function and the prevention of cognitive impairment and vascular dementia.

Introduction

A 2007 report by the American Heart Association in 2007 [1] estimated that one out of three Americans, or 79,400,000 individuals, have at least one type of cardiovascular disease (CVD). CVD is associated with 2,400 deaths per day, the equivalent of one death every 36 seconds [2]. Although the relationship between clinical manifestations of CVD (e.g., stroke, myocardial infarction,) and gross cognitive impairment has been recognized for decades, a

growing body of evidence indicates that even subclinical levels of CVD may be associated with impaired neurobehavioral functioning [3].

This chapter has been divided into six sections: 1) CVD risk factors (hypertension, cholesterol, diabetes, obesity, and the metabolic syndrome); 2) markers of atherosclerosis (including subclinical markers of vascular health, such as intima media thickness, pulse wave velocity, and flow mediated dilation); 3) clinical manifestations of CVD (such as peripheral vascular disease, coronary heart disease, and electrocardiogram abnormalities); 4) common cardiac medications (such as beta blockade); 5) neurocognitive sequelae following cerebrovascular events; and 6) neurobehavioral outcomes associated with cardiac surgery (valve replacement, carotid endarterectomy, and coronary artery bypass grafting).

Neurocognitive Correlates of Cardiovascular Risk Factors

Diabetes Mellitus

The global prevalence of established diabetes mellitus (DM) was estimated to be 2.8% in 2000 and is projected to be 4.4% by 2030 [3]. From 1992-2002, the age-adjusted prevalence of DM increased 54% among U.S. adults [4, 5]. The presence of DM has been associated with poorer cognitive function [6], more rapid cognitive decline [7, 8], and a greater incidence of cognitive impairment [9]. Multiple cross-sectional studies have shown that individuals with either Type I or Type II diabetes demonstrate poorer cognitive performance compared with healthy controls [6]. Desmond and colleagues [10], for example, found that the presence of DM was associated with deficits on measures of abstract reasoning in a sample of 249 stroke-free older adults. Similarly, in a study of 1,300 community-dwelling individuals, aged 24 to 81 years, van Boxtel and colleagues [11] found a strong relationship between DM and poorer cognitive functioning on tests associated with abstract reasoning and visuospatial performance. Launer and colleagues [12] reported similar findings, noting that the presence of DM was associated with reduced scores on the Mini Mental Status Examination in 3,974 community-dwelling older adults.

Previous reviews have reported that the presence of DM was most consistently associated with poorer performance on tasks of memory, whereas cognitive tasks associated with frontal lobe functioning appeared to be spared [13]. These findings have generally been supported in more recent studies. Knopman and colleagues [14], for example, found that individuals with DM showed a more rapid decline on tests of psychomotor speed and executive function. Fontbonne and colleagues [15] also reported cognitive decline associated with DM, noting that DM was associated with more rapid decline on tests of memory, psychomotor speed, and executive function. Interestingly, the authors did not find significant differences between healthy individuals and those with impaired glucose functioning. In an examination of 9,679 community-dwelling Caucasian women, Gregg and colleagues [16] found that DM was associated with more rapid cognitive decline, particularly on tasks associated with psychomotor sequencing and executive function. More recent prospective studies have reported a different pattern of results, however. For example, Elias and colleagues [17]

reported that individuals from the Framingham study with non-insulin dependent DM showed greater rates of dysfunction on tests cognitive tests associated with visual memory. Furthermore, the duration of DM was associated with increased risk for lower performance on tests of verbal memory and concept formation.

A recent of review of the relationship between DM and cognition found that cognitive decrements in type II DM are most consistently observed on measures of verbal memory and processing speed, whereas preserved function is observed on measures of visuospatial, attention, semantic, and language function [18]. Furthermore, there is some evidence that deficits in cognitive function are associated with poorer glycemic control. Interestingly, the largest available prospective cohort study investigating the relationship between glycemic control and cognition failed to support this hypothesis, failing to find adverse effects of severe hypoglycemic events on cognition [19, 20].

Potential Mechanisms: Individuals with diabetes have an approximate three to five fold greater risk of experiencing a cardiovascular event compared with their non-diabetic counterparts [5]. Furthermore, previous cohort studies have demonstrated that impaired glucose tolerance is associated with an increased risk of vascular dementia [21]. The mechanism for this association may be related to the non-enzymatic glycation of lipoproteins in diabetic patients, which may enhance uptake of cholesterol by scavenger macrophages [22]. Alternatively, this may also lead to a prothrombotic tendency and anti-fibrinolytic state. The relationship between type-II diabetes and cognitive dysfunction is thought to be mediated by development of insulin resistance and impairment of beta cell function: both of which lead to hyperglycemia and subsequent vascular complications [23].

Recent population-based studies have demonstrated that the metabolic syndrome may be associated with leukoariosis, or increased white matter lesions, among otherwise healthy individuals. Park and colleagues [24] have demonstrated that the presence of metabolic syndrome factors, including DM, was associated with greater severity of leukoariosis in a roughly continuous fashion. Further, in examining the contributions of individual components, they noted that elevated blood pressure, impaired fasting glucose, and hypertriglycemia were all independently associated with an increased risk of leukoariosis. In addition to its association with white matter damage, recent evidence suggests that individuals with DM may exhibit reduced gray matter volume in the prefrontal cortex [25] as well increased medial temporal lobe atrophy [26], and this effect appears to be independent of other cardiovascular risk factors, such as hypertension [27].

Previous reviews among type I diabetics are also useful in elucidating the mechanisms by which DM impacts cognitive function [22]. In type I diabetics, both acute and chronic hypoglycemia predict poorer cognitive performance [22]. Acute periods of hyperglycermia may actually be associated with enhanced memory, as glucose is a substrate for acetylcholine, among other neurotransmitters. Chronic glucose elevations, however, have been associated with decreased acetylcholine synthesis in animal studies, as well as cortical neuronal loss. Chronic hyperglycemia induces biological toxicity through glycation of proteins, altered redox potential and signal transduction, and generation of reactive oxygen species [28, 29]. Based on previous findings, glycemic control appears to most strongly predict function on cognitive tasks that are dependent on the hippocampus and surrounding structures [30]. Hyperinsulinemia may act by different mechanisms [22]. For example,

elevated serum insulin levels can cross the blood-brain barrier and may cause a decrease in cholinergic transmission by down-regulation of their receptors in the hypothalamus and hippocampus. The primary hypothesized mechanism of action, however, is through hyperinsulinemia's association with atherosclerosis, as discussed in greater detail below.

Hypertension

It is estimated that nearly one in three adults has hypertension, defined as systolic blood pressure greater than or equal to 140 mm Hg or diastolic blood pressure greater or equal to 90 mm Hg, and nearly 40% have prehypertension, defined as casual blood pressure readings of 120-139/80-89 mm Hg [31]. Hypertension is one of the leading causes of disability in the world and is associated with incident coronary heart disease and stroke in a dose-response fashion [32-34]. Of the cardiac conditions described in this chapter, the association between hypertension and cognitive decrements has historically received the greatest attention.

Early evidence of the relationship between hypertension and brain function were published in the 1920's, when hypertensive encephalopathy was first recognized [35]. Recent studies have examining the relationship between hypertension and cognition have garnered greater attention as hypertension has been associated with greater incidence of mild cognitive impairment [36, 37], Alzheimer's disease (AD) [38-40] and Parkinson's disease [41], raising the possibility that hypertension may result in cortical damage above and beyond its association with white matter degradation [42].

Chronicity has been identified as a key moderator of the relationship between hypertension and reduced neurocognitive function. Accordingly, the most convincing studies demonstrating a relationship between high blood pressure and lower cognitive performance have come from longitudinal examinations out of the Framingham Heart Study. Elias and colleagues [43, 44], for example, have demonstrated that higher blood pressure levels are associated with poorer performance on the Wechsler Adult Intelligence Scale (WAIS). In a study of 1,702 unmedicated adults from the Framingham study, Elias and colleagues [45] found that both blood pressure levels and chronicity of blood pressure elevation were associated with poorer cognitive performance assessed biannually over a 5-year period. Moreover, Elias noted a graded relationship between reduced blood pressure levels and improved cognitive performance on a composite variable of attention and memory. These findings were replicated by Elias and colleagues in a sample of 1,695 stroke-free individuals assessed longitudinally [46]. Singh-Manoux and colleagues [47] reported similar findings in a longitudinal examination of 5,838 middle-aged adults from the Whitehall II study.

The combination of type II, or non-insulin dependent DM, and hypertension may be particularly detrimental to cognitive performance. Elias and colleagues [17] studied this relationship among Framingham participants, finding that both the diagnosis and duration of DM were prospectively associated with poorer performance on multiple neuropsychological measures. Similar findings were noted by Elias and colleagues [44] in a 19-year prospective study of Framingham participants. Elevated systolic blood pressure levels were associated with a decline in visualization-performance ability and speed. Further, when blood pressure was controlled in their growth curve analysis, the age-related decline in cognitive abilities

was partially attenuated, indicating that blood pressure levels may partially mediate the normal cognitive decline observed with age among healthy adults.

Other prospective studies have reported similar findings. Swan and colleagues [48], in a Western Collaborative Group Study, found that blood pressure assessed during middle age predicted lower levels of cognitive performance when participants were reassessed 25 to 30 years later. Furthermore, blood pressure was associated with self-reported dementia at this later follow-up. Similarly, in a longitudinal study of 717 participants from the Western Collaborative Group Study, Swan and colleagues [49] demonstrated that those individuals who showed consistently elevated blood pressure assessed in middle age and again thirty years later showed poorer verbal learning and memory performance than participants exhibiting normal blood pressure on both occasions. More recently, data from the Framingham Offspring Study have shown that high blood pressure and left ventricular mass, which often results from sustained elevations in blood pressure, were associated with poorer performance on various tasks of abstract reasoning [50].

The relationship between elevated blood pressure and cognitive dysfunction has been expanded in recent years to an investigation of incident Alzheimer's disease (AD), a disease previous thought to be largely the result of genetic predisposition. Recent reviews have found empirical support for the hypertension and AD association in later life [51], but few studies have investigated this relationship prospectively. Reitz and colleagues [37] examined the association between hypertension and the development of mild cognitive impairment, which may precede the development of AD. Among the 918 individuals free from mild cognitive impairment at baseline, those individuals with hypertension were significantly more likely to develop mild cognitive impairment and amnestic mild cognitive impairment at follow-up. Moreover, hypertension was related to the extent of executive function change, a cognitive domain thought to have the greatest vulnerability to blood pressure changes [52, 53].

There are several factors that may moderate the relationship between hypertension and cognitive performance [54]. As mentioned above, the chronicity of hypertension appears to be an important determinant of the extent of cognitive impairment, with longer duration of high blood pressure associated with greater impairments. Recent evidence suggests that gender may also moderate the relationship between hypertension and cognition. Waldstein and colleagues [55] found preliminary evidence for gender differences by demonstrating that, among older adults, hypertension was associated with poorer cognitive performance in multiple domains, but that this effect was stronger for women compared to men. In contrast, there was some evidence that the neurocognitive performance for men with hypertension was equivalent to their normotensive counterparts on tasks of working memory. Waldstein and colleagues have also noted age, education level, and hypertension status as potential moderators [56]. Although interesting, it is unclear whether these factors serve as moderators of the hypertension and cognition relationship in the larger population and the mechanisms for this association remain unclear.

Potential mechanisms: Approximately 95% of individuals with hypertension have elevated blood pressure without a definitive cause, which is referred to as *essential* hypertension. Blood pressure is largely determined by two factors: cardiac output and total peripheral resistance. From a systems perspective, both cardiac output and total peripheral resistance are determined by the function of three systems: the heart, blood vessel tone, and

the intravascular volume regulation by the kidney. Various regulatory mechanisms within these systems, such as baroreceptor reflexes, help to continually modulate the system. Despite the complexity underlying blood pressure regulation, there are several primary mechanisms by which hypertension may be associated with neurocognitive dysfunction.

Cerebral alterations underlying cognitive dysfunction may include vascular remodeling, impaired cerebral autoregulation, insults to the cerebral microvasculataure, white matter lesions, unrecognized lacunar infarcts, and Alzheimer-like changes such as amyloid angiopathy and cerebral atrophy. White matter lesions and retinal vascular changes, both of which can be imaged noninvasively, may reveal the general condition of the cerebral vasculature or the presence of arteriosclerotic or hypertensive encephalopathy [57]. Although age-related changes in cognition may be due, in part, to the associated changes in vascular and cerebral health discussed below, hypertension-associated changes in cognition have been reported among younger samples as well [58], indicating that hypertension mechanisms may confer poorer cognitive function independent of age.

Neuroanatomical changes associated with hypertension include an increased prevalence of hyperintensities in the periventricular and deep white matter. Notably, individuals with adequate hypertension management tend to exhibit fewer WMH [59]. Moreover, poorer blood pressure control has been associated with more extensive white matter pathology, cerebral atrophy, and ventricular enlargement [60]. Although many cross-sectional studies have demonstrated a relationship between hypertension and white matter hyperintensities, de Leeuw and colleagues [61] recently examined this data prospectively, demonstrating that higher blood pressure levels were associated with greater white matter hyperintensities. Consistent with previous findings, the duration of hypertension was a significant moderating factor and this effect was most pronounced among patients aged 60 years and above.

The association between hypertension and white matter damage may be observed even among individuals with more severe, diffuse white matter lesions. Lipohyalinosis is the predominating type of magnetic resonance imaging (MRI) lesion among individuals diagnosed with leukoariosis [62, 63], first identified by Fisher [64] in describing damage to the small arteries commonly observed among hypertensive patients [65]. The pathogenesis of white matter damage is complex, but appears to be initiated by arterial hypertension, which leads to smooth muscle proliferation with subsequent reduction of the lumen external diameter ratio and thickening of the vessel wall. According to experimental animal models, this may result in damage to the endothelial lining, resulting in thickening of the basal lamina and deposition in the vessel wall of amorphous eosinophilic material representing escaped plasma proteins [66]. Irregular lumen diameter eventually develops, most likely as the result of unequal resistance to weaknesses of the elastica and media [67].

Decreased cerebral blood flow and impaired metabolism have been observed in individuals with hypertension and this may differentially affect the frontal, temporal, and subcortical areas of the brain, which are particularly vulnerable to ischemia [68]. Functional imaging studies among individuals with hypertension indicate that cerebral blood flow may be reduced in these individuals. Hypertensive individuals show smaller cerebral blood flow responses during memory tasks [69]. This finding is not surprising given that hypertension may affect autoregulation of cerebral blood flow through its influence on vascular hypertrophy and vascular remodeling. This may lead to decreased vasodilation and hypoxia

of the cerebrovascular tissue. Furthermore, various cellular and neurochemical disturbances occur in the presence of hypertension. For example, ion-transport mechanisms may be disturbed, leading to increased intracellular sodium and calcium, thereby promoting hypertrophy and vasoconstriction. Central neurochemical systems including the catecholaminergic and serotonergic systems may also be disturbed.

Cholesterol

Data from several population-based studies indicate that approximately 30-60% of adults have high cholesterol [5], which is associated with a greater incidence of stroke [70]. Serum cholesterol is the main lipid constituent of neuronal membranes and myelin [71, 72] and although its role in the pathogenesis of atherosclerosis is well-known [73], cholesterol is also involved in the delivery of various nutrients to the brain [74]. The dual role that cholesterol may play in both preserving cognitive function through nutrient supply and lowering cognitive function through its association with atherosclerosis make it a particularly difficult cardiovascular risk factor to examine. The epidemiological literature has focused primarily on the relationship between cognitive function and total cholesterol (TC), although more recent studies have examined the relative concentrations of high-density (HDL-C) particles and low-density lipoprotein (LDL-C) particles.

Recent epidemiological studies found that have found higher levels of total cholesterol may be associated with poorer neuropsychological performance. Yaffe and colleagues [75] found that higher total cholesterol and LDL levels were associated with poorer cognitive performance and a greater likelihood of developing mild cognitive impairment. Similarly, Elias and colleagues [76] examined the association between total cholesterol and measures of abstract reasoning, attention/concentration, word fluency, and executive functioning, finding that higher total cholesterol was associated with lower performance across measures. Among middle-aged and young adults, multiple studies have reported similar findings. Kasl, Brooks, and Rogers [77], for example, found that intelligent quotients, school grades, and word generation performance was negatively associated with TC. Muldoon and colleagues [78] found that the Information and Vocabulary subtests from the WAIS were negatively correlated with total cholesterol in 177 healthy young adults. Conflicting results also exist, however. Benton [79], for example, found a positive association between total cholesterol and speed of mental processing.

Potential Mechanisms: Cholesterol may have dual influence on cognitive performance, both as a causal agent in the atherogenic process and as a necessary transporter of vitamins and other essential chemicals to the cerebral tissue [80]. Elevated LDL levels, for example, correlated closely with atherosclerosis development. In contrast, higher levels of HDL protect against atherosclerosis. The mechanism of this action is hypothesized to be HDL's ability to transport lipids away from peripheral tissue back to the liver for disposal [81]. Alterations in brain cholesterol homeostasis, such as that seen among individuals with elevated cholesterol levels, may also directly alter neurotransmission and synaptic plasticity [82]. In addition, higher LDL levels have been associated with greater oxidative stress, inflammation, decreased endothelial nitric oxide synthase, and reduced coronary blood flow [83].

Obesity

Approximately 50% of U.S. adults are either overweight or obese, although various rates have been reported [5, 84]. An emerging line of research suggests that obesity, particularly central adiposity, may be a risk factor for cognitive decline and dementia [84]. Elias and colleagues [85] examined the association between obesity and hypertension in a prospective study of 551 men and 872 women from the Framingham study, followed over an 18-year period. Among male participants, hypertension and obesity were associated with poorer cognitive performance, particularly on tasks of memory, and the presence of both risk factors had a cumulative effect on poorer cognitive performance. Notably, among middle-aged and elderly men in this sample, obesity and hypertension predicted poorer performance independently of other known risk factors, such as cigarette smoking, cholesterol, and DM.

Potential Mechanisms: The mechanisms by which obesity is associated with poorer cognitive function are poorly understood [29]. This relationship is primarily explained by the interrelationship between obesity, DM, and atherosclerosis, although somewhat different mechanisms of cerebral glucose regulation have been proposed [86]. Furthermore, studies investigating the association between obesity and cognition frequently draw their samples from populations of lower socioeconomic status, which is associated with other environmental factors that may influence this relationship.

Multiple Risk Factors

Few studies have investigated the relationship between multiple risk factors simultaneously to elucidate their individual contributions. Verdelho and colleagues [87] conducted such a study among 638 patients from the baseline assessment of the Leukoaraiosis and Disability in the Elderly Study (LADIS). Individuals aged 65-84 years with any evidence of age-related white matter changes were included in the study. Individuals with DM showed poorer performance on test of attention, language, praxis, and some test of memory (such as word recall). Hypertension, in contrast, was associated with worse performance on measures of executive function and processing speed. Patients with peripheral vascular disease performed significantly worse on global measures of cognition as well as measures of memory.

In addition to their individual contributions, the presence of multiple CVD risk factors may be associated with poorer neurocognitive performance through their interrelationship with the metabolic syndrome. Although various definitions have been employed, the United States National Cholesterol Education Program for Adults Treatment Panel III defines metabolic syndrome as three or more of the following five risk factors: 1) fasting plasma glucose $\geq$ 100 mg/dL, 2) high density lipoprotein cholesterol <40 mg/dL in men or <50 mg/dL in women, 3) triglycerides $\geq$150 mg/dL, 4) waist circumference $\geq$102 cm in men or $\geq$ 88 cm in women, 5) systolic blood pressure $\geq$130 mm Hg / 85 mm Hg diastolic or drug treatment for hypertension [88, 89].

Yaffe and colleagues [90] conducted one of the largest prospective trials investigating the association between metabolic syndrome and cognitive decline in a sample of 2,632 older

African-American and Caucasian adults. Individuals with metabolic syndrome at baseline showed a greater incidence of cognitive impairment at fiver year follow-up. Interestingly, the authors also found that the higher levels of inflammatory markers may have moderated this effect, such that those participants with metabolic syndrome and inflammation were significantly more likely to develop cognitive impairment compared to individuals with metabolic syndrome alone. Komulainen and colleagues [91] reported similar findings among 101 elderly women, showing that greater levels of metabolic risk factors were associated with poorer memory during a 12-year follow-up.

In another study, Yaffe and colleagues [92] investigated the longitudinal association between metabolic syndrome and cognition in 1,624 older Latino adults. They found that individual components of the metabolic syndrome (abdominal obesity, hypertriglyceridemia, low HDL, hypertension, and hyperglycemia) did not contribute significantly as independent predictors, but seemed to act synergistically in predicting cognitive impairment after three years of follow-up.

More recently, Dik and colleagues [93] examined the contributions of individual components of the metabolic syndrome to cognitive performance in multiple domains. The authors found that hyperglycemia was the only risk factor that contributed significantly to performance in all cognitive domains. In contrast, lower HDL cholesterol appeared to be uniquely associated with poorer performance in the areas of information processing speed and fluid intelligence.

Atherosclerosis

Indices of Subclinical Atherosclerosis

Atherosclerosis is a disease of the arterial system in which the lumen of the artery becomes narrowed by fatty deposits and fibrous tissue that accumulate on the intimal layer of the vessel wall [94]. It is postulated that atherogenesis is promoted by the abnormal accumulation of lipids, cells, and extracellular matrix within the arterial wall, eventually leading to the formation of atherosclerotic plaques. Plaque formation may result in arterial narrowing or, following plaque rupture, thrombosis, which may result in angina pectoris, myocardial infarction, and stroke [81].

Increasing evidence indicates that atherosclerosis as the process underlying the development of coronary heart disease, progresses in a graded fashion with target damage (e.g. myocardial infarction) occurring in later stages [33]. Accordingly, the use non-invasive assessment techniques to identify markers of subclinical atherosclerosis have gained increasing attention in the past decade [95]. Among these, three indices of atherosclerosis have been primarily investigated: intima media thickness, pulse wave velocity and pulse pressure, and flow-mediated dilation.

Intima Media Thickness

Intima media thickness (IMT) is considered to be a surrogate marker of atherosclerotic burden that can be assessed non-invasively using B-mode ultrasound techniques. The vessel walls consist of three layers, the intima, media, and adventia, with IMT assessing the distance from the edge of the intima to the outer edge of the media [96]. Examinations of IMT typically conduct assessments at any of three locations in the carotid artery: the internal carotid artery, carotid bifurcation, and common carotid artery. As a measure of cardiac risk, IMT assessed at any of these locations has been shown to have strong associations with incident myocardial infarction and stroke [97].

Beginning in the mid-1990s, reports began to emerge showing an association between higher levels of IMT and various neuropsychological decrements. Kaplan and colleagues [98] found that IMT assessed in the common carotid artery was associated with neuropsychological performance on several standard tests, including the Mini-Mental Status Exam, as well as tests of memory, complex psychomotor sequencing, and verbal fluency. Auperin and colleagues [99] made similar findings after adjusting for vascular risk factors, reporting that IMT was associated with performance on the Min Mental Status Exam and the Digit Symbol Substitution Test from the WAIS. Poorer Digit Symbol performance was also found to be associated with higher IMT levels in a sample of approximately 14,000 men and women participating in the Atherosclerosis Risk in Communities study [100]. Similarly, Haley and colleagues [101] found that higher IMT was associated with poorer performance on tests of executive function, attention, and psychomotor speed among 199 community volunteers. No association was found between IMT and cognitive tests assessing language, memory, or visuospatial skills, however.

Several prospective studies also provide convincing evidence that IMT may be associated with cognitive decline. Among 838 individuals from the Rotterdam Study, Slooter and colleagues [102] found that elevated IMT, as well as other comorbid conditions such as history of stroke or myocardial infarction, was associated with lower MMSE scores during a 3-year follow-up. Haan and colleagues [103] found that greater decline in Mini Mental Status and WAIS Digit Symbol performance was associated with elevated IMT levels. Interestingly, in both the Haan et al [103] and Slooter et al [102] studies, the association between IMT and cognitive decline was moderated by the presence of apolipoprotein E genotype.

Komulainen and colleagues [104] recently found that greater levels of IMT were associated with greater risk for slower cognitive speed and poorer memory. In a study of middle-aged and elderly men, Muller and colleagues [105] found that increasing levels of IMT were associated with lower scores on memory performance, and higher pulse wave velocity was associated with lower scores on processing capacity and executive functioning.

Pulse Wave Velocity and Pulse Pressure

Pulse wave velocity and pulse pressure are commonly used indices of arterial stiffness. Because pulse wave velocity is a direct measure of arterial stiffness, whereas pulse pressure is considered a surrogate measure [106, 107], pulse wave velocity is considered a more

specific measure of subclinical atherosclerosis. Fujiwara colleagues [108] found that individuals performing more poorly on the Mini-Mental Status Examination (scores < 24) demonstrated higher pulse pressures and pulse wave velocity. Poels and colleagues [109] similarly found that higher pulse wave velocity was associated with poorer performance on the Stroop test, and, notably, this association remained after adjustment cerebrovascular risk factors. Interestingly, despite the cross-sectional associations noted between pulse wave velocity and cognition, Poels and colleagues [109] did not find an association between pulse wave velocity and cognitive decline, or risk of dementia during an approximate 4.5 year follow-up.

Hanon and colleagues [110] conducted pulse wave velocity assessments in 308 geriatric outpatients reporting memory impairments. Patients were classified into one of four groups: Alzheimer's dementia (41%), vascular dementia (6%), mild cognitive impairment (27%), and normals. Pulse wave velocity was higher (i.e. worse) in subjects with vascular dementia and AD compared with mild cognitive impairment patients. Similar differences were observed between mild cognitive impairment and normals, with mild cognitive impairment patients showing higher pulse wave velocity, possibly indicating a graded relationship between pulse wave velocity and cognitive compromise. Moreover, incrementally higher pulse wave velocity levels were associated with increased risk of AD. Although the sample was entirely clinical and did not utilize a control group, this study was unique in that it provided an adequate sample size to examine differences in vascular health between subgroups of patients experiencing cognitive dysfunction, helping to elucidate the relative contribution of vascular pathology to each disorder.

Only one study, to our knowledge, has investigated the associations between measures of vascular health, cognitive performance, and brain lesions. Scuteri and colleagues [111] investigated this relationship in 84 elderly subjects referred for memory complaints. Carotid-femoral pulse wave velocity, brain morphology, and scores on the Mini-Mental Status were all assessed in this cross-sectional study. Pulse wave velocity and Mini-Mental Status were indexed continuously and, based on their brain imaging results, patients were classified as having either normal brain imaging, subcortical microvascular lesions, or cortical atrophy. Higher pulse wave velocity was associated with poorer MMSE performance as well as poorer self-reported personal independency, independent of age, sex, education, DM status, LDL and HDL cholesterol, prevalent cerebrovascular disease, antihypertensive medications, and nitrates. Pulse wave velocity was also higher among individuals exhibiting cortical atrophy on brain imaging compared with patients with normal brain imaging. Interestingly, on closer examination of brain computed tomography imaging, individuals with subcortical microvascular lesions showed better pulse wave velocity compared to patients with normal brain imaging, although this difference was not significant.

In a longitudinal study, Waldstein and colleagues [107], recently examined the relationship between arterial stiffness and cognition among 582 participants from the Baltimore Longitudinal Study of Aging. Increasing levels of pulse pressure was associated with greater declines on tests of verbal learning, nonverbal memory, working memory, and a cognitive screening measure. Findings were virtually identical for pulse wave velocity, such that higher pulse wave velocity levels at baseline were associated with a more rapid cognitive decline. Moreover, these findings were independent of multiple cerebro-vascular risk factors,

such as body mass index, cholesterol, smoking status, antihypertensive usage, and cardiac conditions (such as prior myocardial infarction).

Endothelial Function

Flow mediated dilation is a non-invasive assessment of endothelial function that is typically assessed at the brachial artery [112]. In this procedure, images of the brachial artery are obtained during a resting period and again during reactive hyperemia, induced after inflation of a pneumatic occlusion cuff placed around the forearm for 5 minutes at suprasystolic pressure [113]. Although the causative nature of the arterial stiffness and endothelial dysfunction relationship is subject to debate [95], emerging theories of atherosclerosis indicate that endothelial cells, perhaps due to their ability to regenerate through endothelial progenitor cells, may be the modulatory force controlling the progression of atherosclerosis [114]. endothelial cells play a critical role in a both structural and signaling capacities of the vasculature [115].

Dede and colleagues [116] examined differences in flow mediated dilation of the brachial artery, a non-invasive measure of endothelial cell function, between individuals with AD and healthy elderly controls using a case-control methodology. Patients with AD had significantly lower flow mediated dilation compared to controls and these differences persisted after adjustment for age. Furthermore, strong, inverse correlations were found between flow mediated dilation and progression of AD pathology, indexed by the Clinical Dementia Rating scale, as well as Mini Mental Status scores. This study's cross-sectional methodology limits the generalizability of these findings, but these results nevertheless underscore the importance of arterial health and cognitive function among individuals at various stages of functioning.

Although few studies have assessed the relationship between cognition and subclinical vascular health after adjustment for multiple cerebrovascular risk factors, data from our lab indicate that this association may remain strong in the presence of cerebrovascular risk factors [117]. We recently assessed the relationship between executive function, working memory, verbal recall, cerebrovascular risk factors, and subclinical vascular health in a sample of 198 middle-aged and older adults with major depression (MDD). Cerebrovascular risk factors were indexed by serum cholesterol levels (HDL and LDL) as well as the Framingham Stroke Risk Profile, a composite measure that assesses risk of 10-year incident stroke. The Framingham Stroke Risk Profile was reacted based on retrospective analyses from the Framingham heart study , and incorporates multiple sources of data, such age, systolic blood pressure, blood pressure medication status, presence of DM, heart disease, atrial fibrillation, and left ventricular hypertrophy to create a composite measure of risk. In our study, subclinical vascular health was indexed two measures: IMT and flow-mediated dilation. Consistent with the literature discussed above, we found that lower levels of high density lipoprotein and higher Framingham Stroke Risk Profile were associated with poorer executive function. Higher Framingham Stroke Risk Profile levels were also associated with poorer working memory. Furthermore, lower IMT and higher flow-mediated dilation were associated with better executive function, and this association persisted after adjustment for

all cerebrovascular risk factors, as well as age, education level, and depression severity. Flow-mediated dilation was also associated with working memory after similar adjustment, although IMT was not related to working memory in our sample. Most notably, when all cerebrovascular risk factors and markers of subclinical health were entered into a regression model simultaneously, flow-mediated dilation remained a strong predictor of executive function, whereas the relationship between executive function, IMT, and cerebrovascular risk factors was attenuated.

Potential mechanisms: The endothelium serves structural, metabolic, and signaling functions in healthy individuals. Progressive endothelial cell dysfunction, and subsequent reduction in nitric oxide bioavailability, may play a central role in the pathogenesis of the atherosclerotic process [115], as well as the contributions of various cerebrovascular risk factors such as cigarette smoking [113], hypertension [118], hyperlipidemia [23], DM [23], and obesity [119, 120]. Endothelial dysfunction may be caused by a number of factors, both physical and chemical. Disrupted blood flow at the arterial branch, for example, may result in dysfunctional by disturbing laminar flow. Although neuroimaging studies investigating the effects of endothelial cell function are limited, Hoth and colleagues [121] recently demonstrated that endothelial dysfunction is associated with increased white matter hyperintensity volume. Moreover, endothelial dysfunction was not associated with total cerebral volume and non-endothelium dependent dilation was not associated with WMHs, indicating that the endothelium's effect on cerebral integration may be specific to white matter. Toxic chemical environments secondary to cigarette smoking, elevated lipid levels, or diabetes can all promote endothelial dysfunction by increasing reactive oxygen species.
Furthermore, these risk factors may promote dysfunction by impairment of the endothelium as a permeability barrier, release of inflammatory cytokines, increased transcription of cell-surface adhesion molecules, altered release of vasoactive substances, and interference with normal antithrombotic properties.

Endothelial dysfunction may be associated with cortical dysregulation via several mechanisms. Vascular endothelial cells may play a role in the secretion of the precursor substrate of the neurotoxic A β-protein, leading to the destruction of cortical neurons, such as that observed in AD [110, 122]. Endothelial cells have been reported to produce an excess of free radicals [123] and their dysfunction has been associated with microcirculatory abnormalities and large artery atherosclerotic disease [124]. There is also evidence to suggest that the vasodilator responses to acetylcholine and serotonin are lost early in the atherosclerotic process [125].

As atherosclerosis progresses, endothelial dysfunction eventually results in intima medial thickness, which limits cerebral blood flow due to structural limitations on the carotid and cerebral arteries. Several studies have evaluated the impact of atherosclerotic burden on brain function *in vivo*. Haley and colleagues [126] examined the functional magnetic resonance imaging correlates of a working memory task. Higher levels of IMT was associated with weaker signal intensity, indicating reduced blood flow, in the right middle frontal gyrus, independent of age and white matter hyperintensities.

Clinical Cardiovascular Disease

Peripheral Vascular Disease

Chronic atherosclerosis of the lower extremities is referred to as peripheral artery disease, The cognitive effects of peripheral vascular disease have been described in detail [127]. Recently, Laurin and colleagues [128] conducted a prospective community-based study of 2588 Japanese American men to examine the relationship between indices of peripheral vascular disease and the development of dementia among a dementia-free sample. They found that an increased ankle-to-brachial index, a non-invasive measure of peripheral vascular disease, was associated with incident dementia and vascular dementia. Notably, these findings were independent of blood pressure, body-mass index, DM, cholesterol, and smoking status.

Coronary Heart Disease

Myocardial infarction has been associated with an increased prevalence of dementia [129, 130] and reduced processing speed [131]. Gorelick and colleagues [130], for example, examined the association between history of myocardial infarction and multi-infarct dementia in 61 patients using a case-control methodology. The authors found that a history of myocardial infarction was independently associated with a diagnosis of multi-infarct dementia. Barclay and colleagues [132] have proposed the term *circulatory dementia* to describe patients with vascular disease and non-Alzheimer's-type dementia, hypothesizing that cognitive deficits observed in cardiac patients may be the result of multiple infarcts, acute or chronic hypoxic damage secondary to arrhythmias, cardiac failure, or small-vessel disease of the brain.

Electrocardiographic Abnormalities

Cardiac arrhythmias have also been associated with variability in cognitive performance, although studies have focused almost exclusively on atrial fibrillation. Atrial fibrillation has been associated with an increased incidence of mild cognitive impairment and dementia in population-based studies [133], as well as poorer cognitive performance across a range of domains [134]. Kilander and colleagues [135] studied this relationship in a sample of 952 community-dwelling men (mean age at testing = 72.4), finding that those men with atrial fibrillation performed more poorly on cognitive testing than their healthy counterparts. Furthermore, this relationship was not altered after controlling for diastolic blood pressure, heart rate, diabetes, and ejection fraction. In contrast to the diabetes, duration of atrial fibrillation diagnosis does not appear to be associated with lower cognitive performance [134].

Cardiac Medications

Cardiac medications, such as anti-hypertensive agents, are commonly prescribed among individuals with hypertension, coronary heart disease, and cerebrovascular risk factors. Although hypertension medication-usage may are effective in reducing incident stroke and cognitive impairment [136], some cardiac medications have been associated with subtle reductions in cognitive performance. In a comprehensive review, Jonas and colleagues summarized the effects of hypertensive medications on cognitive performance [137]. Classes of anti-hypertensive medications were reviewed separately due to their different modes of action.

Beta-Blockers

Beta-blockers regulate blood pressure by reducing cardiac output and reducing rennin release. Beta blockers have generally been associated with small decrements in many attention-related abilities, but do not appear to have an effect on short-term memory or perceptual skills [137]. Studies investigating the effects of beta blockers on psychomotor function generally report equivocal results, although small decrements in performance have been reported. In contrast, improvements in long-term memory have been demonstrated with beta blocker usage, probably as the result of improved blood pressure control [137].

Angiotensin Converting Enzyme Inhibitors

Angiotensin converting enzyme (ACE) inhibitors decrease concentrations of aldosterone, increase bradykinin, and reduce the circulating levels of angiotensin II. ACE inhibitors have generally been found to improve performance on tests of sustained attention, complex attention, and mental flexibility. In contrast, memory performance appears to be unaffected by ACE inhibitor treatment, although one study among older hypertensive women found a positive relationship between ACE inhibitor treatment and improved memory performance [138]. Perceptual and psychomotor skills have not been extensively studied as they relate to ACE inhibitor treatment, although the few studies that have examined these relationships generally reported equivocal findings [139, 140].

Diuretics

Diuretics can be a first line of treatment for hypertension and also may be added to existing treatment regimens when target blood pressure levels are not achieved with monotherapy. For this reason, it is difficult to determine whether the cognitive decrements associated with diuretic usage are the result of medication-specific factors or the severity of hypertension of the samples in which this relationship was investigated [141]. Diuretic usage has generally not been associated with cognitive decrements in the areas of psychomotor

skills, memory, and attention, although small decrements in attention have been reported [139]. The relationship between diuretic treatment and perceptual skills has not been investigated using randomized designs.

More recent studies of this relationship have reported small cognitive decrements associated with the use of other antihypertensive medications. For example, using a prospective cohort design, Agostini and colleagues [136] examined the association between anti-hypertensive medication use and cognitive decrements among 544 community-dwelling hypertensive men, aged 65 years and over. Over the course of a one-year follow-up, there appeared to be graded relationship between increasing antihypertensive medication usage and performance on tests of motor and balance. Interestingly, no relationship was observed between medication use and performance on tests of executive function.

Recently, several studies have investigated the medication and cognition relationship using randomized controlled trial designs. Muldoon and colleagues [142, 143] have conducted several methodologically rigorous studies investigating the effects of anti-hypertensive and lipid-lowering medications on cognitive outcomes. In one study, Muldoon and colleagues [143] investigated the neuropsychological effects of six anti-hypertensive medications in sample of 198 Caucasian men using a randomized, double-blind design with a 2-week wash-out period. Among the 88 men who completed the trial, enhanced performance on tasks of complex sequencing and working memory were observed as a function of medication usage, as well as modest improvement on tasks of short-term memory. These results are particularly important given the relatively young age of the sample (mean age = 43 years).

Statins

Muldoon and colleagues [142, 144] have also conducted several studies investigating the effects of statin use on cognitive performance. In a study of 209 otherwise healthy adults with elevated LDL levels participating in a trial of lovastatin [144], statin use was associated with small decrements on tests of attention and psychomotor speed. Muldoon and colleagues [142] conducted a similar investigation of the effects of statins on cognitive function among 308 hypercholesterolemic adults, aged 35-70. The authors found that statin use was associated with poorer performance on a range of cognitive tests, including measures of executive function and memory. Although poorer cognitive performance was observed among individuals receiving the active medication, no differences were observed between those participants assigned to receive 10-mg and 40-mg doses, indicating that the detrimental effects of statins may have a threshold effect, such that increasing doses are not associated with correspondingly poorer performance.

Few studies have investigated changes in cognitive performance as they relate to incident events, such as stroke and dementia. Skoog and colleagues [145] investigated this relationship among 4,937 older adults with mild-to-moderate hypertension. Among individuals with low cognitive functioning at baseline, anti-hypertensive medication usage was associated with lower rates of incident stroke and a lesser decline in MMSE performance over the 3 to 5 year follow-up period. In the most comprehensive review to date, McGuinness and

colleagues [146] examined whether randomized controlled trials of blood pressure reduction were associated with improved cognitive performance and reduced risk of dementia. Although the authors reported and an 11% reduced risk of dementia among participants enrolled in blood pressure treatments, this finding did not reach statistical significance. This null finding and the considerable heterogeneity of findings across studies leaves the question of whether blood pressure interventions may reduce the risk for incident dementia open for future examination.

Cognitive Sequelae of Cerebrovascular Burden

Cerebrovascular Risk and Structural Brain Abnormalities

The relationship between cardiovascular and brain health is primarily a function of the heart's ability to supply the cerebral vessels with a constant, adequate supply of blood. As the heart's ability to supply blood to the brain is compromised, either due to inadequate blood pumping from the heart itself or from reduced diameter in the cerebral arteries, cerebral vessels become starved for oxygen, ultimately resulting in areas of demyelination, exhibited as white matter hyperintensities on MRI exam. Furthermore, the 'watershed' arteries perfusing critical areas of the frontal-subcortical circuits of the brain are relatively small in diameter and non-redundant, leaving them particularly vulnerable to the detrimental effects of ischemia [147].

White matter hyperintensities are relatively common among elderly adults [148] and have been shown to increase with age [149]. However, white matter hyperintensities may also be caused by greater cerebrovascular risk factors, due to their ischemic properties [150, 151]. Recent studies have examined this relationship using diffusion tensor imaging and chemical shift imaging (CSI) in order to examine the age-related in changes seen in white matter. Charlton and colleagues [152], for example, found that increasing age is associated with greater functional anisotropy, a measure of white matter degradation, and that functional anisotropy is similarly associated with information-processing, working memory, and executive function.

An emerging line of research suggests that cerebrovascular risk factors may be associated with lower regional grey matter volume, in addition to the extant associations observed with white matter. Gianaros and colleagues [42] recently reported that higher blood pressure levels were associated with lower grey matter volume in the supplementary motor area. Moreover, these findings were noted after controlling for age, total brain tissue volume, educational history, severity of carotid atherosclerosis, and the extent of white matter hyperintensities.

Knopman and colleagues [153] conducted an important study investigating the relationship between cardiovascular risk factors as a predictor of cerebral atrophy. In their study, 1,812 individuals were followed for a six year period. The presence of DM, hypertension, prevalent heart disease, intima media thickness, and fasting glucose were all associated with ventricular size. Also, hypertension, smoking status, and intima media thickness were associated with a greater prevalence of white matter hyperintensities. Murray and colleagues [154] investigated the relative contributions of various cerebrovascular risk

factors to white matter hyperintensities in a sample of nondemented elderly adults. They found that hypertension, LDL, total cholesterol, and glycated hemoglobin were all associated with greater white matter hyperintensities.

Few studies have investigated the relationship between cerebrovascular risk factors, brain lesions, and cognitive performance concurrently. Those studies that have examined these factors together provide valuable insight into the interrelationships between these factors. Seshadri and colleagues [155] conducted a longitudinal study among individuals from the Framingham study, examining the relationship between Framingham Stroke Risk Profile levels at baseline, brain morphology, and cognitive performance. The authors found that higher FSRP levels were associated with reduced total cerebral brain ratio (TCBVr) and that lower TCBVr was associated with poorer cognitive performance.

Inzitari and colleagues [156] recently investigated the relationship between cerebral WMHs and global functional decline in a prospective study of 639 patients from the LADIS study. They found that among elderly, non-disabled patients, increasing WMHs were associated with greater likelihood of global functional decline during a 1-year period.

Cognitive Outcomes Following Revascularization Interventions

Vascular disease may impact brain health on a number of levels, from subclinical manifestations to full-blown cerebrovascular events, such as stroke. Among individuals with identified vascular disease, various forms of revascularization procedures are available to decrease the risk of incident vascular events by reducing vascular obstructions. Although the cognitive consequences of vascular intervention may vary by disease typology (e.g., occlusions in the coronary or carotid arteries) and interventional procedure (coronary artery bypass grafting (CABG), angioplasty, and endarterectomy), many share similar mechanisms of action. We provide a brief review of the cognitive sequelae of major vascular interventions. For a more complete review of this area the interested reader is referred elsewhere [157].

Coronary Artery Bypass Grafting Surgery

Coronary artery bypass grafting (CABG) may be the only option for individuals with more severe CAD. Despite its frequent usage among cardiac patients, many individuals may experience cognitive decline in the immediate post-operative period, with cognitive deficits reported in 30-80% of patients [158-161]. Although stroke and cerebral aneurysm are the most concerning post-operative consequences, more subtle neurocognitive decrements may be associated poorer quality of life and increased medical cost [158]. Newman and colleagues [159], for example, evaluated 261 patients undergoing CABG and found that 53 percent were experiencing cognitive decline at discharge. The number of patients with cognitive decline dropped to 36 percent at six weeks and continued to improve to 24 percent at six months. Interestingly, during a five year evaluation, 42 percent of patients were experiencing

cognitive decline, possibly reflecting the additional influence of normal aging processes following CABG.

Several studies have examined the longer term cognitive status of patients following CABG. Selnes and colleagues have conducted several longitudinal exams to assess the long-term cognitive consequences of CABG [162, 163]. In a longitudinal examination of 140 patients undergoing CABG, the authors found that CABG patients showed virtually identical improvement in the first year following CABG compared to nonsurgical controls. Similarly, a nonsignificant decline in overall cognitive function was observed between post-operative testing and a three year follow-up and this effect was observed in the nonsurgical controls as well. In a separate study, Selnes and colleagues [162] investigated the cognitive performance of 102 patients approximately 5 years following CABG. The authors found that patients experienced declines in visuoconstruction and psychomotor speed over the 5 year follow-up, but improved in executive function. Population-based data from the Cache County Study have demonstrated that individuals undergoing CABG may show a steeper rate of cognitive decline compared with healthy control participants. More importantly, differences in cognitive decline were not evident immediately following CABG, but emerged more than five years post-operatively.

An emerging line of research investigates the intra-operative factors that predict poorer post-operative cognition [164]. Boodhwani and colleagues [164] identified intraoperative normothermia, impaired left ventricular function, higher educational level, elevated serum creatinine and reduced creatinine clearance, prolonged intubation time, intensive care unit stay, and hospital stay as factors associated with poorer post-operative cognition. Stanley and colleagues [165] examined the relationship between post-operative atrial fibrillation and neurocognitive performance, finding that individuals who developed atrial fibrillation after CABG exhibited poorer cognitive function six weeks after surgery.

In recent years, the effects of on-pump and off-pump CABG procedures have been investigated. Off-pump CABG may be associated with the production of fewer microemboli [166], which has been associated with cognitive decrements in some studies [167]. In a randomized controlled trial, Hernandez and colleagues examined differences in cognitive function among 102 patients undergoing conventional CABG (on-pump) compared to 99 individuals randomly assigned to receive off-pump CABG. Using a comprehensive neuropsychological battery, the authors reported only marginal differences between groups, with off-pump patients demonstrating lower performance on tasks of processing speed and executive function at discharge (Trail Making Test sections A and B) and very marginal differences in spatial attention at six month follow-up. In the largest trial to do so, van Dijk and colleagues [168] conducted a longitudinal study comparing on and off-pump cognitive effects. After 5 years of follow-up assessments, they found no differences between groups in cognitive performance, quality of life, or cardiac events.

Potential Mechanisms: Several mechanisms have been proposed as underlying the post-operative decline observed in many CABG patients. Not surprisingly, differences in patients characteristics, such vascular diseases and history of neurologic illness, as well as surgical complications may be associated with a more rapid cognitive decline [169]. Age may also be a determining factor of post-CABG cognitive decline. Potter and colleagues [170] investigated this relationship among 232 twin pairs from the Duke Twins Study of Memory

in Aging, in which participants were classified into three age groups (63 to 70, 71 to 73, and 74 to 83). Participants aged 63 to 70 at the time of their CABG exhibited improved cognitive performance compared to their twin counterparts, whereas no effect was observed in the two older groups.

The primary mechanisms postulated to reduce cognitive performance following CABG include microemboli showers, hypoperfusion, and systemic inflammatory response, although other factors, such as atrial fibrillation, anesthesia, depression, and genetic factors have also been examined. Studies utilizing Doppler imaging have demonstrated that microemboli showers are common during cardiac surgery, particularly during the cannulation and clamping/unclamping [171]. Furthermore, post-mortem examinations of post-CABG patients have reported small capillary cerebral arteriolar dilatations, which occur in large number as a result of micro-embolisation [157, 172]. Ebolisation of aortic atheroma or other area of has been associated with an increased risk of stroke [158]. Cerebral hypoperfusion may be associated with reduced washout of small emboli and greater cardiovascular injury [173, 174]. The effects of inflammation may contribute to the severity of neurological injury [175], but most likely are not solely responsible for the neurocognitive declines observed [157]. Individuals at greater risk of inflammation appear to have a greater risk of cognitive decline following cardiac surgery [176].

Valve Replacement Surgery

Cardiac valve repair or replacement, such as mitral and/or atrial valve repair, may improve left ventricular ejection fraction (LVEF) and cardiac prognosis. These procedures are particularly common among individuals with significant aortic stenosis. Several groups have noted neurocognitive deficits following mitral valve repair. Zimpfer and colleagues [177] have reported neurocognitive decline in 52% of individuals receiving biological valves and 45% receiving mechanical valves one week post-operatively. For example, Gimm and colleagues [178] examined post-operative differences in neurocognitive performance among 40 individuals undergoing either mitral valve repair or mechanical valve replacement. The authors reported that cognitive performance continuously worsened over the subsequent 4-month period among those individuals receiving mechanical valve replacement. In contrast, no change was observed among individuals undergoing mitral valve repair.

Neurobehavioral changes have also been observed following cardiac valve replacement procedures. Ebert and colleagues [179] have demonstrated that these deficits may be more severe than those exhibited following CABG. For both CABG and valve replacement, deficits in fluency, arithmetic, and working memory have been observed. More recently, the effects of mechanical valve replacement have been examined. Zimpfer and colleagues [180] examined the long-term changes in P300 evoked potential following aortic valve replacement, finding that P300 latency had increased approximately 7 days post-operatively. When patients were assessed again 4 months following surgery, P300 latencies had returned to pre-surgical levels and remained normal up to 3 years post-operatively. Interestingly, P300 recovery has been shown to remain lower during recovery for individuals undergoing biological valve replacement, in contrast to findings observed with mechanical valves [177].

Potential mechanisms: Recent studies have investigated the mechanisms by which valve replacement may confer a greater risk of cognitive decline. Imaging studies indicate that atrial valve repair may be associated with a greater prevalence of silent cerebral infarction and white matter damage [181]. Furthermore, the severity of preexisting white matter lesions may predict the occurrence of new post-operative lesions.

Carotid Endarterectomy and Carotid Stenting

Eastcott and colleagues [182] were the first to report successful surgical correction of an extracranial carotid atherosclerotic lesion in 1954. Carotid Endarterectomy (CE) is now a commonly used surgical procedure, elected to prevent recurrent stroke and/or transient ischemic attack among individuals with significant stenosis of the carotid arteries. The primary objective of this procedure is the removal of the source of arterial embolism [183] by excising atherosclerotic blockages from the extracranial portion of the internal carotid artery. Carotid artery stenting (CAS), in which a metallic stent is placed in the carotid artery to maintain blood flow, has gained increasing favor in recent years as a less invasive means of reducing the risk of cerebrovascular events. Moreover, recent meta-analyses have demonstrated that CE and CAS may be equally effective in reducing patient risk [184].

Although the benefits of carotid endarterectomy in preventing stroke have been extensively examined [185], the cognitive effects of this procedure have received somewhat less attention. Many studies investigating these effects have noted cognitive decrements in the immediate post-operative period, although these frequently resolve and may have less clinical significance in predicting patients' long-term recovery, so the long-term effects of carotid endarterectomy are emphasized here. In 1977, Asken and Hobson were the first to attempt a review of cognitive changes following endarterectomy [186]. Due to the inconsistent findings and methodological flaws of the existing literature at that time, Asken and Hobson could not say with any certainty whether carotid endarterectomy was associated with consistent changes in intellectual function. Principal among the methodological limitations were the virtual absence of control groups across trials.

Several groups have conducted long-term follow-up studies among small groups of non-randomized patients, although fewer randomized trials have been conducted. These studies have tended to report small cognitive improvements across a range of cognitive domains (Incalzi, et al 1997; Lind et al, 1993). Few randomized controlled trials have been conducted, however. Meyer and colleagues [187] conducted a small, randomized trial of 8 patients approximately 26 months post-operatively. Patients were randomly assigned to either medical management or CE with medical management. The authors found no marked changes in cognitive function among patients in either group, nor did they note any group differences.

Heyer and colleagues [188] recently conducted controlled, prospective study of investigating the neuropsychological sequelae of carotid endarterectomy. In their study, 80 individuals undergoing carotid endarterectomy and 25 undergoing lumbar spine surgery were compared approximately one month post-operatively. Individuals receiving carotid endarterectomy performed more poorly on the Rey Complex Figure test and Halstead-Reitan Trails B compared with controls, although these effects were relatively subtle. This study was

particularly important in elucidating the relative contributions of the CE procedure itself with the effects of anesthesia, which is used during all CE procedures. The authors utilized an age-matched group of older patients undergoing spine surgery, which shares anesthesia techniques but differs vastly in surgical procedures.

In the most updated systematic review of the cognitive effects of carotid endarterectomy, Lunn and colleagues [189] reported that the majority of studies reported positive findings, although there was substantial variability between studies. Studies which found improvements in cognition following carotid endarterectomy tended to have longer follow-up periods and tended to use repeated neuropsychological testing, which may have been influenced by practice effects. One consistent finding was that verbal fluency and memory were most likely to benefit from surgery. Furthermore, patients with surgery on the left carotid artery tended to improve on verbal tasks while those with right carotid surgery tended to show improvement on visuospatial and performance tasks.

Nevertheless, a substantial minority of studies found no change in cognition following carotid endarterectomy and the trajectory of findings appeared to vary by publication date, with studies conducted prior to 1984 tending to report positive findings. In contrast, studies published later tended to report equivocal findings. Furthermore, there was substantial variability in methodological factors such as sample size, patient and control group, acuity of CVD, type of cognitive testing performed, and timing of postoperative assessment. Given the heterogeneity in methodologies present, the authors concluded that it was not possible to draw a clear conclusion regarding the impact of carotid endarterectomy on cognition.

Carotid Artery Stenting: Recent systematic reviews indicating that carotid endarterectomy and carotid artery stenting may be equally effective in reducing adverse cerebrovascular events have garnered increasing attention as to the cognitive consequences of carotid artery stenting, despite the more recent development of carotid artery stenting as an interventional technique. Grunwald and colleagues [190] conducted a prospective study of 10 individuals undergoing carotid artery stenting, finding that performance on a battery of six neuropsychological tests was unchanged post-operatively. This study was limited, however, by a small sample, size, lack of a control group, and a short follow-up period (48 hours). Recently, Xu and colleagues [191] conducted a prospective study of 54 individuals with high-grade stenosis undergoing carotid artery stenting compared with 54 control participants with similar comorbidities undergoing carotid angiography. Individuals receiving carotid artery stenting showed significant improvement on tests of complex psychomotor sequencing, working memory, and memory recall 12 weeks post-operatively. When compared with control participants, however, memory recall and verbal ability were the only measures shown to have significantly improved. The authors interpreted this finding to indicate that carotid artery stenting may be associated with cognitive gains specific to verbal memory.

Recently, Berman, Pietrzak, and Mayes [192] conducted a systematic review of the literature to ascertain changes in cognitive function following carotid endarterectomy and carotid artery stenting. The authors reported that carotid endarterectomy has generally been found to improve cognitive function, particularly in long-term follow-ups. Too few studies have investigated the effects of carotid stenting on neurocognitive function to draw

meaningful conclusions, however, and those studies that have investigated this relationship have reported mixed results.

Potential Mechanisms: Improved cerebral perfusion appears to mediate the improvement observed in neurocognitive performance among individuals undergoing carotid endarterectomy and carotid artery stenting. In support of this claim, Moftakhar and colleagues [193] found that improved cerebral perfusion following extracranial carotid stent placement was associated with cognitive performance, and this effect was strongest among patients receiving anterior stents. Similarly, Fukunaga and colleagues [194] found that carotid endarterectomy may be particularly beneficial among individuals with cerebral perfusion reserve was diminished (<15%) prior to intervention. Intraoperative ischemia and postischemic hypoperfusion are postulated to mediate the cognitive changes seen after CE [195], although they may develop at subclinical levels in the absence of neurocognitive changes. Recent studies have found support for these findings, demonstrating that substantial increases in cerebral blood flow may be seen immediately following carotid endarterectomy [196]. Biomarkers of cerebral injury have also been investigated as potential correlates of post-operative neurocognitive decline. Although an emerging line of research, important biomarkers, such as S100B, have been shown to predict post-operative cognitive dysfunction [197].

Conclusions

This chapter provides a comprehensive review of the literature demonstrating a strong relationship between cardiovascular health and neurocognitive performance. Prospective population studies have consistently demonstrated that deficits in neurocognitive functioning are associated with cardiovascular risk factors such as hypertension, dyslipidemias, and abnormalities in glucose metabolism. In addition, patients with subclinical atherosclerosis and clinical coronary heart disease have been shown to perform more poorly on a variety of neurocognitive tasks. Although many treatment options are available for individuals with more advanced CVD, pharmacologic and surgical interventions may be associated with cognitive decrements.

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Chapter 2

Psychological Factors and the Triggering of Acute Cardiac Events

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Abstract

A body of evidence suggests that acute psychological stress can trigger acute cardiac events such as myocardial ischemia, acute coronary syndrome, apical ballooning syndrome, cardiac arrhythmias and sudden cardiac death. Psychological stress may provoke endogenous changes including biomechanical, prothrombotic, vasoconstrictive and proarrhythmic forces referred to as internal triggering mechanisms. These mechanisms may initiate the cardiac incident and/or favor its progression to a more severe clinical disease. Psychological factors also likely contribute to the increase in cardiac events associated with war, terrorist attacks, and natural disasters and may play a role in the major chronobiologic phenomena that affect cardiovascular diseases such as circadian, weekly and seasonal pattern. Complete elimination of psychosocial factors as potential triggers of cardiac events is not realistic. Successful management will probably include individually adjusted combination of medicamentous and other measures. Additional understanding of association between cardiovascular diseases and psychological factors may help in improving both prevention of triggering and treatment of acute cardiac diseases.

Introduction

The role of chronic effect of psychological factors for the development of atherosclerosis and associated cardiovascular disorders in the long term perspective has been well explored. However, there is evidence to suggest that psychologically stressful everyday activities and circumstances are linked to the major acute cardiac pathologies. We now know that acute psychological stress may in a major way contribute to the potentially deadly events such as

myocardial ischemia, acute coronary syndrome, apical ballooning syndrome, cardiac arrhythmias, and to sudden cardiac death. Although these disorders usually occur in patients with progressed pathomorphological changes, it has been suggested that some of them may occur with less severe, or sometimes even without detectable cardiac disease (Figure 1). Therefore, in addition to chronic effects, acute effects of psychological states have become an object of interest for clinical investigators in order to determine vulnerable patient subgroups, modes of triggering of cardiac events, and preventive strategies to decrease the risk of acute triggering by psychological factors.

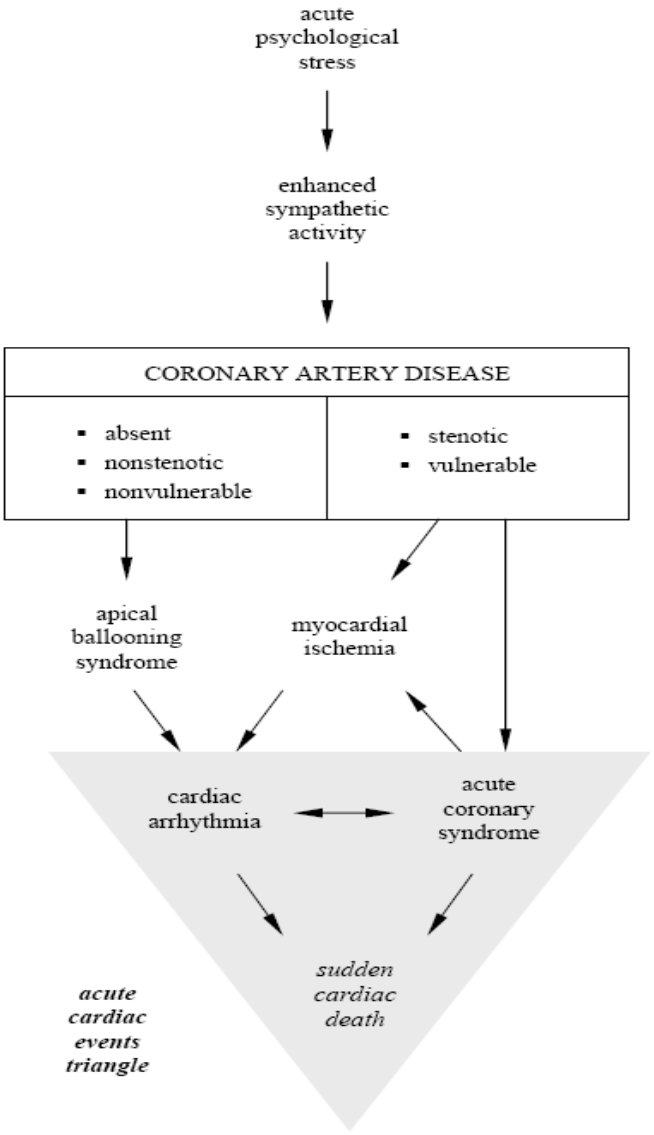

Figure 1. Regardless of the presence and severity of coronary atherosclerosis, acute psychological stress may trigger acute cardiac events. Development of a cardiac arrhythmia or acute coronary syndrome may lead to the sudden cardiac death. These three disorders are comprised within the “acute cardiac events triangle”.

The investigators constantly update terminology for the elements of triggering of cardiac events. To emphasize the acute nature of the whole process, the term acute risk factors has been proposed in 1994 for pathophysiological mechanisms involved in causing the onset of acute cardiovascular diseases [1]. More recently, the terms acute, modifying and chronic risk factors, internal triggering mechanisms [2-5], as well as patient, plaque, blood and myocardial vulnerability [6, 7] have been redefined and proposed in a more complete concept of susceptibility to acute cardiovascular diseases and underlying pathophysiological mechanisms.

The term chronic risk factors has been used for well-known conditions and diseases such as diabetes, smoking, hypertension, hyperlipidemia and others, that may produce pathomorphological changes in the cardiovascular system. The effect of chronic risk factors usually takes years to manifest as clinical disease and most commonly affects individuals in middle and old age. Although in comparison to other chronic factors they are often very difficult to assess precisely and objectively, a number of psychological and psychosocial variables are considered to be causally related to cardiovascular diseases [8-13].

In contrast to chronic risk factors, the term modifying factors has been introduced for factors that may influence the segments of vulnerability through biochemical, pathophysiological or electrophysiological processes over a limited time course of their presence, rather than changing the underlying heart disease [2, 5]. They may change individual susceptibility to an acute cardiac event and/or susceptibility to triggering by a particular acute risk factor.

Apart from chronic and modifying factors and superimposing upon them, acute risk factors represent a group of everyday activities and events that suddenly and transiently, in an acute manner, increase the risk of acute cardiac disease [2, 3]. In addition to heavy physical activity and having a meal, psychological stress belongs among three most important and most frequent external triggers of cardiac events. Other, less frequent triggers are exposure to bad weather conditions, cocaine or marijuana use, coffee or alcohol consumption, sexual activity and toilet activities such as defecation and micturition [4]. Some clinical and experimental data suggest that psychological stress may be more dangerous in comparison to other triggers for the same patient because its triggering and accompanying mechanisms somewhat differ from the mechanisms associated with other above-mentioned triggers eventhough most of them generally operate through a typical “sympathetic triggering pattern” [2, 3].

The concept of patient vulnerability is based on the three elemental components. A tendency toward increased blood coagulability has been referred to as vulnerable blood. A diseased myocardium, whether ischemic or non-ischemic, susceptible to the development of malignant arrhythmias has been referred to as vulnerable myocardium [6, 7]. Synonyms “vulnerable”, “high-risk” or “thrombosis prone” plaques are used for atherosclerotic plaques at risk of occurrence of endothelial injury associated with either rupture, erosion or calcified nodule. In that scenario, the consequent intravascular thrombosis leads to the onset of acute coronary syndromes, including unstable angina, acute myocardial infarction and sudden ischemic death [3, 14, 15]. As a result of the joined effect of the three components of vulnerability, individual patient vulnerability represents the likelihood of developing a cardiac event in the near future.

A number of studies have described the association of psychological stress with clinical events, and clinical and experimental investigations have provided knowledge concerning the possible pathophysiological processes that may determine the final form of the acute disease. There is also a possibility that some longer-acting psychological factors can modify components of patient's vulnerability, thereby additionally increasing the likelihood of "acute cardiac events triangle", including acute coronary syndromes, malignant arrhythmias, and sudden cardiac death [2]. Regarding the prospect of wider fluctuations in cardiovascular morbidity and mortality, there are two types of circumstances indicative of strong psychological background. The first is increase in incidents associated with war threats such as air raids and missile attacks, documented for example in Croatia [16] and Israel [17]. The second is a marked rise in the occurrence of myocardial infarction [18-20], takotsubo stress cardiomyopathy [21] and sudden cardiac deaths [22] during massive earthquakes in stricken regions worldwide. Perhaps, mass population character of natural and man-made disasters potentiates adverse psychological effect leading to an increase in the occurrence of cardiac events.

Acute Pathophysiological Consequences of Psychological Stress: General Internal Triggering Mechanisms

In patients with ischemic heart disease, acute psychological stress may provoke a spectrum of potentially adverse endogenous changes. Such changes, referred to as internal triggering mechanisms [2, 3], may start the cardiac incident and/or favor its progression to a more severe clinical disease. It is important to note that these mechanisms are rather sudden and intense, but only transient. They operate within a time course of several hours, for psychological triggering most likely up to two hours, then fade and return the risk of incident to basal values. Internal triggering mechanisms can also be described as forces to emphasize the possibility of synergistic effect of multiple processes often coexisting and increasing a tendency toward a particular pathophysiological mechanism.

Acute psychological stress produces four major pathways of internal triggering mechanisms (Figure 2) including biomechanical, prothrombotic, vasoconstrictive and proarrhythmic forces. These forces are provoked by rapid and intense activation of the sympathetic nervous system and may cause disorders of the acute cardiac events triangle. Such a triggering pattern is also responsible for acute cardiac events following exercise, sexual activity, cocaine or marijuana use and consumption of alcohol or coffee.

Biomechanical forces is a combined term for all mechanical impacts and interactions among a variety of neighboring structures within the heart caused by each heart contraction [2-4]. Biomechanical forces consist of intraluminal hemodynamic forces, and a group of intramural and perivascular forces. The former include acutely increased blood pressure and pulse pressure which primarily endanger shoulder regions of vulnerable coronary plaques [3]. In considering more local processes, hemodynamic forces include flow-generated endothelial shear stress and blood pressure derived tensile stress. While low endothelial shear stress seems to be the most substantial factor in atherogenesis and development of coronary

atherosclerotic plaques [23], episodes of sudden increase in that stress following exposure to external triggers are responsible for a significant number of cases of plaque rupture or erosion [3,24]. Finally, intramural and perivascular forces include enhanced arterial twisting and bending caused by myocardial contractions. The intensity of all biomechanical forces is proportional to the level of activity of the sympathetic nervous system [3].

A clot that covers an injured surface of ruptured or eroded plaque is the principal component of acute coronary atherothrombosis and an important target for early therapeutic approach. A prothrombotic state is characterized by a tendency toward easier initiation and more extensive clot formation, which may result from several causes. An increase in both blood viscosity and fibrinogen concentration have been described after massive earthquakes [25, 26]. Increased viscosity and reduced plasma volume increase the concentration of procoagulant factors and platelets, prolong the period of contact between the endothelial surface and circulating blood, and probably increase peripheral vascular resistance. This may cause worsening of the preexisting endothelial dysfunction, whereas relatively increased coagulability in areas of slow blood flow may produce morphological damage of endothelial cells and start intraluminal thrombosis even without significant plaque rupture or erosion. Endothelial dysfunction itself may increase the leaking of intravascular components to the sub-endothelial compartment [27], thereby additionally increasing the arterial pressure [28, 29] and closing a vicious circle at this circulatory level.

It seems likely that the more provocative the psychological challenge, especially in terms of the magnitude of increase in blood pressure, the stronger increase in hematocrit and reduction in plasma volume. The most important mechanism seems to be the increase in hydrostatic pressure and capillary filtration consequent to the rise in arterial pressure [30-33]. As an additional mechanism, it has been suggested that an inflammatory-like response, which may be also induced by psychological stress [34], could increase vascular permeability [35].

Individual reactivity may play a role in the mental stress induced changes affecting blood rheology. One study [36] reported that, independently of endothelial function, participants who developed myocardial ischemia during public speaking and star trace tasks had more significant reduction in plasma volume in comparison to those who did not develop ischemia under the same conditions. Several sex differences in this regard have also been reported. At baseline conditions, men have higher hematocrit values and seem to show an apparent hemoconcentration in response to mental stress [30, 32]. On the contrary, hemoconcentration was either not observed [32] or was much weaker in women [30].

Another important segment of hematological response to acute psychological stress is platelet activation, primarily resulting from the sympathetic nervous system stimulation. Increased concentrations of circulation catecholamines stimulate platelets through binding to α_2 and $ß_2$ adrenergic receptors on the platelet surface [37]. Circulating monocyte-platelet aggregates are early markers of an acute coronary event [38, 39] and could be indicators of the platelet activation in general [40]. Strike et al [41] reported that monocyte-platelet aggregates increased by 100% and neutrophil-platelet aggregates by 85% during emotional stress tests among patients whose acute coronary syndrome was likely triggered by such a stress. Conversely, an increase in platelet aggregates was not present among patients whose coronary incident was unrelated to emotional stress. This observation further supports the

notion that some coronary patients may be particularly susceptible to coronary incident triggered by emotionally stressful circumstances.

Vasoconstrictive forces may act as a biomechanical factor since vasoconstriction may itself trigger plaque rupture and the onset of acute coronary syndrome [1, 3, 6, 7]. However, in other cases of acute events, the presence of vasoconstriction is held to be an independent internal triggering mechanism significantly contributing to the myocardial ischemia, apical ballooning syndrome and remaining disorders of the acute cardiac events triangle. It is well established that psychological stress can stimulate inappropriate response of the coronary artery tree. While some studies reported on the mental stress-induced vasoconstriction of atherosclerotic and stenotic segments of coronary arteries [42, 43], others have reported on an augmented blood flow and lower mental-stress flow reserve in arterial segments without significant stenoses [44, 45]. Therefore, more severely diseased coronary segments seem to be susceptible to a typical and more powerful vasoconstriction in response to acute psychological stress, whereas regions with less severe atherosclerotic lessions could be susceptible to a microvascular dysfunction.

Psychological stress could cause cardiac arrhythmia through three different pathophysiologic pathways [2]. A direct neurocardiac impact, catecholamine induced metabolic changes, and an indirect effect through the myocardial ischemia.

Sympathetic stimulation is mediated by efferent innervation which is scattered throughout myocardium and conduction system. Recent data have elucidated the link between central influences and arrhythmogenesis. Lateralization of brain activity during psychological stress may cause asymmetric stimulation of the heart with more or less localized areas of inhomogeneous repolarization [46]. Such a disturbed repolarization is a milieu of electrical instability and increased risk of arrhythmia [47]. There is evidence that asymmetry of cerebral activity in response to psychological stress may be more pronounced in coronary patients. In comparison to control periods as well as in comparison to healthy individuals, mental stress in coronary patients caused hyperactivity in the cerebellum, the right visual association cortex, the left parietal cortex, the left anterior cingulate, and the left fusiforme gyrus. At the same time, decreased activity has been observed in the right thalamus, the right superior frontal gyrus, and the right middle temporal gyrus as assessed by positron emission tomography [48].

From an electrophysiologic point of view, psychological stress can produce a transient prolongation of the QTc interval [49, 50] which may lead to the development of malignant ventricular arrhythmias in patients with coronary disease [51]. Acute psychological stress induces increase in T-wave alternans, independent of the increase in heart rate [52]. It also increases the electrical termination threshold during electrophysiological testing, alters the circuit of ventricular tachycardia and accelerates arrhythmia's rate [53]. A synergistic effect of proarrhythmic forces and myocardial ischemia, both being promoted by acute psychological stress, could be particularly concerning. In that context, a reduction in the threshold for ventricular fibrillation during anger like-state has been observed in experimental animal model [54].

In addition to other proarrhythmic effects mediated by sympathetic nervous system arousal, acute psychological stress stimulates catecholamine secretion. Circulating adrenaline lowers the levels of serum potassium, magnesium and calcium which additionally favor the

proarrhythmic state [2]. A body of evidence suggests that in the same patient, acute psychological stress is a more powerful arrhythmia trigger than exercise [2, 5]. This may be at least partly due to a protective effect of the increase in serum potassium released from the skeletal muscles during exercise while intense psychological stress may enhance adrenaline-induced electrolyte distortion.

In conclusion, internal triggering mechanisms of acute psychological stress comprise a typical sympathetic triggering pattern with accompanying adverse hemorheological and metabolic changes. Beside these mechanisms, several acute effects of brief psychological stress may affect the vulnerability of the atherosclerotic plaques. They include an increase in concentration of inflammatory cytokines over a couple hours [34, 55] and impairment in vascular endothelial function lasting for up to 90 minutes after exposure to stress [56]. The last two mechanisms may change plaque configuration toward a more vulnerable state when biomechanical, vasoconstrictive and prothrombotic forces have more chance to initiate an acute coronary syndrome. At present, many issues regarding internal triggering mechanisms are not understood and a number of factors are likely yet to be discovered. A much more complex issue is the final consequence of interplay among all endogenous changes for an individual patient.

Myocardial Ischemia

Although myocardial ischemia is a reversible condition, its pathogenesis is important for the understanding of endogenous consequences and internal triggering mechanisms produced by acute psychological stress. However, it is even more illustrative of inconsistencies in the current knowledge in the area of triggering acute cardiac events. The occurrence of myocardial ischemia, even when it is not associated with acute coronary syndrome, heightens the risk for other pathologic conditions such as apical ballooning syndrome, ventricular arrhythmias, and sudden cardiac death.

Mental stress-induced myocardial ischemia has been convincingly documented by various techniques such as electrocardiography [57, 58], echocardiography [59-61], radionuclide isotope assessment [62-66], positron emission tomography [67], and nuclear VEST [68-70]. However, there is a wide range of diverse findings regarding the prevalence of myocardial ischemia induced by psychological stress among both healthy individuals and patients with coronary artery disease.

Among pathophysiologic mechanisms underlying myocardial ischemia associated with an acute emotional disturbation, the crucial ones are components of sympathetic triggering pattern including increased heart rate, blood pressure, myocardial contractility, cardiac output and both systemic and coronary arterial resistance [2, 3, 5]. The ischemia is caused by a raised heart rate-blood pressure product and elevated myocardial oxygen demand. Abnormal vasomotor response followed by decreased myocardial blood supply often contributes to the ischemia.

Similar to the differences suggested for proarrhythmic forces, the ischemic response to psychological stress occurs at a lower rate-pressure product than myocardial ischemia induced by exercise in the same individual patient with coronary disease [63, 71, 72]. Defects

in myocardial perfusion occur with similar or lower frequency with mental stress than with exercise in those with normal or moderate left ventricular dysfunction [73]. The situation is worsened if severe left ventricular dysfunction is present. According to another recent investigation, psychological stress may induce myocardial ischemia in some 30% of coronary patients in whom ischemia was not inducible with exercise or chemical nuclear stress tests [74]. In considering differing mechanisms that may underly those observations, two possibilities emerge. The first is a greater likelihood of the coronary vasoconstriction associated with mental stress. Impaired response of coronary microcirculation and endothelial dysfunction may contribute to a differing cardiovascular response of psychological stress versus physical activity. Nonetheless, although several studies have confirmed the presence of coronary vasoconstriction associated with mental stress, the observed changes were highly variable [43, 44, 75]. The second is the relatively more sudden rise in blood pressure with an increase diastolic pressure accompanying psychological stress, in contrast to normally decreased or stationary diastolic blood pressure during exercise [76-78]. Increased left ventricular end-diastolic pressure and greater increase in heart rate seems to additionally worsen the hemodynamic condition in those with a left ventricular dysfunction, making them particularly susceptible to the emotionally induced ischemia.

There are unequivocal data on whether the rise in catecholamine levels correlates with emotionally caused myocardial ischemia. It has been reported that increase in adrenaline during mental stress negatively correlated with the change in ejection fraction [79], others have observed no such correlation [80], and one study suggested a greater relative increase in noradrenaline in patients who developed vasospastic angina and depression of ST segment during mental stress [57].

It is clear that acute psychological stress may induce ischemia both in patients with and without significant ischemic heart disease, as well as in those both with and without damaged left ventricular function. However, there are a number of inconsistencies between studies, their methodologies and results. At the moment, there are no conclusions about relations among the degree of angiographic severity of coronary lesions, systemic and coronary vascular bed behavior, ejection fraction response and rise in catecholamine levels in causing emotionally-induced myocardial ischemia. Further research must further elucidate these relations and define subgroups more susceptible to an ischemic response.

Acute Coronary Syndrome

Episodes of acute psychological stress, and in particular anger, have been identified as possible external triggers of acute myocardial infarction. It has been estimated that increased risk of triggering exists during the first hour after an outburst of anger, and the excess risk may remain for an additional hour [81, 82]. Möller et al [81] observed that the triggering effect of anger was less pronounced in those more accustomed to episodes of anger and suggested a distinction between short- and long-term consequences of anger.

In uncontrolled clinical studies, psychological stress more often precedes the onset of acute myocardial infarction in women [4, 83]. However, it is not clear whether the acute episodes of anger and other psychological stress more significantly increase the relative risk

of infarction in women [82]. Perhaps women are more often exposed to stress due to their more marked response to daily events due to unconscious perceiving of various circumstances as threatening and stressful.

Several further subgroup differences regarding the emotional triggering has been suggested. According to ECG criteria, acute psychological stress has been reported to more often precede the onset of myocardial infarction of inferior than anterior site [84] and non-Q-wave than Q-wave infarction [85]. An association between low socioeconomic status and triggering of myocardial infarction has been reported by one [82] but not confirmed by another investigation [81]. A recent study investigating the triggering of acute coronary syndrome in general [86], observed that triggering by both exertion and anger more likely resulted in ST segment elevation myocardial infarction than in non-ST segment elevation infarction or unstable angina. However, triggering by anger was associated with lower socioeconomic status as defined by deprivation and was more common in younger patients. The last observation is in accordance with a secondary analysis of our data [83-85] showing similar association between younger age and exposure to emotional stress before acute myocardial infarction (unpublished data). Again, it may be only speculated whether younger people are more susceptible due to more vivid reactions and temper, perhaps driven by a greater hormone levels.

Clinical research on psychological triggering of acute coronary syndrome has suggested more defined subgroup differences and an important role of individual reactivity than has been seen for other acute cardiac events. The general conclusion is that psychological stress is likely to be more associated with vasoconstriction, this vasoconstriction is relatively transient and, because of that, the final myocardial damage is smaller than in other occasions of acute coronary syndromes [85]. A further suggestion is that predominant internal triggering mechanism of acute coronary syndrome involving the left anterior descendent arterial tree is an atherothrombotic process, whereas vasospasm may be more important as an internal triggering mechanism contributing to acute coronary syndrome involving the right coronary artery and inferior cardiac wall [84]. The strongest support for the link between acute psychological stress and vasospasm is the greater association of stressful events with development of non-Q than Q-wave infarctions [85]. Nevertheless, since acute coronary syndrome comprises a wider spectrum of coronary atherothrombotic incidents including unstable angina, acute myocardial infarction and sudden ischemic death, it still remains to be explored whether acute psychological stress is more significantly associated with one of these entities.

Cardiac Arrhythmias

Psychological stress has been causally related to ventricular tachyarrhythmia, cardiac arrest or sudden cardiac death [2, 5, 87-90]. Proarrhythmic mechanisms underlying this association have their origin in the sympathetic arousal as described above (Figure 2). Controlled data from the study performed in 42 patients with implantable cardioverter defibrillators (ICD) showed that anger was significantly more likely to be present at the time

immediately preceding an ICD shock than during the control period one week later at the same time of day and day of the week [88].

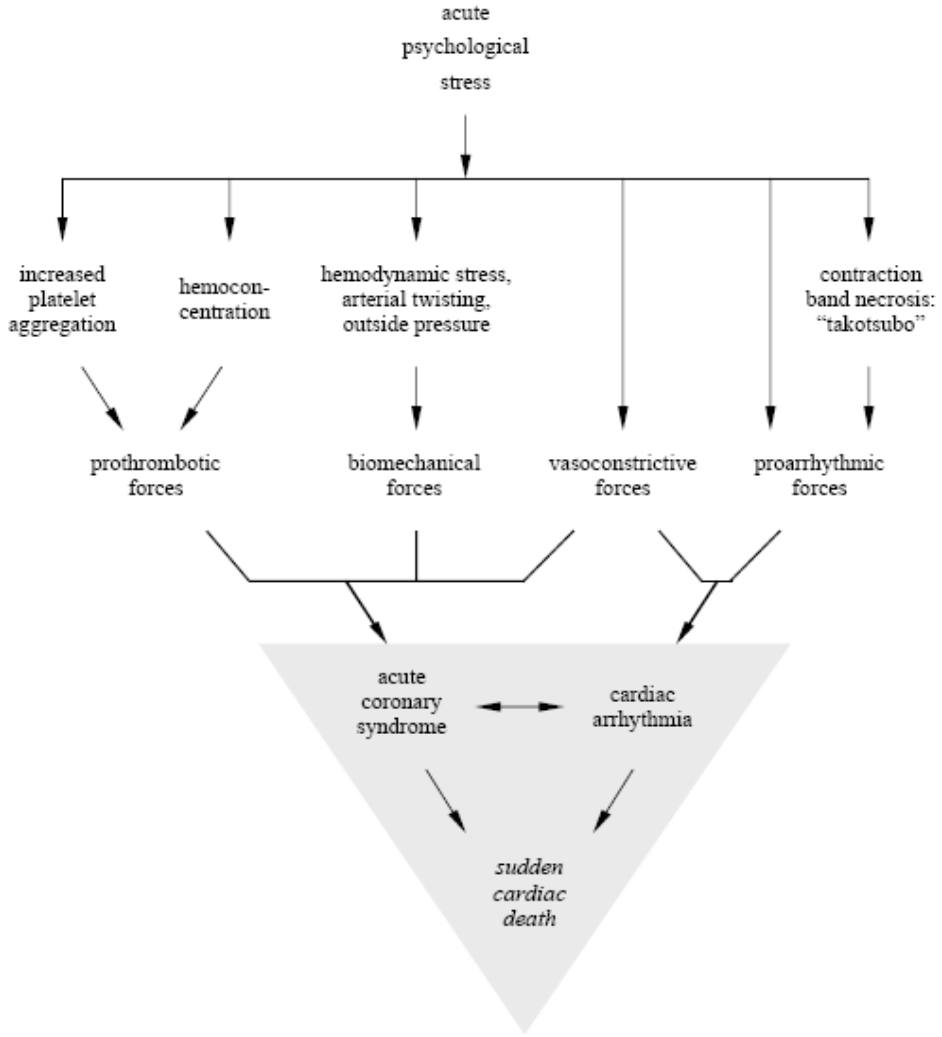

Figure 2. The four major pathophysiological pathways sometimes may lead to acute cardiac events triangle. Pathways include internal triggering mechanisms that may be defined as biomechanical, vasoconstrictive, prothrombotic and proarrhythmic forces.

Holter ECG also offers a possibility to store and analyze the ECG record in order to precisely determine arrhythmia episodes and relate them to eventual psychological stress or some other potential external trigger. In one such study, where statistical and methodological design provided the possibility of simultaneous control for several types of external triggers, we found a clear association of acute episode of emotional stress with both single ventricular ectopic beats [91] and ventricular tachycardia [5] independently of possible physical or meteorologic triggers. Multiple measurements were used as control periods and every patient served as his/her own control.

Based on multiple comparisons and variations in the level of associations, we suggested that reduced cardiovascular ability results in a more severe imbalance of the autonomic nervous system in response to external stress and greater likelihood of ventricular arrhythmia. Because of that, anxiolytics and ß-blockers might have been more protective for such patients by reducing the overall occurrence of arrhythmia and abolishing the late morning peak in sympathetic activity [5]. Our results also suggested that triggering potential of external factors differs in causing single ventricular ectopic beats and ventricular tachycardia, suggesting a complex pathway leading from simple rhythm disorders to a malignant arrhythmia. While single ectopic beats seem to be more directly associated with the pathomorphological disease, central mechanisms and an associated balance of the autonomic nervous system seems more important in the genesis of more complex arrhythmias.

We showed that circadian rhythm of occurrence of ventricular arrhythmias exists independently of exposure to all possible external triggers, including psychological stress [5, 91]. Although psychological and physical stressors both provoke proarrhythmic forces of the sympathetic triggering pattern, our results supported the view that psychological stress could be a more powerful arrhythmia trigger than physical activity.

Apical Ballooning Syndrome

Stress cardiomyopathy, takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome are the terms describing left ventricular dysfunction following a marked acute psychological stress or traumatic experience [92-94]. A typical clinical presentation of this syndrome is transient akinesia of the apical region of the heart, morphologically resembling of octopus trap used in Japan, i.e. pot with a round bottom and narrow neck. The disorder typically occurs in older women with shortness of breath and sudden chest pain on presentation, accompanied by electrocardiographic changes and slight elevation of cardiac enzymes mimicking an acute myocardial infarction. Coronary angiogram reveals either non-significant stenoses, or more commonly, normal coronary arteries.

Transient changes in coronary blood flow including multivessel epicardial spasm and diffuse coronary microvascular dysfunction are proposed as underlying mechanisms. They may produce brief periods of ischemia and contractile dysfunction and may be stimulated by the increase in catecholamine levels immediately after emotional stress. There is also a possibility of direct catecholamine-mediated myocyte injury [95]. Greater contractile dysfunction of the apical compared to other portions of the heart may be caused by the greater ß-adrenergic receptor density and enhanced sensitivity to sympathetic stimulation of this region [96].

Although it may be preceded by both physical and emotional stress [92], it seems more likely that psychological stress has the pivotal role in triggering of this disorder primarily affecting post-menopausal women [93, 94, 97]. The reasons for this phenomenon are still under debate. Reduction in estrogen levels has been associated with altered endothelial function [98] and coronary vasoreactivity [99]. Sex hormones probably have an influence on the sympathetic neurohormonal axis, but the nature of this influence and its consequences on cardiovascular system are complex and poorly understood as yet. Although men have higher

levels of basal sympathetic activity than women [100], women may be more vulnerable to a sudden change and rise in sympathetic tone and catecholamine levels. However, women seem to be more prone to sympathetically-mediated myocardial stunning [101].

The importance of the transient left ventricular apical ballooning syndrome in the context of present considerations mirrors the fact that it is often triggered by acute psychological stress and, although the prognosis is generally excellent, complications in the form of cardiogenic shock (4.2%) or ventricular fibrillation (1.5%) may occur. Further research is necessary to shed additional light on the aethiology, pathophysiology and treatment of this syndrome.

Conclusions

It may be concluded that various psychological variables may act as chronic, modifying or acute risk factors for cardiovascular diseases. On some occasions, they may directly cause an acute cardiac disease. As with any other health problem, association of psychological factors with acute cardiac events is multileveled. Future research should provide additional insight into the areas of individual reactivity to psychologically stress, differences in exposure, mass events, chronobiologic variations and means of prevention.

Varying individual response of the human cardiovascular system may make some patients more prone to emotional and psychological triggering, may determine the moment of onset and affect the course of cardiac incident. Current knowledge suggests that the risk of acute cardiac event changes over time, is associated with the long-term psychological situation as well as with everyday circumstances, and importantly depends on the individual cardiovascular condition and reactivity. Baseline and demographic variables that may underlie individual differences in response to stress include gender, the presence of coronary artery disease, left ventricular function, and brain activity. These variables may partially influence the differences in intensity of induced internal triggering mechanisms including hemodynamic, vasoconstrictive and prothrombotic forces.

Generally speaking, there are several groups of measures that could be useful in lowering the risk of emotional or psychological triggering. Efforts to control traditional chronic risk factors are effective for all aspects of cardiovascular protection. Overall reduction of cardiovascular risk also reduces the risk that an acute cardiac event will be triggered by some external trigger including psychologically provocative situations. Better detection and understanding of coronary atherosclerosis and other cardiac diseases, and accompanying components of patient vulnerability – plaque, blood and myocardial – may indicate persons whose disease is about to be transformed to a, possibly fatal, acute event. Unfortunately, an acute event is often the first clinical manifestation of the disease. In patients with defined and clinically manifested disease, we are well aware that psychological stress may trigger an incident. Stabilization of components of the patient vulnerability should be the primary goal in all subgroups of patients.

Four types of medication have shown possible effect for the prevention of psychological triggering. In animal model studies, anger-like stresses may increase the myocardial vulnerability and provoke abnormalities in rhythm, but may be prevented by ß–blocking

agents [54, 102]. In patients who in the setting of psychological stress present with life-threatening ventricular tachyarrhythmia, ß-blockers reduced the occurrence of arrhythmic episodes [103]. In the general population, where among external triggers emotional stress appeared most powerful in provoking ventricular arrhythmia, ß-blockers showed protective effect, particularly in men and the elderly [5], most likely due to the interference of ß-blocking therapy with the components of the sympathetic triggering pattern.

In two study settings, ß-blockers and calcium antagonists have exerted a similar beneficial effect. The incidence of emotionally-induced myocardial ischemia was reported to be lower in patients taking either of these two drugs [58]. Next, among those who respond to emotional stress with the fall in ejection fraction, atenolol or nifedipine prevented such a response [64]. While the effect of ß-blockers may be explained by the abolition of sympathetic activity, explanation for calcium antagonists is much more speculative. Locally released noradrenaline from the nerve terminals may produce a direct toxic lesion and necrosis of the myocyte [95, 104, 105]. High noradrenaline levels may disturb the normal function of calcium channels. The channels may remain opened, thereby allowing the calcium influx and potassium efflux. Both of these currents may contribute to damage of myocyte and its membrane leading to changes ranging from reversible ones to cell death.

Beneficial effects of aspirin in cardiovascular protection are well recognized. Protective mechanisms encompass general prevention of atherothrombotic events and anti-inflammatory properties [106]. Although the observed associations were slightly below the statistically significant level, two reports have suggested the possibility of protection against psychological triggering of acute coronary atherothrombosis. In a case-crossover study that was the first showing the potential of anger in triggering acute myocardial infarction [82], there was a trend toward the lower risk of triggering in patients receiving aspirin. In another study [41], the patients whose acute coronary syndrome was likely triggered by emotional stress were apparently less using aspirin than those whose incident was not triggered by such a stress.

Anxiolytics may reduce the risk of emotionally and otherwise triggered ventricular arrhythmia probably through more complex mechanisms. Our studies provided a link between central influences and triggering of ventricular arrhythmias by psychological and other external triggers. Beside ß-blockers, anxiolytics independently reduced the overall frequency of ventricular tachycardia and blunted the late morning peak in occurrence in all population subgroups, but the effect was more pronounced in men and the elderly. Perhaps, anxiolytics may abolish an impairment of the autonomic nervous system caused by centrally-induced sympathetic storm after the stress. Medicamentous therapy of anxiety and similar disorders could be particularly considered in highly vulnerable patients, like those in coronary care units, or during the short intervals before permanent stabilization of an unstable disease.

Medicamentous intervention that would reduce myocardial vulnerability could be important for patients whose ischemia in some myocardial regions cannot be resolved by invasive, surgical or other treatment. Moreover, a better assessment of individual reactivity to acute psychosocial stress may be the base for an individual adaptation of medicamentous therapy. For example, more dynamic reactors may be prescribed somewhat higher dose of ß–blocker than it would be otherwise.

Non-medicamentous psychological or psychiatric therapy dealing with anxiety, anger, depression and other conditions may also decrease the susceptibility for acute events. The primary idea is to reduce cardiovascular reactivity to stressful circumstances. In addition to anger management programs, several therapeutic options have shown promising results. A body of evidence suggests that coronary patients who were taught relaxation therapy have lower resting heart rate and the incidence of non-fatal and fatal cardiac events [107]. There are also suggestions for the beneficial effect of yoga [108], meditation [109] and hypnosis [110] in reducing proarrhythmic effect of psychological stress and on other segments of cardiovascular risk profile.

Psychological factors obviously can trigger isolated events of acute cardiac disease. Psychological background certainly contributes to the increase in cardiac events associated with war, terrorist attacks and natural disasters. Furthermore, the world of emotions may play the role in major chronobiologic phenomena that affect cardiovascular diseases. It is now clear that there is a nonuniform temporal distribution of these diseases, and the most prominent features are circadian, weekly and seasonal pattern of occurrence. Although in this regard the role of psychological factors is rather speculative, their subtle influence seems to be present. Complete elimination of psychosocial factors as potential triggers of cardiac diseases is not realistic. However, a successful management will probably include a combination of medicamentous and other measures, individually adjusted. These measures are complementary, and combined they could be effective in an individual patient or in a particular subgroup of patients with a heart disease. Additional understanding of the role of psychological factors in causing acute cardiac events may help in improving both prevention and treatment of such events.

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Chapter 3

Spiritual Influences on Cardiovascular Risk

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Abstract

Both acute and chronic stress can be harmful for the cardiovascular system. Depression is also a risk factor for stroke. The positive effects of spiritual influences are outlined for their possible preventing effects. Religious attendance and prayer have been shown to reduce the mortality rate of cardiac diseases. Psychosocial factors should be considered in the delivery of care and the outcome.

Introduction

Everybody is aware of psychological influences on cardiovascular system. People become pale for fear and scarlet for anger but more subtle changes have been signaled by recent researches. Physiological and psychological factors are interconnected and intermingled. They are complementary rather than alternative. Spiritual influences can be considered as a beneficial antidote against stress.

Acute Stress Disorder is said to last for a minimum of 2 days up to a maximum of 4 weeks and occurs within 4 weeks of initial stressor. The initial event could be seriously harmful for the persons or their peers. Chronic stress permits people to cope with steady difficulties requiring continuous adaptation. Individual resources are required and when they initiate to be insufficient, a biological loan is required, which is charged on the whole organism, thus generating a risk for cardiovascular, neurotic and psychosomatic complications.

Psychosocial stress has been implicated in the very high rates of hypertension and subsequent cardiovascular morbidity and mortality.

Chronic stress and the burden of care caused by Alzheimer's disease are associated with reduced immunity, and increased cardiovascular risk, hyper-reactivity of sympathetic and platelet activation. It has been speculated that this activation is a defense mechanism limiting hemorrhage of animals captured by predators. It has been found among caregivers only, that increased symptoms of depression and anxiety are associated with delayed nor-epinephrine recovery, increased reactivity and delayed platelet P-selectin recovery [1]. These changes may represent a shift from caregiving stress to cardiovascular risk. The stress expansion may turn into depression among caregivers [2]. Depression is in this case a defense mechanism. Although these analyses are limited to cross-sectional data, they suggest that the subjective experience of stressful circumstances is a proximal and powerful determinant of depressed mood. The more objectively understood burdens of care appear to act as the trigger that initiates the progression of stress to depression by engendering subjective feelings of overload and entrapment in the caregiver role.

The influence of depression on the risk of stroke has not been extensively studied. However, several epidemiological studies raise the possibility that a relation exists. In one study of elderly individuals, higher depressive symptoms increased the risk of stroke [3]. Many older individuals with depression developed later in life have evidence of subtle cerebrovascular disease. Vascular depression is identified as the mood problems occurring in patients suffering from ischemic changes in the brain. The vascular changes may be related to atherosclerosis, hypertension, or myocardial infarction. Post- stroke depression negatively affects outcome either during hospitalization or after discharge. Both basic and instrumental activities of daily living are negatively influenced [4-12]. On the other hand, depression is less associated with functional outcome than neurological signs and cognitive impairment [13].

Many other variables and their combinations may affect stroke outcome, like diastolic blood pressure [14] and homocystein [15]. Interleukin-1 [16], Interleukin-6 [17], C-Reactive Protein and other inflammatory markers may lead to platelet dysfunction, abnormalities in blood coagulation, endothelial dysfunction, autonomic dysfunction and abnormalities in heart rate variability A prospective study provides evidence that depressive mood represents a real risk factor for cerebrovascular accidents [18]. Nevertheless, inflammation does not fully explain the relationship between depression and cardiovascular disease. A prospettive cohort study measured C-reactive protein and interleukin-6. The main outcome of the study was incidence of cerebrovascular events (hospital stays for nonfatal myocardial infarction, stroke, congestive heart failure, and related mortality). Depression was a significant predictor of cerebrovascular disease but both depression and inflammatory biomarkers remained independent predictors of outcome [19].

One can foresee a growing endeavor for identifying the transducer mechanisms from either strong emotional state or weak but steady to cardiac death. Proper prevention measures could be applied for reduction of mortality rate.

Sudden Death

Stressful events appear to trigger malignant ventricular arrhythmias and myocardial infarction in cardiac patients [20]. Interesting observations that go beyond Science are collected from both Chinese and Japanese American Communities, who consider the fourth day of the month as unlucky. There is an explanation. Indeed, the words “death” and “four” have completely different ideograms, but the sound is the same, i.e. *shi*. Yet, statistics indicate that these Communities have a peak of mortality particularly on that day, differently from white Americans [21]. Indeed, white controls, matched on age, sex, marital status, hospital status, location and cause of death, showed no similar peak in cardiac mortality. No compensatory drop in number of deaths followed the peak of mortality in those Oriental Communities. The high peak on the fourth day of the month was particularly evident for deaths from chronic heart disease and still larger for deaths from chronic heart disease in California. Thus, the high cardiac mortality can increase on psychologically stressful occasions in a silent way. Recurrent fear of death when the 4^{th} day of the month is approaching appears to impair the quality of life in a silent way.

Even holidays can be dangerous. Cardiac mortality is highest during Christmas/New Year's holidays independently of climatic factors [22]. The increase in mortality rate for cardiac and non-cardiac diseases is still present after adjustment for trends and seasons. The high rate in mortality during holiday is increasing over time, both for cardiac and non-cardiac mortality. Whereas death on the fourth day of the month is unexplained by confounding variables, such as changes in the diet and in drug regimens, alcohol intake, leisure and work, the possibility that holiday-induced delays in getting treatment could be an alternative explanation of mortality at Christmas/New Year time. For Catholic people St. Andrew Avellino is the patron against sudden death. The Saint suffered from acute stroke while he was celebrating Mass.

Faith, Spirituality, Religion

Faith is defined by St. Paul: Now faith is the assurance of things hoped for, the conviction of things not seen (Hebrews, 11,1). Spirituality and religiosity are close concepts and not synonymous. Spirituality is taken to mean believing, valuing, or devoted to some high power beyond the corporeal world. Spirituality is concerned with the trascendent with addressing ultimate questions about life meaning, assuming that there is more than what can be seen or understood [23, 24]. By contrast, religiosity involves a doctrinal system that is shared by other people. Religious participation, more than spirituality, may account for beneficial effects on health and survival, since religiousness is linked to a group of worshippers sharing doctrine, communication, control and habits. Therefore, social participation, rules, style of life, dietary restrictions and moderation can explain the benefits.

A recent interest in the rehabilitative field has arisen [25-28]. A holistic, inclusive and client-centered rehabilitation is in demand. This rehabilitation will focus on the spiritual self, beyond the physical, cognitive and social selves. These issues are important in people with disability of fast onset (e.g, stroke, brain and spinal injury). In a model of spirituality one axis

indicates intrapersonal, interpersonal and transpersonal relationships. There are five themes on the other axis: awareness, closeness, trust, vulnerability, and purpose [25]. Relying on religion is an active coping strategy [29]. According to the Authors a collaborative relationship with God can help. The complex of stimuli, perception, and reactions to internal and external demands challenge the organism's adaptation resources. In that model [14] people appraise stress-producing events using primary appraisal ("Is the event potentially harmful?") and secondary appraisal ("Can I cope with it?"). A stress reaction may ensue depending on various mediators such as social support, personal hardiness, problem-solving style. Empirical research on the role of religion in counseling has increased considerably. Religious and nonreligious people tend to experience the same amount of stress, but religion may help people deal better with negative life events and the attendant stress. Religious community is like a shelter where prevention, promotion and mutual collaboration foster coping strategies against negative events of life.

Fear of death is most prominent during midlife and not late-life. Neuroimaging studies led to the "vascular depression" hypothesis. Depression was found to be a strong predictive factor leading to stroke, while religiosity seemed to be a 'protective' factor. A possible interpretation is the vascular etiology of the late-life depression. Religiosity could be interpreted as absence of depression, and, therefore, mainly as absence of vascular lesions [30]. Depression has been studied more extensively than other mental health outcomes. One of the few longitudinal studies showed that religiousness and active participation to service were inversely correlated with depressive symptoms, whereas private religiosity failed to have the same effect [31]. Lower mortality rates for those who attend religious services [32] are only partially explained by possible confounding variables (demographic data, health status, physical functioning, health habits, social functioning and support, and psychological state). The association between self-reported religious attendance and subsequent mortality over 5 years for older residents was examined by proportional hazards regression. Interaction terms of religion with social support were used to explore whether other forms of social support could substitute for religion and diminish its protective effect. Persons who attended religious services had lower mortality than those who did not. Higher religious attendance is apparently linked to longer survival. Level of participation in private religious activities can also be beneficial, on condition that activities of daily living are preserved. A study [33] considered prayer, meditation, or Bible study by self-report at baseline, along with a wide variety of socio-demographic and health variables. During a median 6.3-year follow-up period, a third of the subjects died. Those reporting rarely to never participating in private religious activity had an increased relative hazard of dying over more frequent participants, but this hazard did not remain significant for the sample as a whole after adjustment for demographic and health variables. Religion is important for Hispanics living in the United States, particularly older Hispanics. Weekly church attendance may reduce the risk of mortality among older Mexican Americans [34]. Indeed, the results showed that those who attended church once per week exhibited a 32% reduction in the risk of mortality as compared to those who never attended religious services. Moreover, the benefits of weekly attendance persist in a model controlling for confounding variables (socio-demographic characteristics, cardiovascular health, activities of daily living, cognitive functioning,

physical status and mobility, social support, health behaviors, mental health, and subjective health).

Successful aging is also considered to be influenced by positive spirituality, the so-called forgotten factor, and leaders in gerontology are criticized when they fail to consider its growing evidence [35]. Over 40% of hospitalized medically ill elderly people spontaneously reported that the religious faith was the most important factor that enabled them to cope. Recent articles have emphasized the importance in Medicine of religion and spiritual involvement in better health outcome, including greater longevity, coping skills even during terminal illness, whereas anxiety, depression and suicide attempts decrease [36, 37]. A fairly consistent positive relationship was found between life satisfaction and religiousness [38].

In respect of inpatients after stroke, there have been no systematic investigations and no studies of managed care networks. Yet, religious experience is not only part of multiculturalism but also consistent with the overall direction of postmodern culture. It is surprising that only a few articles on stroke are found [12] mainly addressed to the question of benefit mechanisms of attending religious services. Yet, some articles already outlined the role of religion and spiritual beliefs in rehabilitation units. According to the authors, spiritual and religious beliefs are probably important to many rehabilitation patients since life satisfaction and quality of life can be positively influenced.

When a patient is referred to a rehabilitation center, a stressful occurrence takes place, i.e. an event or a series of events or life conditions that demand adjustment. The complex of stimuli, perception, and reactions to internal and external demands challenge the organism's adaptation resources. In Pargament's model [29] people appraise stress-producing events using primary appraisal ("Is the event potentially harmful?") and secondary appraisal ("Can I cope with it?"). A stress reaction may ensue depending on various mediators such as social support, personal hardiness, problem-solving style.

Although religiosity appeared to be unrelated to stress among caregivers of patients suffering from dementia, nevertheless one stressor, namely feelings of role overload, was correlated with greater levels of self-perceived religiosity [2].

Personal Contribution

Depression occurs in about a third of patients with recent stroke. A research was aimed at testing the hypothesis that Faith can dampen depression. One hundred and thirty-two consecutive Italian patients were enrolled after their first stroke without comprehension or mental impairment [39].

Dependence and Depression were evaluated. Spiritual and religious beliefs were assessed by means of the Royal Free Interview (RFI) [40]. The instrument has high criterion validity, predictive validity, internal consistency and test-retest reliability. A translated and validated version into Italian [33] was used. High scores indicate strong religious and spiritual belief.

The Hospital Anxiety and Scale (HADS) [41] is a self-assessment scale to measure both anxiety and depression. Higher scores mean higher psychological distress. The subscales are also valid measures of severity of the emotional disorder.

Fifty-five cases of the patient population (41.6 %) had a total score above the cut-off of 10 (range 11-36). Fifty-five patients (41.6 %) had a value above 5 at the Anxiety sub-scale and fifty-seven patients (43.2%) had a value above 5 at the Depression sub-scale.

Logistic models were carried out on dichotomized HADS scores (respectively under and above 10). For each unit increase in RFI scores we observed a 5% decrease in HADS scores. The relationship between RFI and HADS scores was not affected by the adjustment for socio-demographic factors and cognitive functioning and after further adjustment for functional dependence, comorbidity, living conditions and marital status. In this model the other significant variable was functional dependence. The analysis of HADS subscales “Anxiety” and “Depression” gave similar results, with a 4% and 5% decrease in HADS scores, respectively, for each unit increase in RFI scores. Thus, HADS score is significantly associated with RFI scores in a negative way. Patients without emotional distress have higher score at RFI. Both depression and anxiety are influenced.

Prayer

Prayer is the act of attempting to communicate with a superior presence, with a sequence of words, with special postures or movements. The worshippers can request help, assistance, guidance, and forgiveness for themselves or for other persons. Prayer is also the way for expressing thoughts and emotions in a divine link. For stroke survivors, prayer is a basic part of recovery [42]. Some participants used specific prayers, such as the Rosary and religious poems, each day of the week, to pray for themselves and others. Other participants resumed their usual patterns of praying, mostly during church services. Prayer appears to be the most common form of religious coping and even non religious people often turn to prayer in the throes of suffering. Several themes focus on how prayer is used for coping after stroke. They are Connecting to God, Considering self, others and nature, Ways of praying, Becoming more focused on everyday, Reaching back to early family life, Linking present and past, Finding strength, Being unburdened and comforted.

Rosary and Mantra have been scientifically investigated [43]. The word Rosary means "Crown of Roses". Our Lady has revealed to several people that each time they say a Hail Mary they are giving her a beautiful rose and that each complete Rosary makes her a crown of roses. The Holy Rosary is composed by decades. Each one is recited in honor of a mystery. Generally, 5 decades are recited at time while meditating at on one set of mysteries. It is customary to recite bead by bead for every Ave Maria of the decade. Beads are like a clock.

During recitation of Ave Maria and the Yoga Mana the effects are similar, namely slowing respiration to around 6/min and thus having a marked effect on synchronization and also increased variability in all cardiovascular rhythms. This was seen not only in the respiratory signals but also in the RR interval, systolic and diastolic blood pressures, and in the trans-cranial blood flow signal. Free talking reduced the respiratory rate more irregularly. The spectral peaks of respiration and of all cardiovascular signals were synchronized during the Ave Maria and the Mantra sequences, as they occurred at the same frequency. The spectral peak of respiration was narrower during Rosary than during spontaneous breathing and free talking, as a consequence of more regular breathing. Enhanced cardio-vascular

oscillation synchronized sympathetic and vagal outflow, inducing rhythmic fluctuations in cerebral blood flow. Rosary and Mantra are similar from the physiological point of view, because they are historically connected. The Rosary was introduced to Europe by crusaders, who took it from the Arabs, who in turn took it from Tibetan monks and the Yoga masters of India.

Trascendental Meditation

Transcendental Meditation (TM) requires the individual to repeat the Mantra. An induced state of consciousness, different from waking, sleeping or dreaming is reached, like a state of restful alertness. The person experiences pure consciousness and becomes quieter and quieter, carefree. TM was examined for the first time in 73 residents at a home for older subjects [44]. Half of them were assigned to a daily meditation and half were not. After 3 years none of the meditation group died, but 25 percent of the no-meditation group had died. Since then, TM has been exploited for controlling hypertension in subjects at risk, like African Americans who suffer disproportionately higher cardiovascular disease mortality rates than do whites. Psychosocial stress influences the development and progression of atherosclerosis. Stress reduction with the TM program was associated with reduced carotid atherosclerosis compared with health education in hypertensive subjects [45]. The randomized controlled clinical trial evaluated the effects of the TM program on carotid TM in hypertensive African American men and women, over 20 years of age, in a 6- to 9-month interval. From the initially enrolled 138 volunteers, Forty-three percent of them completed pretest and posttest carotid intima-media thickness data. The assigned interventions were either the TM program or a health education group. The TM group showed a significant decrease of -0.098 mm in the carotid wall compared with an increase of 0.054 mm in the control group. African Americans are in proportion the largest ethnic group to receive TM. The impact of TM program on cardiovascular reactivity was also studied in adolescents with high normal blood pressure [46]. The TM program appeared to have a beneficial impact upon cardiovascular function at rest and during acute laboratory stress in adolescents at-risk for hypertension. Another research was carried out to compare intervention groups on mortality rates after adjustment for study location [47]. Mean follow-up was about 7 years. Compared with combined controls, the TM group showed a 23% decrease in the primary outcome of all-cause mortality after maximum follow-up. Secondary analyses showed a 30% decrease in the rate of cardiovascular mortality and a 49% decrease in the rate of mortality due to cancer in the TM group compared with combined controls. These results suggest that a specific anti-stress strategy used in the prevention and control of high blood pressure, such as the TM program, may contribute to decreased mortality from all causes and cardiovascular disease in elderly people suffering from systemic hypertension. A randomized controlled was again carried out in African-American subjects. Interventions included 20 min TM twice a day, or progressive muscle relaxation, or participation in conventional health education classes. The TM group showed a significant decrease in blood pressure compared to controls. Women practicing TM had higher decrease of blood pressure then men [48]. In addition, the TM subjects required a reduced dosage of hypotensive medication.

Spirituality influenced recovery of patients after an acute myocardial infarction by providing the participants with inner strength, comfort, peace, wellness, wholeness, and enhanced coping [49]. Spiritual issues are a new field in Medicine enabling the team to understand the experience at the onset of a cardiac disease from the perspective of the ill person. Medical doctors should identify patients' perceptions of how their coping strategies influence recovery, because they can be exploited. Five phases to discovering meaning and purpose were: (a) facing mortality, (b) releasing fear and turmoil, (c) identifying and making lifestyle changes, (d) seeking divine purpose, and (e) making meaning in daily life [49]. Middle-aged and older patients facing a major medical crisis-cardiac surgery can reach hope and dispositional optimism through the use of prayer as a coping strategy [50].

The opinion that religious orientation may be an important variable affecting cardiovascular reactivity in older adults is shared by other authors [51]. Older extrinsically religious individuals demonstrated exaggerated reactivity compared to younger participants and older intrinsically religious individuals. Older intrinsically religious participants did not differ from younger persons. Similar results were found for analysis of baseline data. Extrinsic participants had greater reactivity during the interpersonal confrontation condition than did intrinsic individuals.

A New Doctor-Client Relationship

The relationship between religiosity and well being is seen with some restriction. In caregivers to a patient with dementia three variables were considered, such as: i) care-related stress, ii) religiosity, and iii) depression. In spite of high rates of self-described religiosity, church attendance and frequency of prayer, religiosity appeared to be largely unrelated to stress and stress expansion [2]. However, one stressor-feelings of role overload was correlated with greater levels of self-perceived religiosity, among caregivers who have health problems of their own.

However, the caregivers' world is different from the patients' world. Some patients dare not call for basic spiritual care by their clinicians and could censure doctors for ignoring their spiritual needs. On the other hand, most clinicians think that spiritual interventions would be really beneficial, but are aware of little training in providing basic spiritual assessment or care. Nowadays, professional associations and educational institutions are beginning to provide information on how to connect spirituality and practice [52]. Some authors suggest that physicians ignore patient spirituality because they may not have the knowledge or skills to engage religiously their patients in meaningful discussions about their spiritual needs without offending them [53]. Indeed, doctors should neither recommend proselytizing nor inviting patients to engage in religious activities. Similarly, no recommendation should be addressed in life situations even though these activities are associated with health benefits. Doctors should not turn themselves into passionate preachers. Nevertheless, it is important for physicians to take patient's religious or spiritual feelings into consideration in the practice of medicine in an effort to provide a more holistic care. Doctors should be aware of some particular belief, when they can be dangerous for the client's health. This is the case for the

4th day of the month for some communities. Preventive care, including psychological support, could offset negative events.

Our results endorse the importance of coping during illness that may lessen the feeling of vulnerability Supporting spirituality may enrich the patient-physician relationship. Psychosocial factors influence the delivery of care and the outcome. A review found fairly consistent inverse associations of religiousness with rates of depression and suicide [54]. Suicide is less common in persons who believe that life is a gift from God. Therefore, subjects who were granted with such a gift would commit a mortal sin in case of suicide.

A new "ethic of friendship, marked by wisdom, candor, and respect" can be applied in physician-patient relationship, since patient's beliefs may have a role in coping with illness and all the patients are treated regardless of their religious or spiritual attitude "in a technically excellent manner and with a spirit of love" [55,56].

On the other hand, let us look at some unpleasant observations [57] *'The observed lack of rehabilitation nursing, nurses' disengagement from the team and nurses' observed lack of warmth towards patients on the stroke unit were all surprising findings. Further research needs to examine whether such findings would be reproduced in stroke units elsewhere. If so, it might be that the better outcomes achieved on stroke units are despite rather than because of the nursing they receive there'*

Hopefully, these whipping observations ought to disappear.

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Chapter 4

Psychological Risk Factors in the Development of Hypertension

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Abstract

Hypertension is a potent cardiovascular risk factor, thus the prevention and treatment of this condition is of major importance. Acute stress can induce transient increases in blood pressure and other psychosocial factors have been implicated in the development of hypertension. However, the effects of stress reduction interventions on cardiovascular outcomes have been inconsistent, thus the importance of psychosocial factors remains a matter of debate. One intriguing question that remains partly unanswered is why a similar level of stress exposure might lead to the development sustained hypertension in some individuals but not in others. Emerging evidence is beginning to demonstrate that the specific nature of the stressor, genetic factors, and behaviors such as sleep and physical activity may be important when considering psychological risk factors for hypertension.

Introduction

Essential hypertension is the chronic elevation in blood pressure of unknown origin, which is generally defined as blood pressure persistently above 140/90 mmHg. The condition is prevalent in 15-25% of the adult population in most countries [1], and is estimated to cause 4.5% of current global disease burden. In particular, hypertension is a potent risk factor for stroke and coronary mortality [2], thus presents a major concern to world wide health organisations. The lowering of blood pressure in hypertensive patients through the use of pharmacological treatment has been shown to significantly reduce the risk of stroke and myocardial infarction [3], although some of these drugs may have adverse side effects and are not cost effective. Therefore, this has stimulated researchers to investigate lifestyle

approaches for prevention and treatment of hypertension. Patients now tend to be classified not only in relation to the grades of hypertension but also in terms of the total cardiovascular risk resulting from the coexistence of different risk factors, organ damage and disease. Thus, lifestyle modification has enormous potential for controlling blood pressure and overall cardiovascular risk. Current recommendations emphasize weight loss in those who are overweight/obese, sodium reduction, increased physical activity, limited alcohol intake, and smoking cessation [3], although psychological risk factors are not widely recognised. Indeed, the fundamental question of whether psychosocial stress causes hypertension in humans has been difficult to evaluate using an experimental approach because of ethical constraints. Thus, evidence is mostly derived from observational studies, natural experiments, and laboratory studies to show whether stress modifies disease relevant biological processes. This chapter will focus on these lines of evidence and will specifically consider the role of subacute and chronic stressors, chronic psychological states, interactions with genetics and other risk factors, and interventions using psychological approaches. There has been a vast amount of animal research in this area, which has produced far from consistent findings, thus the present chapter will primarily focus on studies with human participants.

Sympathetic Nervous System

The sympathetic nervous system (SNS) is thought to play a pivotal role in many of the psychophysiological effects that will be described later. The peripheral SNS innervates tissues throughout the body, especially the heart, vasculature, and adrenal medulla. The adrenal medulla responds with systemic catecholamine release (predominantly epinephrine), whereas norepinephrine is released from terminals that line the vasculature. The SNS is primarily responsible for rapid, short term alterations in cardiovascular function during mental and physical stress, and also has metabolic effects (insulin resistance and lipolysis) and varied immunological effects (release of cytokines and acute phase proteins). A number of investigators have attempted to bring about chronic hypertension using neurogenic methods, such as direct stimulation of the defence area in the brain [4], exposing rats to noise [5], and operant conditioning of primates [6]. However, only temporary elevations in blood pressure are generally observed, thus suggesting that the SNS is important in the short term regulation of cardiovascular function but not in long term control of arterial pressure. There are a number of other neuroeffector mechanisms that may influence the long term regulation of blood pressure. The renal sympathetic nerves not only cause renal vasoconstriction but also enhance the release of renin and promote reabsorption of sodium and water from the renal tubules. Thus, high levels of renal SNA can shift the pressure natriuresis curve and facilitate the maintenance of hypertension by interfering with the ability of the kidney to compensate for an increase in arterial pressure through pressure natriuresis. The SNS can also exert long term trophic effects on vascular muscle [7], thus causing structural changes in blood vessels that increase vascular resistance and the vasomotor response to vasoconstrictor stimuli.

Subacute and Chronic Stress

It is well known that acute stress results in elevated blood pressure. Indeed, the well defined phenomenon of *white coat syndrome* describes an elevated pressure response that some individuals experience when their blood pressure is measured by a physician, which is largely induced by anxiety. White coat hypertension may be a cause of cardiovascular dysfunction [8], although this is still an area of debate. In the laboratory setting mental challenges such as public speech or mental arithmetic can produce sizable increases in blood pressure, elevated cardiac output, increases in total peripheral resistance and local skeletal muscle vasodilatation. Other alterations that are characteristic of the classic defence response include activation of the renin-angiotensin system in order to conserve sodium and thus promote conservation of water, insulin resistance in order to sustain adequate levels of blood sugar for the brain to function, and increased immune surveillance in case of injury or infection. The reactivity hypothesis suggests that a recurrent pattern of exaggerated SNS activity may up-regulate basal blood pressure levels over time and also contribute to atherosclerotic processes. Prospective studies have demonstrated that heightened blood pressure responses to acute mental stressors is associated with hypertension at follow up after statistically controlling for other risk factors [9], although this association probably explains only a small amount of the variance in the prediction of hypertension and causality remains an issue. For example, de Geus et al [10] have recently demonstrated the existence of stress specific genetic effects in relation to blood pressure reactivity that may also independently relate with susceptibility to hypertension. Other factors that might determine individual stress reactivity patterns remain largely unknown, but previous research has focused on personality traits, chronic stress states, and health behaviors such as diet and physical activity levels. Research that has focused on the influence of background life stressors on acute cardiovascular stress reactivity has, however, produced conflicting findings demonstrating both positive and negative associations between ongoing stressors and reactivity [11]. These findings may reflect an adaptation response, whereby heightened reactivity is displayed in the early stages of stress exposure that is attenuated as the ongoing stressor becomes chronic. Such a process is commonly referred to as ‘allostatic load’ [12].

Biological stress responses may also be important – in a prospective study of British civil servants a heightened interleukin (IL)-6 response to mental stress predicted greater blood pressure at 3 years follow up after statistical adjustment for various confounders at baseline [13]. This data is corroborated by animal work, which demonstrated the hypertensive response to acute stress was attenuated in IL-6 knockout mice [14]. Emerging data is also beginning to demonstrate the importance of recovery from acute stressors [15], which suggests that poorer recovery of blood pressure is related to a number of adverse health outcomes.

Acute psychological trauma has profound effects on blood pressure. For example, the World Trade Centre terrorist attacks in New York on 11th September 2001 produced a substantial and sustained increase in the blood pressure of participants from the local community [16]. Parati et al [17] demonstrated a 20% increase in systolic blood pressure following a moderate intensity earth quake that struck central Italy, which was followed by a long lasting period of enhanced blood pressure variability and blunted nocturnal blood

pressure fall. Data from a meta-analysis also shows that individuals with posttraumatic stress disorder (PTSD) have higher levels of basal cardiovascular activity relative to comparable groups of individuals without PTSD, suggesting increased SNS activity [18]. Daily, enduring stress has also been associated with cardiovascular responses. In a 30 year prospective study, Italian nuns living in secluded order demonstrated remarkably stable blood pressure in comparison with the age related rises seen in lay women from the same region [19]. These effects were attributed to differences in psychosocial stress among the women. Numerous studies have investigated the effects of work stress on cardiovascular risk. Several plausible biological pathways may mediate this association, including increased working day ambulatory blood pressure and reduced parasympathetic influence [20], and higher levels of LDL cholesterol and inflammatory markers [21]. However, the findings from prospective cohort studies in relation to work stress and hypertension risk have been generally inconsistent [22-27], which may reflect variation in the definitions of work stress, different gender effects, and interactions with other factors such as social support. Indeed, in a recent Canadian cohort job strain was associated with elevated blood pressure in the presence of low marital cohesion but high marital cohesion ameliorated this effect. Interestingly, this association was found among women but not men [28]. The quality of close relationships appears to be an important predictor in itself. Prospective studies link marriage to better cardiovascular health, but marital dissatisfaction and discord predict adverse health outcomes [29].

Chronic Psychological States

Chronic psychological states refer to enduring mood states such as depression and anxiety, and personality traits such as type A behavior. In particular, depression has gained substantial attention as an independent predictor of hypertension, cardiovascular disease and all cause mortality, and is often comorbid with chronic diseases that can worsen their associated health outcomes [30]. In a meta-analysis of 10 prospective cohort studies, there were moderate effect sizes for associations of anger, anxiety, and depression as predictors of hypertension [31], although no moderator effects were demonstrated. A number of mechanisms may underlie the cardiovascular risk associated with depression, which include inflammatory pathways, changes to sympatho-vagal balance, and alterations in hormone and catecholamine circadian rhythms. These adverse changes may partly develop through poor regulation and lack of adaptation to acute stressors. Prospective data has linked work stress, such has as high demands and low job control, with higher incident depression [32, 33] and during the 3 to 6 months preceding the onset of depression, 50 to 80% of depressed persons experience a major life event [34]. Evidence from psychophysiological studies shows that depressive symptoms are related to exaggerated cardiovascular stress reactivity [35] and impaired neuroendocrine functioning [36]. Health behaviors such as physical activity, diet, alcohol, and smoking may also partly mediate some of the health risks of depression, although the relevance of these mediators has not been well established. The association between mental health and cardiovascular risk factors may also be bi-directional. In a

prospective cohort study of 633 Finnish men, higher levels of cardiovascular risk factors in midlife was associated with poorer mental health in the elderly after 29 years follow up [37].

Genetics and Additional Moderators

There are a number of factors that may be important when considering psychological risk factors for hypertension. Certain factors including family history of hypertension may increase risk whilst others such as physical activity may be protective. Offspring of hypertensive parents are characterised by a hyperactive sympathetic nervous system that results in exaggerated cardiovascular responses to mental stressors, as well as demonstrating a number of early patho-physiological abnormalities that may precede the onset of hypertension [38]. In a prospective cohort of 103 men, the combination of high stress reactivity and familial hypertension resulted in a 7 fold increase in the relative risk of elevated blood pressure at the 10 year follow up, compared to men without family history [39]. Other studies have shown that polymorphic variation within various genes may contribute to inter individual variability in blood pressure reactivity to mental challenge. For example, genes that encode for alpha and beta adrenergic receptors [40], endothelin-1 [41], and the serotonin transporter [42] have been implicated. There is also data to suggest blacks have reduced nitric oxide dependent vasodilator activity during mental stress, which may partly explain the increased prevalence of hypertension in this group [43].

Given that sleep influences complex activity of the cardiovascular autonomic mechanisms that control blood pressure, it is not surprising that the association between stress and sleep is likely to be important in relation to hypertension risk. Worry, intrusive thoughts, and depressive symptoms delay the onset of sleep and may affect sleep quality [44, 45]. Prospective evidence has linked short sleep duration with hypertension risk [46] and sleep deprivation increases SNS activity and produces other metabolic disturbances [47]. Indeed, in depressive patients elevations in inflammatory markers were found to be partly as a result of disturbances of sleep initiation in this population [48].

The interaction between psychosocial factors and health behaviors also seems to be important. Exercise training has robust anti-hypertensive effects [49] and has a favourable impact on other cardiovascular risk factors such insulin resistance, inflammatory markers, and lipid profiles. Exercise and physical fitness has been associated with lower cardiovascular and biological reactivity to mental challenge [50, 51], and better mental health, such as reduced levels of depression [52]. However, poor mental health is often associated with physical dysfunction that is likely to cause reduced physical activity levels thus a bi-directional relationship probably exists. Obesity is another important risk factor for hypertension that is also closely associated with psychosocial factors although the effects may partly interact with physical fitness [53]. Thus, taken together the interaction of genetics, sleep, obesity, and physical activity with psychosocial factors may be important in the development of hypertension.

Stress Reduction Interventions

There is an extensive literature relating to the effects of psychosocial interventions on various cardiovascular endpoints. Early animal work showed that treatment with the beta-blocker propranolol inhibited the development of coronary atherosclerosis in behaviourally stressed monkeys fed an atherogenic diet [54]. Stress management training has been used extensively in hospital based rehabilitation programs [55] and is consistently associated with improved autonomic and hormonal regulation. The Canadian Hypertension Society have stated that the magnitude of the reduction in blood pressure obtained with multi-component, individualized cognitive behavioral intervention for stress management is comparable in some studies to that obtained with weight loss or drugs, although single-component interventions such as biofeedback or relaxation are less effective [56]. Indeed, stress reduction through transcendental meditation has been examined in relation to the treatment of hypertension although the evidence remains equivocal, largely because of methodological weaknesses in the published data [57]. Nevertheless, in a secondary analysis of hypertensive patients treated with transcendental meditation, there was a 30% reduction in the rate of cardiovascular mortality among the treatment group in comparison with controls after a mean of 7.6 years follow up [58]. Other notable trials have produced conflicting results; in one of the largest trials of 2481 myocardial infarction patients suffering from depression and low perceived social support, treatment with cognitive behavior therapy had no effect on event free survival after 29 months follow up despite significant improvement in psychosocial outcomes [59]. However, in a secondary analysis of the ENRICH trial the use of selective serotonin reuptake inhibitors to treat depression showed a reduction in subsequent cardiovascular morbidity and mortality [60]. In a randomised trial of 134 stable heart disease patients, exercise and stress management training improved cardiovascular function during mental stress testing, enhanced cardiac autonomic control, and reduced emotional distress compared with usual medical care [61]. In summary, evidence regarding the efficacy of stress reducing interventions on cardiovascular outcomes is inconsistent and further trials are required that are adequately powered to investigate relevant outcomes.

Conclusion

There is moderately strong evidence to suggest that psychosocial factors contribute to hypertension (see Table 1). Acute and enduring stressors directly impact on blood pressure control. However, one intriguing question that remains partly unanswered is why a similar level of stress exposure might lead to the development sustained hypertension in some individuals but not in others. This issue may be partly explained by genetic predisposition, personality style and the environment that determine how we react and adapt to life stressors, and ultimately determine individual susceptibility to hypertension. In addition, individual physiological responses and adaptation to stressors are likely to be influenced by health behaviors such as physical exercise, sleep, and diet. Lifestyle approaches that encompass all of these factors should therefore be considered in the treatment of hypertension and identifying those at high risk.

Table 1. A summary of the effects of psychosocial factors and health behaviors on hypertension risk

Psychosocial factor/ health behaviour	Cardiovascular effects	Hypertension risk
Acute stress (laboratory induced or traumatic life event)	↑↑↑ SNS and HPA activity, BP, HR, IL-6, APP	↑↑
Chronic stress (work stress, marital strain, life adversity, etc)	↑↑ SNS and HPA activity, ABP, HR, inflammation	↑↑
Mood state (depression, anxiety, etc)	↑ inflammation, ↓ HRV	↑↑
Sleep disturbance	↑↑↑ SNS activity, metabolic dysfunction	↑↑
Physical exercise	↓↓↓ BP, lipids, inflammation ↑↑↑ HRV, insulin sensitivity	↓↓↓
Obesity	↑↑↑ SNS activity, BP, lipids, inflammation, diabetes	↑↑

SNS, sympathetic nervous system; HPA, hypothalamic pituitary adrenal; BP, blood pressure; ABP, ambulatory blood pressure; HR, heart rate; HRV, heart rate variability; IL, interleukin; APP, acute phase protein.
↑↑↑ strong evidence from controlled trials.
↑↑ moderate evidence from observational studies.
↑ weak or inconsistent evidence.

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Chapter 5

Reactive Changes of Cardiovascular Functions due to the Psycho-emotional Load

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Abstract

Many clinical, epidemiological as well as animal studies bear out the participation of stress in the present proliferation of the cardiovascular diseases. In human pathology the interaction with the environmental psycho-emotional or psychosocial stimuli represents the main part of the chronic stress origin. Activation of the sympathetic system plays a significant role in the cascade triggering the cardiovascular (CV) component of physiological reactions to different stimuli and situations, including stress response. On the other side sympathetic influences are associated with the alterations of function and structure of the heart and vessels including endothelial dysfunction and impairment of the local vasoregulatory mechanisms. There is a considerable variability in the CV stress responses due to genetic predisposition, postnatal development, different reactivity of the CV tissues, environmental risk factors, life style, pathophysiological processes, etc. Some contributions to this topic are reviewed in this paper.

Introduction

The statistical data show that the cardiovascular diseases (CVD) are still the leading contributors to the death rate, account for about one third of premature deaths, are the first in the order of hospitalization reasons and duration [1, 2]. Evidence-based medicine and population studies repetitively confirmed the increased blood pressure as a significant risk

factor of the CVD morbidity and mortality, namely because of its etiologic role in the ischemic heart disease, myocardial infarction, heart failure, cerebrovascular disease and stroke. The arterial blood pressure (BP) routinely measured in the physician's office, and widely used in human as well as animal experimental studies, provides useful clues to the cardiovascular status of the investigated subjects. Blood pressure is a very variable hemodynamic function governed by a complex of neurogenic, hormonal and local regulations and influenced by many factors of the internal and external environment of the organism. The opinion differs whether the slow, developmental, age-dependent increment of BP is physiological, or not. This process may be influenced by some pathogenetic risk factors, causing a steeper or outlasting rise of BP. These speculations are based on the BP developmental trends observed in ethnic groups with minimal prevalence of hypertension in their original environment, where the adolescent BP increase does not occur, and the adult BP values remain at the level seen in the industrial countries in 8 - 9 years old children [3, 4]. Although the genetic factors play a substantial role in the pathogenesis of CVD, their expression is often modified by environmental influences specific for the particular stage of development. On the other hand the impact of environmental risk factors during ontogeny of subjects carrying abnormal genetic information, might differ significantly from that, observed in healthy, non-stigmatized individuals (for details see 5).

In the everyday life, animals and humans are engaged in various activities, requiring rapid, specific and integrated adjustments of different physiological functions, to face particular situation as a whole and in an appropriate manner. The interaction with their social environment is in socially organized species, including man, a notable source of these situations, involving also a wide spectrum of stressing psycho-emotional stimuli. Here we review a piece of our experience with cardiovascular adjustments, which often form an important link in reactions to the more or less emotionally charged situations.

Emotion and Defense Reaction

Emotion is a subjective experience. As such it is rich, varied, concrete and personal – but very difficult to define or study. When an emotional provoking situation is encountered, the organism responds all over. The more violent the emotion - the stronger is the involvement of the whole system. The sensory messages reach the cortico-hypothalamic brain centers and set off a considerably complex somatomotor, autonomic and hormonal response – the so called defense reaction – with mobilization of the organism to "flight or fight". The CV system has proved to be the most sensitive in this respect. Nervous impulses are passed on to the higher brain centers and simultaneously downward to activate the autonomic nervous system and hormonal regulations. Emotion then can be described in terms of conscious experience, behavioral and physiological response. In addition, the hypothalamic neuron pools govern such important functions as water intake and loss, food intake, temperature regulation, sexual behavior etc.

Psychophysiological Reactivity Testing in Cardiovascular Physiology

Testing of psycho-physiological reactivity in relation to CVD was used to identify physiological processes vulnerable to psychosocial stimulation, to identify sensitive individuals who are at risk for the development of later CVD, to take prophylactic measures, to evaluate pharmacological interventions etc. Several tasks and tests were used to evoke the psycho-emotional stress situation: the conflict color – word interference test (Stroop test), stress interviews, stress games, recently video games.

A large amount of studies was published using the probably most consistent test of mental arithmetic (MA), which involves increased alertness with intellectual and emotional strain. After a resting period, the subject is unexpectedly asked to perform mental arithmetic, which usually consists in doing continual serial subtractions of a two digit number from a four digit one, pronouncing the results as rapidly as possible, while being controlled, harassed and criticized.

Integrated Responses of the Cardiovascular System

Integrated responses of the cardiovascular system to emotional stress are due to activation of the cortico-hypothalamic brain centers, and mediated to the heart and vascular smooth muscle cells via efferent sympathetic and parasympathetic pathways, hormonal hypothalamic-pituitary-adrenal and renin-angiotensin systems, in interplay with locally produced potent vasorelaxing and vasoconstricting substances. From the local chemical factors, the L- arginin-nitric oxide system (NO) is at present recognized as the most potent, on intact endothelium dependent, vasodilating regulatory substance. On the other hand, its disturbances due to endothelial dysfunction are considered to be an early risk factor for CVD. Studies on social stress induced hypertension, in genetically predisposed borderline and spontaneously hypertensive rats suggest, that elevated levels of NO may represent a protective mechanism, to prevent development of hypertension in normal control animals, while reduced vascular NO production in animals with familiar predisposition for hypertension, may significantly contribute to its development [6, 7].

Sympathetic Vasomotor Outflow in Human Muscle and Skin Nerves

With regard to vascular regulation, the effect of sympathetic activation and of catecholamines depends on density of the sympathetic nerve endings and on the presence, proportional distribution and affinity of adrenergic $\alpha 1$ (vasoconstrictory) and $\beta 2$ (vaso-dilatatory) receptors in different vascular regions.

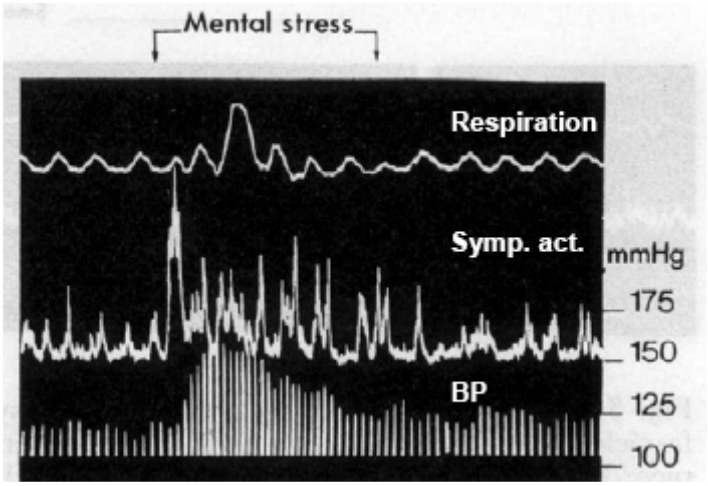


Figure 1. The effect of MA test on sympathetic activity in a peroneal nerve fascicle innervating skin. (Reproduced from Delius et al. 1972 a, with author's permission) [11].

Preceding detailed studies on peripheral arterial and venous reactions to several maneuvers causing circulatory adjustment in man [8, 9], have formed background data for well-documented studies of Delius et al. [10, 11], on sympathetic vasomotor outflow in human muscle and skin nerves. Spontaneous sympathetic activity in muscle and skin nerves has different characteristics.

In muscle nerves it consists of bursts of impulses occurring pulse synchronously in short irregular sequences, separated by periods of relative silence. The impulses cause vasoconstriction, but there is a complex modulation of their outflow predominantly reflecting the homeostatic baroreceptor control (for instance vasoconstriction due to head-up tilting). In different situations it is superimposed by other regulatory mechanisms (e.g. during muscle work). Mental stress is associated with a reduction in strengths of the pulse-synchronous sympathetic discharges in muscle nerves, at the same moment as the blood pressure increases. This may be interpreted as baroreflex-induced, and/or as direct central inhibition of the sympathetic outflow to the vascular bed of skeletal muscles [10].

On the other hand the sympathetic skin nerve activity consist of a mixture of vasoconstrictor and sudomotor impulses, which, under resting conditions, appear in irregular bursts of varying duration. Mental or emotional stress always significantly increased the sympathetic skin nerve activity, even preceding the blood pressure rise and usually evoking vasoconstriction (Figure 1.) [11]. This was particularly evident with the mere suggestion of the MA test being repeated again [11].

Cardiovascular Responses to Psycho-emotional Stress

With emotions following cardiovascular changes are usually seen: 1. Heart - the heart rate and contractility increase with an increase in cardiac output 2. Resistance vessels - the

blood flow to skeletal muscles and the coronary blood flow are increased, the kidney and splanchnic flow decrease, the skin blood flow implies regional differences in the neurohumoral regulation, and so it was reported to be decreased, unchanged, or even increased due to release of kinins, following the cholinergic activation of the sweat glands. The total systemic vascular resistance increases or decreases depending on the balance between vasoconstriction and dilatation. 3. The arterial blood pressure is usually increased. 4. Capacitance vessels – the cutaneous veins are constricted and the splanchnic capacitance is decreased. These changes, which prepare the body to take action, are analogical to those during exercise.

Already half-century ago, experimental studies of emotional stress in man have shown that exactly the same cardiovascular changes occur in man, as in experimental animals [12, 13]. The cardiovascular changes of the defense reaction do not need an extreme distress to be fully displayed. They are already repeatedly evident in daily life with trivial stimuli producing an alerting response.

Studies on stress in animals have demonstrated that prolonged or repeated situations producing the autonomic-hormonal-metabolic mobilization for the defense reaction can interfere seriously with the normal functioning of the body. Repeated situations with defense reactions aroused, but dissociated from willingly suppressed somatomotor components of “fight or flight”, may lead to pathophysiological states [14]. Multifactorial analysis identified suppressed aggression to be associated with the greatest blood pressure increments, particularly in hypertension prone subjects, i.e. those in the upper normal and borderline pressure range [15]. Psychological factors play a permissive role in high blood pressure development, rather than being its consequence.

The central autonomic pattern of cardiovascular reactions to forced MA test mediated via elevated sympathetic nervous system activity, can be traced by the psychogenic heart rate, cardiac output and blood pressure increases, by some electrocardiographic markers, by redistribution of the peripheral vascular resistance, by direct recording of sympathetic activity in the skin and muscle nerves and by the released stress hormones.

The Effect of Psycho-emotional Stress on Resistance and Capacitance Blood Vessels of the Extremities

Differential nervous vasomotor control is the most important factor in systemic cardiovascular homeostasis. On one hand it permits the maintenance of an adequate central arterial pressure, on the other it is the prerequisite - with contribution of the local regulatory factors - for a flexible distribution of blood to different organs. Circulation in the vascular bed of extremities is not only a sensitive marker of the peripheral hemodynamics with regard to the responses of the organism to the physiological impulses and situations, but also an indicator of possible structural changes due to physiological or pathological processes acting for a longer time.

Methods of Measurement

Most of the basic human studies on peripheral vasomotor reactivity in muscle and skin reported in this paper, were performed in the past by various plethysmographic techniques of blood flow (BF) measurement, in different segments of the extremities, and expressed in terms of ml / 100 ml of tissue . min. Plethysmography is a composite measurement of blood flow through all the tissues enclosed in the segment.

Forearm and calf plethysmography is a representative measurement of muscle blood flow, as muscle is the chief component accounting for 59 -71% of the total volume of these segments. Skin, with a very low vasomotor reactivity in these parts, represents up to 13%, the rest are bones and tendons, the BF of which does not influence the test.

The opposite is true for the acral parts of extremities with excessive vasomotor reactivity. Measurements in hands and feet, with minimal volume of muscles, prevailing bones and tendons, quantify the skin BF. Nevertheless, the computerized high-tech measuring techniques of today did not really change these principles of BF evaluation in representative limb segments.

"Venous tone" (VT) was used as a term to describe the change in pressure measured in superficial veins of the distal forearm or hand using the occluded limb technique. It quantifies the active constriction of the capacitance vessels [16].

The Effect of Mental Arithmetic on Muscle and Skin Blood Flows

Active muscle vasodilatation is the most constant characteristic response to the sustained stressful mental arithmetic test. On the other hand the resistance as well as capacitance skin vessels usually respond by a significant constriction, i.e. by decreased BF and increased VT [9]. Respective control and reactive BF values are reproduced in (Table 1) and reactive changes in (Figure 2).

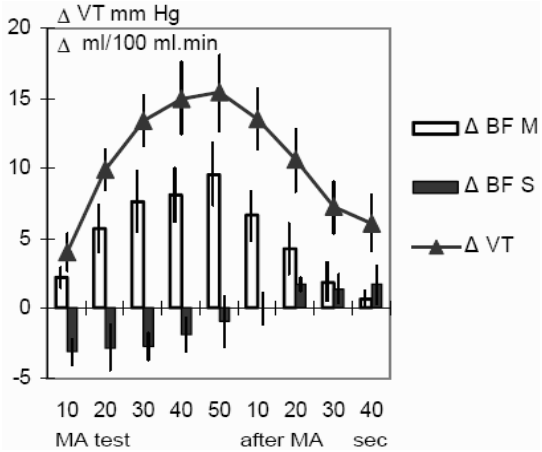


Figure 2. Simultaneous peripheral vascular reactions, during and after the mental arithmetic test. Venous constriction documented by VT, arteriolar vasodilatation in muscle by increased BF M and vasoconstriction in skin by decreased BF S. Initial values at rest set at zero.

Table 1. Muscle and skin BF at rest and during mental arithmetic test

ml / 100 ml. min			
	Control	MA test	MA test max
Forearm muscle BF	4.49	9.39 209 % < 0.01	11.8 263 % < 0.001
Calf muscle BF	4.47	5.81 130 % < 0.02	7.27 163 % < 0.001
Hand skin BF	5.6	2.4 43 % < 0.01	1.8 32 % < 0.001
Foot skin BF	3.4	Variable ± changes n. s	

Increased muscular BF (besides vasoconstriction in skin, intestine and kidneys, tachycardia, increased blood pressure, rapid respiration and pupillary dilatation), plays an essential part also in the defense reaction produced in animal models by stimulation of the respective brain areas [17].

Capillary Blood Flow in Subcutaneous Tissue and Muscle

Using tissue clearance of low molecular weight radioactive tracers we documented, that the pattern of emotional vascular response, quantified previously by total segmental blood flow changes, involved all consecutive vascular sections including its nutritional, capillary part [18].

During the MA test, the capillary BF in the forearm muscle increased, whereas in the subcutaneous tissue it decreased. The significant regional difference observed in the total segmental BF at rest, was confirmed in the resting capillary BF as well. Comparing to the arms, it was by 20-30% lower in the corresponding segments of the lower extremity [18].

Active Venoconstriction

As cardiac output is dependent upon venous return, changes in venous capacity, due to the sympathetic vasoconstrictor activity can profoundly influence the efficiency of the cardiac pump. An increase of efferent sympathetic discharge which in general is a part of the defense reaction – in our case of the MA stress test reaction - elicits a significant venoconstriction, documented here by an increased venous tone in the forearm, in the average up to 218 % of its resting value (Figure 2). It is extended beyond the arteriolar constriction in skin, with an after-effect lasting about 1 min. longer than the MA test, closely correlated in amplitude and duration with the increased forearm BF [9]. Seemingly the active

venoconstriction represents a neurogenic compensatory mechanism preventing the pooling of blood in regions with an increased muscular BF.

Regional Differences in the Vasomotor Reactivity

Practically in all human studies the measurements of the peripheral skin and muscle blood flow were performed in the segments of the upper extremity (hand and forearm). In spite of this, the results were generalized. In one of our studies based on the simultaneous segmental BF measurements on the upper and lower extremities [8], we revealed, that there are significant regional differences in the response of the skin and muscle vessels to the psycho emotional stress (Table 1). The vasodilatation was less pronounced in the calf muscles. Inconsistently with the significant cutaneous vasoconstriction in hands, there was no reaction of the skin vessels in feet. Another reflex vasoconstrictory response induced in skin by a deep breath, however synchronous and comparable in duration in both regions, was significantly less in amplitude in the feet (BF decrease only to 46% of the respective resting values, but down to 17% in hands). It was concluded, that there are differences in vasomotor reactivity comparing the upper and lower part of the body, or more precisely, with higher reactivity and specific sensitivity to emotional stimuli in the upper extremities. The remarks on higher vasomotor excitability in these regions are based on thermoregulatory observations, on clinical description of vasodilatation in hemiplegics etc.

Hypertension

Hypertension is a complex, heterogeneous, progressive type of disease affecting the cardiovascular system, which cannot simply be reduced to a symptom of arbitrarily defined, elevated blood pressure values It holds true above all, in subjects between the dividing lines for normotension, prehypertension and hypertension, still with no clinical signs of some target organ damages, but – more often than not – with an autonomic imbalance, playing not only a primary pathogenetic part, but amplifying the adverse effects of other cardio-vascular risk factors as well. As stated by Julius in 1996 (19) to this repetitively extensively reviewed and recently much debated topics [20, 21, 22, 23, 24, 25, 26] “Interest for the role of the sympathetics in the genesis of hypertension has come full cycle from early enthusiasm, through a period of neglect, to present understanding that strong evidence cannot be ignored”.

The first convincing evidence about the contribution of differentiated sympathetic activation to the onset of human primary hypertension, comes from experimental studies by Brod et al. [12, 13] in the late 1950’s. Hemodynamic analyses revealed in 70% of young hypertensive prevalence for a hyperkinetic circulation at rest, with a high cardiac output, mainly due to the increased stroke volume, in some subjects associated with tachycardia [27]. A number of reports show an increased total BF to forearm muscles in hypertension. Thus, one may assume that the cardiovascular pattern in hypertensive subjects, already at rest, is similar to that displayed in emotional defense reactions, suggesting a permanently increased

sympathetic drive of central origin. However, according to our findings the dilatation in the muscular vascular bed in hypertensives is non-uniform, being even opposite in the lower extremities [8].

The redistribution of the vascular tone was reflected in the nutritional capillary BF as well [18, 28]. Already at rest, in the hypertensives the capillary BF in the forearm muscle was increased in the average to 136 %, in comparison to normotensive controls, whereas it was significantly lower in the calf muscle, representing about 60% of that in controls. The capillary BF in both - hands and feet - was decreased, as expected. Guanethidine causing a highly selective sympathetic blockade, practically eliminated these differences. This suggests, that the hemodynamic pattern of hypertension involved increased sympathetic activity, which was “neutralized” by guanethidine, with following return to a normal, resting distribution pattern of the local tissue blood flows [28].

Different Pattern of Vasomotor Reactions to Psycho-emotional Load in Patients with Chronic Myocardial Infarction

The vasomotor and BP responses to a 60 sec period of an intensive MA test were investigated in a group of patients in a chronic phase of myocardial infarction (MI). In this situation, compared to the controls, the reactive BP and HR increments in the MI group were slightly but significantly smaller, nevertheless longer lasting after cessation of the stimulus. Results of the vasomotor response summarized in (Figure 3), show more pronounced and prolonged vasoconstrictor reactions in skin, which involved the resistance as well as capacitance vessels. In the group of patients the muscle blood flow at rest was significantly lower and as expected its reactive emotional increase was significantly less pronounced and of shorter duration [29].

Peripheral circulation in patients with coronary heart disease is of considerable clinical significance since, on the one hand, it plays a role in maintaining arterial BP and venous return but, on the other, the reflex vasoconstrictor episodes by increasing BP augment the mechanical load on the heart and thereby also the demand-energy imbalance.

When seeking an interpretation for the elevated resting vasomotor tone in the muscular vascular bed, for the proneness of MI subjects to develop vasoconstrictor reactions of higher amplitude and longer duration, and for the in amplitude and duration diminished muscular vasodilatation [29], it seems likely, that an predominant increase of norepinephrine secretion during 24-h and in response to emotional stress, can be accounted for [30].

None of the patients had an evident heart failure, but we have to consider the impaired function of the heart as a possible reason for the observed changes in peripheral hemodynamics and for sympathetic activation. Last but not least, the factor of endothelial dysfunction limiting the production of vasodilating substances in these patients was very probable.

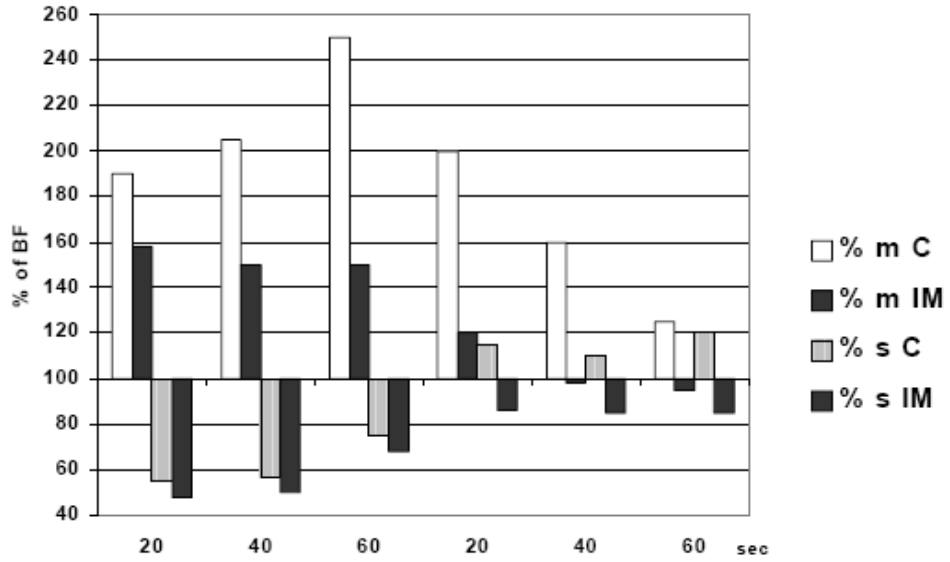


Figure 3. Relative values of muscle (m) and skin (s) blood flow 60 s. during and 60 s. after MA stress test, in patients with MI (black columns), compared to controls (white and dotted). Resting BF before MA was set at 100%. The differences between MI and C were significant at $P < 0.01 – 0.001$.

Sympathetically Mediated Effects of Psycho-emotional Stress on Electrophysiological Parameters of the Heart

The sympathetic division of the autonomic nervous system (ANS) of the heart is entering into action in cases requiring a more complex regulation, when it is not sufficient to influence the cardiac action only by decreasing the activity of the vagus nerve (physical exercise, upright posture, feeding response, emotion, defense reactions etc.). Increase in the impulse rate of cardiac efferent nerves causes an increase in noradrenaline release and via beta-receptors a direct sympathetic stimulation of the myocardial cells. On the cellular level, catecholamines interfere with various components of the action potential, such as amplitude, duration, refractoriness and conduction velocity, depending on the type of cardiac tissue. Consequently they change the course of repolarization, its heterogeneity and asynchrony. Psycho-emotional stress activates sympathetic nerves in the heart, resulting in an increased cardiac nor-epinephrine spillover in the average by 63%, in subjects with normal coronary angiograms [31].

Evidently for methodological reasons, heart rate (HR) and / or R-R interval variability have been used to analyze some aspects of the heart control mechanisms under influence of a variety of physiological stimuli. However, HR variability reflects influences of the ANS mainly with respect to the parasympathetic control of the atrial pacemaker functions. Information on the autonomic nervous control of ventricles cannot be expected form HR variability analysis. It should be looked for in the ventricular complex of the ECG [32, 35].

Numerous experimental studies have demonstrated that minimal local changes of the myocardial action potential pattern can significantly alter the amplitude, duration and polarity of the T wave, with negligible, if any changes in the QRS complex [33]. T wave may be considered as "some kind of a special detector for differences in repolarization of the various parts of the ventricles" [34]. Electrophysiological parameters characterizing ventricular repolarization have repeatedly been shown to carry information on the direct effect of sympathetic activation on the ventricular myocardium [35] – in particular due to psycho-emotional stress induced by mental arithmetic [36, 37, 38, 39], active coping tasks to aversive stimuli [40], smoking [41], head-up tilting, prehypertension and hypertension [32, 42], to adrenergic agonists isoproterenol [38], dopamine [43], or to the opposite effect of beta-receptor antagonists [38, 40]. The finding that beta blockade prevented the task induced T-wave amplitude reduction, confirmed its beta-adrenergic origin [40].

In earlier studies the pattern of ventricular repolarization was evaluated by changes in T-wave shape and amplitude [37, 44]. To enable the quantitative evaluation of the functional changes in repolarization, the maximal spatial T-vector (sTmax) was proposed as a convenient parameter [35, 36].

In our study the magnitude of sTmax significantly decreased during the MA test, almost by 40% in non-sporting university students, whereby its decrement in trained athletes was significantly less – in the average by 17%. [45]. This is in agreement with previous VCG studies documenting a significant diminution of the maximal spatial T-vector [36], or a reduction in T-wave amplitude during this active mental task in healthy subjects [37, 40].

The Effect of Psycho-emotional Stress on Repolarization Parameters of the Body Surface Potential Maps

In the last time increasing attention has been devoted to the study of the information content of the repolarization body surface potential maps (BSPM), in order to gain from different types of these maps more detailed information on the electrophysiological processes in the heart and on their physiological changes.

The cardiovascular response to the forced MA was shown to be accompanied by a marked negativization of the integral QRST BSM values, mainly on the inferior torso and precordium. These changes in the time integral pattern during the MA test, were quantitatively most pronounced in the repolarization phase, and contributed mainly to the changes of the QRST integrals.

Analogical changes in some depolarization and repolarization BSM parameters, probably due to the augmented sympathetic nervous activity, were described in patients, with no cardiovascular diseases, but suffering from panic disorder [46], or treated by antidepressant drugs [47].

Investigations of the myocardial perfusion in patients with coronary artery disease undergoing mental stress test, have detected a high incidence of transient regional myocardial perfusion abnormalities, usually not accompanied by increases of heart rate or diagnostically relevant ECG changes. However subtle ST modifications are generated in many of these

patients that are otherwise unrecognized by standard ECG criteria, but detectable by body surface mapping [48]. "Primary" functional changes of ventricular repolarization may be produced in normal persons by a variety of physiological situations involving autonomic cardiovascular control. These transient alterations in ventricular recovery are of importance namely in subjects at risk for ventricular arrhythmia

Dissociation between the Reactive ANS Controlled Heart Rate Changes and the Direct Myocardial Effect of Sympathetic Activation

At rest there was a strong correlation between sTmax and R-R intervals + BP, accounting for 43% of their variance. In the presence of increasing sympathetic activation of the heart, influencing on one hand directly the ventricular myocardium, but on the other hand only modulating the complex vago-sympathetic regulation of the pacemaker, the association between sTmax and RR intervals becomes weaker, insignificant, or almost absent. For instance during MA test it participated only on 25% of the sTmax variability [49].

In some healthy subjects different physiological situations and maneuvers, varying the activity of the autonomic nervous system (MA stress test vs. isometric handgrip) may intra-individually yield identical reactive heart rate responses (average difference ~ 1%), but simultaneously produce different reactive changes in ventricular repolarization parameters with respective differences of 11 – 33% [49]. These results evidence the possibility of dissociation between the reactive, autonomic nervous system controlled HR changes and the direct myocardial effects of sympathetic activation, even in physiological situations. They point out that HR or HR derived criteria alone, are insufficient to recognize changes in the level of the sympathergic effect on the ventricular myocardium.

Blood pressure and heart rate changes contributing to the repolarization parameters variability may reflect an increased sympathetic outflow to the cardiovascular system in general, but they do not necessarily indicate the site-specific sympathetic drive of the ventricular myocardium [49].

Primary Changes in Ventricular Repolarization Related to Blood Pressure Values in the Normal Range

Significant differences in repolarization parameters e.g. decreased magnitude of the maximal spatial repolarization vector sTmax by 14%, and other, were observed in healthy men, with resting BP already in the range 120-135 / 80-85 mmHg, compared to the group with BP below the limit 120 / 80 mm Hg.

These changes in repolarization parameters similar to those, observed under mental or physical strain, point to some increase of the sympathetic outflow to the ventricles at rest

already in subjects in the first category above the BP limit set for optimal and normal (EHS 03 guidelines), or more strictly for normal and prehypertensive BP (JNC-VII guidelines) [49].

Blood Pressure and Heart Rate Reactivity in Neonates and Children

In contrast to the amount of data published on physiological aspects of BP regulation, on its reactivity, hereditary predispositions, environmental influences, and factors altering its control in the adults, studies devoted to these problems during ontogeny in healthy individuals, including neonates, are relatively rare. However, primary hypertension in children is less frequent than in the adults, and it poses in most children less risk of the immediate target organ damages. May be that's why the involvement of the health care system regarding BP in children is rather low. Neither cardiology, focused on the investigation of the CVD risk factors in the adults, recognizes fully the substantial long-term risks following the elevated BP throughout childhood.

The dynamics of the BP evolution in children is nonlinear. Noninvasive examination of BP by ultrasound sphygmomanometry [50, 51], documented in our study in 150 physiologic neonates [52, 54] that the most steep rise of BP – systolic by 22% and diastolic by 19% - from their respective, first-day average ± SD values, of 57±8 / 33±7 mmHg, - took place in the first postnatal week. At the same time the heart rate 121±9.min^{-1} beats, decreased by 6 %.

Thereafter a relatively intense BP increment, in the average by 2 mm Hg per week, lasts up to the age of about 6 weeks, when the total BP accretion is close to 20 mm Hg. Subsequently the developmental increase of BP, lasting to the adulthood, slows down to 1-2 mm Hg per year for systolic, and l mm Hg for diastolic BP.

Although the BP control in man has been extensively investigated, studies on physiological factors inducing its reactive changes, character of the BP reactions, and their postnatal development in the early infancy, and especially in neonates are scarce, with some doubts about their functional effectiveness.

Sleeping and Waking

At the age of 12-24 h, there were no differences of BP and heart rate levels related to the state of vigilance. They developed gradually and became significant ($P< 0.001$) at the age of 72-96 hours (BP awake 72/40 vs. asleep 63/35 mmHg, HR 127 vs. 115 beats/min), independently on the time of the day [52, 54]. However, at the same time, we documented lower BP values at night, independently on vigilance – approximately at the level of 90 % of the daily mean, showing in about a half of the babies, already in the first postnatal days significant circadian periodicity [53].

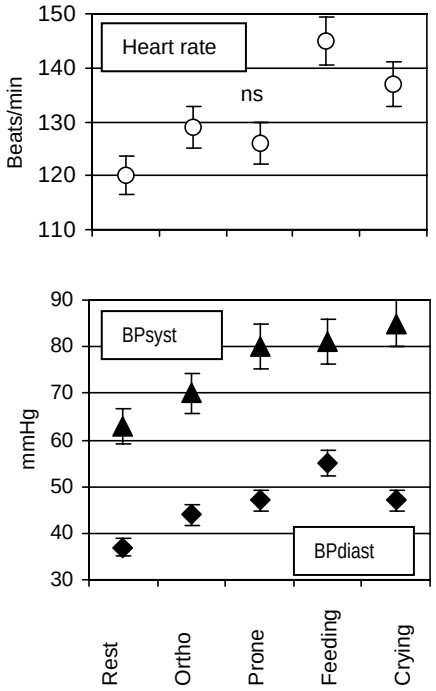


Figure 4. Reactive BP and HR changes in neonates in different situations. All increments, except the HR reaction to the prone position, are significant at P<0.01 – P <0.001.

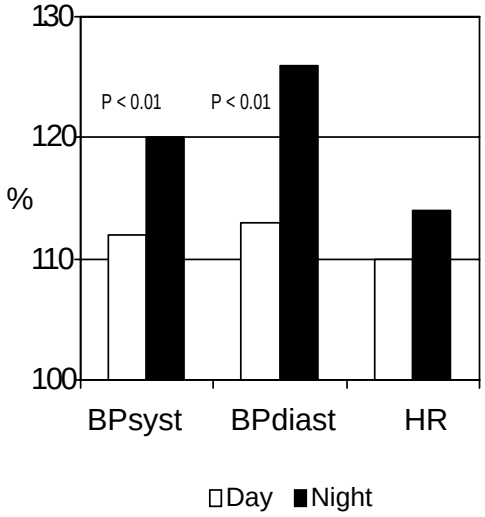


Figure 5. The effect of waking-up and crying on blood pressure and heart rate at night, compared to the daytime reactions in neonates.

Crying and Waking Up

Crying provoked a reactive increment of BP by 22/11 mmHg and of HR by 19 beats/min on the average, with a marked intra – and interindividual variability, dependent mainly on the intensity and duration of crying, length of the expiratory phase, etc. (Figure 4) [52, 53, 54].

Interestingly, waking up from the sleep, or crying at night, provoked a more pronounced increase of BP, in comparison with the day time reactions (Figure 5). This finding has an interesting parallel to the circadian pattern of stress-induced pressure responses in mice with greater BP increases seen during the light period (non-active phase in rodents), than in the active dark period [55].

Feeding Response

Feeding and locomotion are at the top of the class of activities identified as essential to life [56]. Feeding is a complex activity, which has to be divided into two disparate periods: food intake (ingestion, eating, drinking and sucking), and the postprandial period (digestion). There is a substantial difference in the prandial and postprandial cardiovascular component of the reaction. The hemodynamic changes that occur during food intake are not restricted only to the gastrointestinal tract. Due to the cortico-hypothalamic activation, they can be characterized to a certain degree as a part of a generalized sympathomimetic response [57], resulting in a considerable blood pressure and heart rate increase. It was shown in newborn lambs [58], that the hypertensive response during feeding was significantly reduced by combined alpha- and beta- adrenergic blockade and completely eliminated by ganglion blockade in rats [59].

The hypertensive BP response to feeding is universal, more significant in carnivores (dog, cat) and omnivores (pig, baboon, rat) than in herbivores (sheep, goat), and much more pronounced in the young ones, in comparison to the adults of the same species [56, 60, 61. 62, 63].

Among blood pressure and HR changes coincident with different physiological situations and activities in human neonates and infants, the increments during feeding are the most prominent. (Figure4). The breast- feeding caused in infants a significant rise of systolic and diastolic BP and of HR. It is greater during bottle-feeding, and dependent on the body position [51, 61, 62, 64].

Feeding pressure reaction, ubiquitous in mammals, is also in human babies abrupt, immediate, elicited practically by the start of sucking and the first gulp of milk in mouth, outlasting all the feeding time, present in every subject, however inter-individually variable in magnitude, and with return of BP an HR to baseline within several seconds after the end of feeding. It is present also during non-nutritional sucking at a comforter. From this follows, that to quiet a baby for BP measurement by a comforter, causes falsely high BP readings.

Changing Body Position

To estimate the cardiovascular regulatory functions in man, body-tilting maneuvers are commonly used. The BP responses to changes in body position from supine to upright were extensively studied in healthy adults, teenagers as well as in children. Some data on newborns were obtained under variable conditions, only casually in small samples, and with partially contradictory results.

In neonates the head-up tilt to 45^{o} provoked a significant increase in systolic and in diastolic BP, with moderately increased HR (Figure 4). This response was even more pronounced, when the babies were instead tilting, lifted-up on arms. This ”hypertensive type“ of reaction was present in more than 80% of full-term newborns, and still present in about 70% of 3- year old children. In contrast to the decreased venous return and stroke volume due to standing up in the adult, the different proportionality of the blood volume distribution, which is localized in neonates and children predominantly in the large head and in the upper part of the body, results immediately after assuming the upright posture, in an increased venous return, filling of the heart, and higher cardiac output. This is one of the components of the hypertensive type of the reaction.

Highly probably the same mechanism, i.e. an increased venous return from the abdominal region and visceral organs, plays a role in the neonate in the significant BP increment following the change of body position from lying supine to lying prone (Figure 4) [54, 65, 66]. To put a neonate to sleep lying prone (abdominal position) is, based on our results, not recommended. The pronounced, sustained increase of BP, may eventually produce compensatory bradycardic response, and endanger babies prone to SIDS.

Circadian and Ultradian Blood Pressure and Heart Rate Rhythms in Neonates

Since the study of Hellbrugge (1960) [67], the belief persisted, that the circadian rhythms in cardiovascular functions in man, develop gradually several weeks after the birth, and consecutively, with maturation of the respective control systems.

We gained priority by the evidence of the circadian oscillation of BP and HR in neonates, already in the first postnatal days [51, 68, 69]. Later, submitting the data to the population-mean cosinor evaluation, we confirmed their significant circadian periodicity characterized by amplitude of 9 – 10 % of the respective BP mesor values The acrophase in term newborns was close to 11 AM ($P< 0.01$) (Figure 6) (53,69). It was not related to the condition of sleeping or waking.

In addition to the population mean cosinor, the evaluation of individual series of data confirmed the circadian rhythm in BP and HR in more than 50% of investigated babies, with amplitude significantly differing from zero. In comparison to the BP pattern in the adults, a more significant superposition of slow (6-12 h.) and fast (2-6 h) ultradian periodicities was shown [53, 70]. The existence of the circadian rhythm in neonatal BP and HR was later confirmed by others [71, 72, 73]. Seemingly our results are in contradiction with the study of

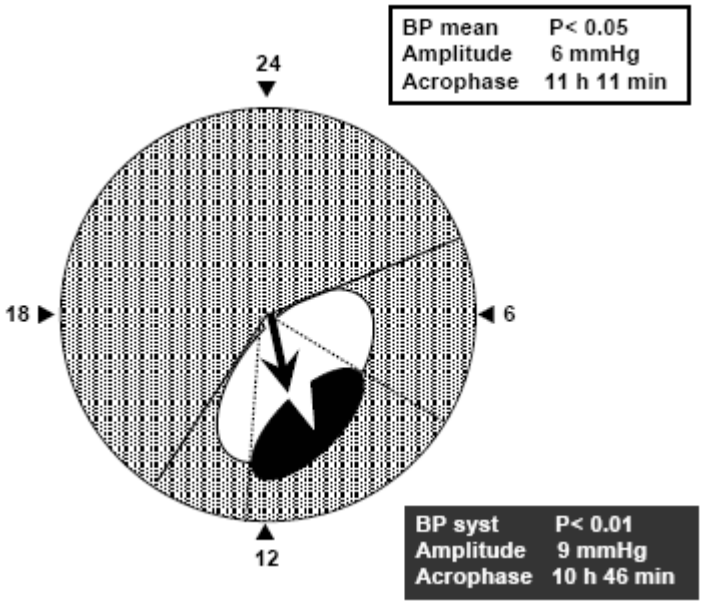


Figure 6. Cosinor summary of the circadian rhythm of systolic and mean blood pressure in neonates. Postnatal age 24 – 48 hours.

Hellbrügge [67], who among many investigated physiological functions, found a normal circadian periodicity in the first week of life only in the electrical skin resistance. For technical reasons he did not measure BP. Nevertheless, as the electrical skin resistance is related to the skin blood flow, i.e. to the peripheral vascular resistance, it may indirectly reflect the blood pressure oscillations.

Concluding Remarks

A great part of BP variability, already in the neonates, arises as a consequence of adaptive processes to various physiological situations and loads. It is apparent, that BP and HR regulatory mechanisms in man are fully functional at birth, however, the responses differ from those of the adult, and they are specific, according to the conditions and needs of the newborn organism.

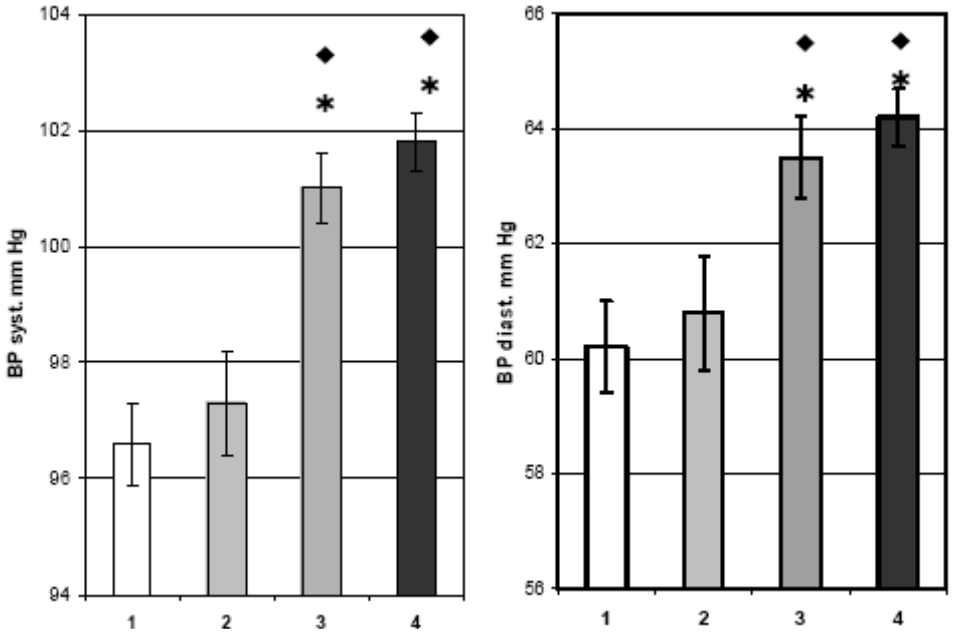
Intraindividual as well as interindividual variability in the neonatal BP and HR rhythmicity is besides the endogenous components, consequence of the synchronizing and/or desynchronizing environmental and social influences and of the coincidence of cardiovascular adaptation to various, random, physiological situations and loads. These factors, although obscured by group evaluation of data, may explain not only the difference in the circadian rhythm incidence between investigated groups, for instance exposed to the rooming-in or nursery environment, but also the discrepancy of data of different authors sustaining or denying its existence.

Non Auditory Effects of Urban Noise in Children

Urban noise – the unwanted mixture of sounds – is an inescapable, permanently increasing, ubiquitous and persistent stressing factor of the civilized environment. About 20% (80 million) of the population in the European Union experience daily noise levels that are believed to have detrimental effects on human health. A further 42% reside in areas, where noise pollution is severe enough to cause occasional serious nuisance [74].

Besides of the specific deleterious effect of the chronic exposure to this stressor on the hearing organ, overviews of available information emphasized the general, long outlasting effect of the noise-pollution on many body functions, causing noxious non-auditory health effects [74, 75]. Several cross-sectional epidemiological studies in the adults have investigated the influence of road traffic noise on circulatory variables. Partly contradictory results indicate that living in streets with high traffic density may increase the occurrence of hypertension beyond the magnitude explained by other factors; either worsens the cardiovascular risk profile. Critical reviews of earlier studies [74, 75, 76] evidenced, that juveniles are not only susceptible to cognitive impairment in noisy environment, but may also react in terms of raised blood pressure.

The aim of our study [77] was to investigate whether persistent exposure to high levels of urban traffic noise might affect the cardiovascular functions already in the early childhood, in the ontogenetic stages characterized by human as well as animal studies, as exceptionally sensitive to environmental factors [5].



1 – quiet areas 2 –noisy home area 3 – noisy kindergarten area 4 – noisy both.
◆ indicate significant (P<0.001) differences of 3 or 4 to 1.
✱ indicate significant (P<0.001) differences of 3 or 4 to 2.

Figure 7. Mean values and standard deviations of systolic and diastolic blood pressure, and heart rate in preschool children visiting kindergartens in noisy >60 dB(A) or very noisy >70 dB(A) areas.

The study population consisted of 758 boys and 732 girls in the age 3-6 years attending the kindergartens in all districts of the Bratislava city. The urban noise levels at respective kindergartens and homes were evaluated according noise maps of weighted average equivalent to sound pressure of 24 hours per working day at 275 places of the city. Prescriptive limit for living and school areas was 60 dBA. Localities under this limit were considered quiet, up to 69 dBA as noisy, 70 and more dBA as very noisy. Only 18% of all children lived and visited kindergartens in quiet places. Others were exposed to permanent noise load over 60 dBA, either at their homes, either at kindergartens, or 28% of them at both places.

In children attending kindergartens in noisy or very noisy places the mean values of systolic BP and diastolic BP were significantly higher ($P< 0, 001$) whereas HR values were significantly lower ($P<0,001$ (Figure 7). Values of the 90th percentile of BP in respective age were significantly higher by 5 to 10 mmHg in comparison with children from quiet places.

All children in this study spent the working time 5 days each week in the public kindergartens, were up to 10 hours under equal regimen concerning the mental and physical activities, sleep or outdoor time, and on similar diet. The objection to the studies in the adults - because of the possible confounding effects of other subjective and environmental BP increasing factors - is here minimalized. Moreover body constitution parameters adjusted for age, and socio-economic indexes were not related to the places of kindergartens or residences. Surprisingly, even BP values did not correlate with body weight or height.

Our results provide therefore very strong evidence that exposure to increased levels of urban traffic noise already over 60 dBA, may lead to elevated blood pressure in very young age, mainly in the susceptible individuals. In spite of the difficult interpretation of the findings in children with regard to the possible health risks in their later life, the environmental factors have to be identified and prevented from the pathogenetic gene-environment interactions, as early as possible in the postnatal development [5, 78].

The mapping of urban noise levels with awareness of its health-risk effects, should be undertaken, to serve local authorities to generate action plans for intended corrective measures, for legislation on noise control, and for future urbanistic planning of the city development. In this respect our results were cited and served as arguments for several experts' reports published in the frame of EU [e.g.79, 80,81,82]

Conclusion

Instead of conclusion – I attach an interesting "piece of good news" on positive emotions and environmental influences. An effort is widely being made to find preventive or therapeutic measures to neutralize the cumulative negative cardiovascular effects of stress and of sympathetic predominance, to allow a rapid return to a state of relaxation. Positive emotions, which also appear to have a control center within the hypothalamus, have been shown to suppress - at least partly - the stress response, and to impair the full development of cardiovascular disorders.

Results from animal experiments indicated, that activation of the positive emotiogenic areas of the lateral hypothalamus abolished, what may be considered as emotionally induced

cardiovascular disturbances, produced by immobilization of the animal and stimulation of the hypothalamic defense area. The increased BP and HR returned to control values, and changes in the ECG STT segment, extrasystoles, or paroxysms of ventricular tachycardia disappeared [83].

It is not necessary to point out the importance and protective effect of regular sport activities in prevention of cardiovascular diseases. Raab et al (1960) described in individuals missing physical exercise, the lasting prevalence of adrenergic influences on the heart, and on the other side the existence of anti-adrenergic regulatory mechanisms in trained sportsmen [84], moreover systematic physical training was shown to suppress anxiety and BP deviations more, than passive rest does [85]. In our study in non-sporting university students, the magnitude of the maximal spatial repolarization vector- sTmax significantly decreased during the psychoemotional MA stress test, almost by 40%, indicating sympathetic predominance, whereby its decrement in trained athletes was significantly less – in the average by 17%. [45].

Investigation of the influence of noise and different kinds of music on the low-frequency (sympathetic) and high-frequency (respiratory) components of the sinus arrhythmia revealed, that the classical music suppressed the sympathetic LF component. With rock music and noise, however, this component increased. A correlation was found between this balance and feeling of comfort and discomfort [86]. Surprisingly this effect seemed to be related more to the tempo than to the difference in style. Rap or Vivaldi at similar faster tempi raised BP and HR more than music with a slower tempo [87].

Do not smoke please, to relax! It increases substantially the sympathetic activity in your peripheral nerves, with concomitant increase of BP and HR. More than that – the presmoking level was not reached until 3 minutes after the smoking ended. This aftereffect is longer than after accomplishing the MA stress test [11].

Rather enjoy a glass of red vine, with a variety of polyphenols derived from grape skin and seeds, responsible not only for its color and taste, but also for the “French paradox” [88]. They are beneficial in preventing the endothelial dysfunction, protecting the vascular nitric oxide synthesis (the most powerful vasodilator), and preserving the integrity of the vascular endothelium [89]. Last but not least these red vine substances prevented the development of chronic social-stress induced hypertension in rats with a positive family history of hypertension (in spontaneously hypertensive or borderline hypertensive strains) [90].

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Chapter 6

The Cardiac Response of a Threatened Brain

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Abstract

The cardiovascular system is influenced by cognitive and emotional factors. Significant and novel stimulation promote bodily changes related to orienting and attention that in the cardiovascular system manifest themselves as heart rate decelerations. However, a more complex response appears when the stimuli are threatening. An intense noise elicits a heart rate response characterized by a pattern of short and long-latency accelerations and decelerations in alternating order, with the first, short-latency acceleration related to vigilance and orienting, and the second, long-latency acceleration, related to defence. This cardiac pattern quickly habituates and is modulated by the emotional context. Complex stimuli, like pictures, promote a triphasic wave response, with an initial deceleration followed by acceleration, and a final long deceleration. However, when phobic subjects are exposed to pictures related to their fear, the pattern changes to acceleration, reflecting the defence response promoted by these stimuli. Data coming from animal and human research on the neural bases of fear have identified the cerebral amygdala as a key structure that detects and responds to threatening stimuli. This structure modulates the behavioural and motor responses, as well as the cardiac and other physiological reactions to those stimuli.

Cardiac Response

Phasic changes in the cardiac cycle have been one of the most studied peripheral reactions in human psychophysiology. Two reasons have led researchers to study these changes: firstly, their relationship with several cognitive (e.g., attention) and emotional (e.g., defence) processes, and secondly their relatively easy recording and analysis. In this chapter,

we will review the cardiac response promoted by aversive, threatening stimuli, both simple and complex, and the brain mechanisms related to the fear response which might be supporting the defence reaction to such stimuli. In addition, we will also present the heart rate changes promoted by neutral stimuli related to attentional processes, i.e. the orienting response, since they are in some cases previous to the defence response.

The cardiac cycle can be divided into three stages namely atrial systole, ventricular systole and ventricular diastole. Through these three stages, the heart ejects the blood to supply the body tissues. When the electrical impulses that activate the heart, which gives rise to a cardiac cycle, are recorded on the electrocardiogram, a series of three waves can be observed: a) the first wave, the P-wave, is related to the atrial systole, or atrial depolarization, b) the second wave, the QRS-complex, reflects the ventricular systole or ventricular depolarization, and finally c) the T-wave, which is related to the ventricular diastole, or ventricular repolarization. One of the most used measures of the cardiac activity is the heart rate, which is a frequency measurement which refers to the number of successive R-waves from the complex QRS, usually specified as beats per minute (bpm), appearing in a time window. Another widely employed measure is heart-period or the time distance between two consecutive R-waves in a time window.

The cardiovascular system is under the control of several subsystems, including a) the local regulatory systems of the heart and blood vessels, b) the humoral mechanisms that modulate the electrolytic balance, and c) the central nervous system influences on the effector components of the cardiovascular system which are under the control of the autonomic nervous system [1]. We will focus on those cardiac changes related to the activity of the nervous system.

The heart is innervated by the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) and heart rate is, consequently, influenced by these two autonomic subsystems. Classically, it was thought that both autonomic branches acted in a reciprocal manner, i.e. the increase of activity in one of them led to a lower activity in the other. Nowadays, however, it has been shown that both branches can vary, not only reciprocally, but also coactively and independently [2, 3]. Both sympathetic and parasympathetic fibres reach the visceral effectors located in the sinoatrial node and the atrioventricular node and can modify the intrinsic heart rate. Parasympathetic or vagal fibres originate in the dorsal vagal nucleus and the nucleus ambiguus, and their postganglionic cells release acetylcholine in the sinoatrial node cells. This neutrotransmitter alters the normal course of spontaneous depolarization of the sinoatrial node cells, leading them to diminish their firing rate. The increase, therefore, of parasympathetic activity provokes a cardiac inhibition, and leads to a decrease in the heart rate [4, 5]. Sympathetic nerve fibres originate in the intermediolateral cell column of the spinal cord, and their postganglionic fibres release norepinephrine. This neurotransmitter also changes the spontaneous depolarization of the sinoatrial node cells, but in a contrary manner to the parasympathetic influences, i.e, eliciting a rise of the cardiac contraction strength and heart rate acceleration [4, 5]. Hence, heart rate acceleration may be provoked by a decrease in parasympathetic activity, an increase in sympathetic activity, or by an interaction (reciprocal or nonreciprocal) of the activity of both ANS branches on the sinoatrial node. In turn, heart rate deceleration may occur by an

increase of parasympathetic activity, a decrease of sympathetic activity or by an interaction between both ANS branches.

The psychological significance of the heart rate changes has been considered from two different points of view: the cognitive, related to the facilitation and inhibition of the information processing, and the motivational, postulating that these situational heart rate changes are indices of psychological mechanisms related to the mobilization of energy of the organism in situations that require a behavioural adjustment [6]. Nowadays, both interpretations have been integrated in order to explain the defence reaction promoted by potential threats.

Orienting and Defence

The Orienting Response

The detection of sudden or unexpected changes in the environment, and paying attention and reacting to them, is critical for survival in humans and animals. In addition, it is also of interest to ignore irrelevant stimuli in order to allocate resources to cope with other, more important events. The orienting response is the first reaction to a novel or significant stimulus and is thought to perform these important functions. Originally, the main function of the orienting response was thought to be the improvement in sensory and perceptual processing of incoming information [7]. It was not considered as a passive response but rather as an active reaction, and, in spite of its name, not a simple reflex but rather an array of responses elicited from higher levels of the central nervous system, allowing the appraisal of the incoming stimulus.

Many researchers have interpreted the physiological changes that constitute the orienting response as the result of central processes that allow an initial exploration of the stimulus relevance, including stimulus registration [8, 9, 10]. The idea is that the flow of incoming, continuously changing, information is automatically processed by a preattentional, mainly unconscious, mechanism. This mechanism has a limited capacity in terms of processing resources, and performs a rapid and automatic evaluation of incoming stimuli, without the need of conscious attention. However, and as happens with novel or significant stimuli, when the initial automatic processing in the short memory storage results in the need for more detailed information processing, there is a shift or “call” to a second attentional mechanism, which is conscious and centrally controlled. This “call” to more processing information resources manifests itself as the physiological responses that constitute the orienting response. These would indicate the allocation of central resources of information processing, requiring more effort and thus activating different sensory and effector systems in the brain. A result of the activity of this second mechanism is the registration of the stimulus in the memory storage.

Overall, the orienting response allows subjects to be conscious of the changes that occur in their environment, to detect them and to concentrate on those that are more relevant. The habituation to irrelevant stimuli is also important, because if the organism did not habituate its orienting responses to irrelevant stimuli, it would be permanently controlled by any new

stimulation and could not perform complex or serial behaviours since they would be continuously interrupted.

The orienting response appears in the face of novel stimuli, or any change in the present or recent stimulation, regardless of its sensory modality. This response habituates, i.e. diminishes in amplitude, and can completely disappear after a series of repeated presentations, and it reappears when there is a change in any stimulus feature. Stimulus novelty includes changes in stimulation, but also the omission of the stimulus, although this last manipulation is less effective than other changes of stimulus parameters in evoking the orienting response.

The amplitude of the orienting response to stimulus change depends on the different stimulus parameters concerned, such as the type of change, be it of simple stimulus features (like intensity or pitch) or sensory modality (auditory to visual, for example), and the information or significance conveyed by the type of stimulus. It may be said that, in general, the more intense the stimulation, the higher the magnitude of the orienting response. Barry and Furedy [11] found that intensity and modality changes interacted multiplicatively in the elicitation of the orienting response.

According to Sokolov's original suggestions, the orienting response could be elicited by any perceived stimulus change. Different researchers propose instead that the novelty by itself is not enough to elicit the orienting response [12], but it is necessary that the stimulus be significant (for example, hearing one's own name). The concept of stimulus significance is a complex one and can be considered from different angles: amount of information, probability of appearance, uncertainty and even novelty, since significance can be also understood as a property of novel stimulation.

Stimuli with higher information content elicit higher orienting responses than those with less information content, which in turn lead to a faster habituation rate [13]. Recent research suggests that both novelty and significance play a role in the elicitation and recovery of the orienting response. Stimulus change is more effective in eliciting a new orienting response if it involves a change in the sensory modality or the semantic category of the stimulation than when it is restricted to changes in simple stimulus features or to the stimulus elements of the same category [14, 15].

The speed of habituation of the orienting response depends on different variables, some of them belonging to the subject, such as the arousal or activation level, and others to the stimulus itself, like significance and intensity. In general, the more intense the stimulus, the higher the initial magnitude and the slower the habituation rate of the orienting response components. The habituation of the orienting response rapidly generalizes to other stimuli whose features are similar to those of the original one. Once habituated, the orienting response may reappear if there is any change in the original stimulus. As occurs with the initial orienting response, its reappearence is more likely and more pronounced when the stimulus intensity increases, or when the sensory modality changes.

The orienting response is not a simple reflex but a reflex system, and as such is composed of an array of sensory, electroencephalographic and autonomic responses aimed at improving the perceptual processing of the novel stimulation and the subsequent reaction of the organism.

The electroencephalographic (EEG) orienting response, also known as alpha rhythm desynchronisation, consists of the disappearance of slow alpha waves and their substitution by a faster, low voltage activity [16]. Some components of the event related potentials (ERP) of the brain to novel stimulation show some characteristics of the orienting response. For example, the amplitude of these ERP components decreases with stimulus repetition and could be considered as orienting responses, although their habituation is not complete. Different researchers point to the N100, or N1, and P300, or P3, components of the ERP to both auditory and visual stimulation, and more specifically the subcomponent P3a of the P300 complex. These waves are more sensitive to novel stimuli and indicate orienting activity [17, 18, 19]. The N100 component habituates faster than the P300 wave, both to auditory and visual stimulation, and is more sensitive to novelty than to significance. On the contrary P300 seems to be more related to stimulus significance [18, 19, 20]. These waves would reflect the rapid processing of a novel stimulus that takes place in the brain shortly after its presentation.

Different autonomic responses have been identified as components of the orienting response. The most widely studied has been the skin conductance response, which presents all the characteristics of the orienting response as originally proposed by Sokolov [7]. It consists of a fast, phasic increase in skin conductance, due to the activation of the sympathetic division of the autonomic nervous system. The skin conductance response is very sensitive to changes in stimulus intensity and significance, and habituates rapidly to stimulus repetition [21, 22].

The Cardiac Orienting Response

Novel stimuli elicit phasic changes in the cardiac rhythm after stimulus onset. It is widely agreed that the cardiac orienting response elicited by low-to-moderate intensity tones (40-70dB) is characterised by heart rate deceleration (Figure 1). Acceleration dominates, in turn, with tones of a higher intensity. Although the cardiac orienting response is mainly decelerative, its topography can show an initial brief deceleration followed by an acceleration, and finally a new deceleration that for many authors is the authentic orienting response. Thus, three phases can be temporally distinguished in the cardiac waveform related to the orienting response, and most research propose that these phases may be related to different stages of stimulus processing at a central nervous system level:

a. An initial, rapid and brief deceleration that some authors have related to a preliminary cognitive process of stimulus registration. This would indicate a rapid stimulus processing. It habituates slowly or not at all with stimulus repetition [23]. Actually, whether this first decelerative component of the cardiac orienting response habituates or not as a result of stimulus repetition has been a matter of controversy for years [24, 25, 26].
b. A secondary acceleration linked with both the aversiveness and the intensity of the stimulus. This acceleration shows more variability and its magnitude and duration depend on different stimulus conditions [23, 27, 28]

c. Finally, a third component, which consists of a deceleration of longer duration than the first one. This deceleration habituates with stimulus repetition and for many authors is the authentic orienting response [23]. It would be related to central nervous system activity that favours attention to the incoming stimulus. The majority of studies show habituation of this decelerative component [8].

A problem that complicates the interpretation of the changes in the cardiac response is the double innervation, sympathetic and parasympathetic, of the heart. Changes in cardiac frequency (acceleration and deceleration) do not indicate in themselves the type of autonomic control which is going on when the subjects are reacting to novel stimuli. Experiments employing pharmacological blockade show that the decelerative cardiac orienting response is due to an intense vagal activity together with a less pronounced sympathetic activation. Both branches of the autonomic systems are activated, but the parasympathetic system dominates [29, 30]. By contrast, the defence response to auditory tones is mainly accelerative, but some decelerative components can be also found. This tachycardic reaction is due to sympathetic activation.

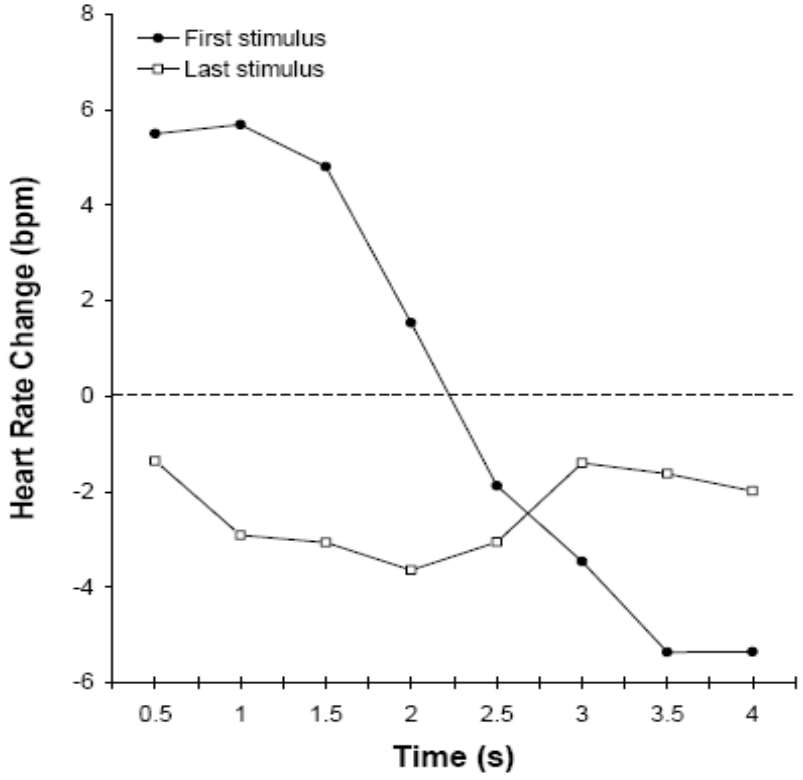

Figure 1. Habituation of the cardiac orienting response. The graph shows the heart rate changes promoted by repeated low-intensity acoustic tones. The response elicited by both the first and the last stimuli of a series of 5 along 4 seconds poststimulus (deviated from a 1-s baseline) can be appreciated.

The Defence Response

In addition to the orienting response, the organism may react to sudden or unexpected stimulation with other responses that Sokolov [7] described as the defence and adaptation reflexes. The defence reflex or defence response appears with high intensity or potentially damaging stimuli, and it shares some characteristics with the orienting response. The defence response has protective functions against intense or threatening stimulation, attenuating the sensory input and facilitating the withdrawal or fight reactions. The renowned psychophysiologist Frances K. Graham [23] introduced a third response pattern to unexpected stimulus, the startle reflex, which would be a different response, more or less midway between the orienting response and the defence response, which appears with sudden and transient stimulation of a moderate intensity. The adaptation reflex is a local and specific reaction that appears to stimuli that require a certain homeostatic adjustment. An example is the peripheral vasodilation or vasoconstriction that respectively follows increases or decreases in environmental temperature.

When confronted with potentially threatening agents, subjects react by displaying a series of behavioural, physiological and cognitive changes in order to protect themselves from the possible damage that these stimuli could cause. In this context, subjects react with fear, and a series of defensive reactions can be observed, like freezing and fight and flight - escape or withdrawal responses [31, 32]. Fanselow [33] has proposed a series of sequential stages occurring in mammals when confronted with a potential threat (e.g., a predator), in which the behaviour and somatic reactions depend on the distance between the animal and the predator. This model has been adapted by Lang and co-workers [34] to explain the chain of reactions appearing in human beings when exposed to potential threats, and is mainly based on experimental research employing symbolic threats like pictures. This model is composed of 3 stages, as follows:

Stage 1. Pre-encounter: In this first phase, the defensive reaction is not yet carried out, but the subject is in a situation similar to those in which a defensive response was engaged in the past due to the presence of a threatening stimulus.

Stage 2. Post-encounter: This phase is mainly characterized by the attention being focused on a stimulus susceptible to be a threat. The typical change appearing in this phase is a freezing behaviour accompanied by cardiac deceleration and increased skin conductance response.

Stage 3. Circa-strike: In this phase, subjects display an active defence behaviour (e.g., fight or flight) that is physiologically accompanied by cardiac acceleration.

According to this model, the reaction of the organism to a threat is composed of a sequence of responses. The initial phase (specifically, stage 2 of Fanselow) is characterized by attentional reactions driven by the threatening event. This phase, in which subjects are vigilant, is related to the detection and analysis of the potential dangerous stimulus [32], and would correspond with the preparatory defence reaction proposed by Masterson and Crawford [35]. This phase is accompanied by increases in both sympathetic –as shown by an increase in the skin conductance responses- and parasympathetic activity –promoting heart

rate deceleration-, but with a predominance of the vagal influences. The final phase (stage 3 of Fanselow) is characterized by actions intended for the active defence of the subject. This stage corresponds to the alarm reaction proposed by Masterson and Crawford [35], where orienting evolves to defence [7, 23], and it is accompanied by an increase in the activity of the sympathetic branch of the ANS leading to greater skin conductance responses and cardiac acceleration.

Hence, from classical studies of orienting and attention, it could be proposed that orienting and defence can be identified accordingly with the direction of their cardiac pattern, with orienting promoting heart rate deceleration and defence evoking accelerative responses. In addition, the habituation rate of both responses is also different. Orienting response habituates quickly, whereas the defence response shows a slow habituation [23].

The Cardiac Defence Response

Graham [23] has identified two different accelerative cardiac responses: the defence response and the startle response. The cardiac startle is elicited by fast rise time and transient stimuli and it has onset latencies below 2 seconds. The defence response, however, is elicited by non-transient, more sustained stimuli and shows latencies above 2 seconds. Turpin [28] noted, however, that this is not an actual differentiation, since the first short-latency cardiac acceleration is a component of the startle reflex, peaking around 4 seconds poststimulus, while a second, long-latency acceleration could be identified, related to the defence response, peaking around 30 seconds poststimulus and provoked by sympathetic activation. Later, Turpin et al. [36] subdivided the startle, short-latency cardiac acceleration into two components depending on their latencies and the characteristics of the stimuli: the first short-latency acceleratory component would appear between 1 and 2 seconds poststimulus and is related to the rise time of the stimulus, while the second short-latency acceleratory component appears between 3 and 6 seconds poststimulus and relates to the intensity of the stimulus.

However, more recent research has found new data that have changed the view of the cardiac defence response and which differs in some respect from this classical conception. The cardiac defence response is a complex pattern of heart rate fluctuations that usually appear when the subject is exposed to aversive stimulation. When provoked by an aversive acoustic stimulus, this cardiac pattern extends over 80 seconds approximately, and it is composed of two accelerative and two decelerative components appearing in alternating order [32, 37]. The first accelerative wave (short-latency) appears immediately after the aversive stimulus, peaking around 3 seconds, and extends between 5 and 10 seconds. The second acceleration wave (long-latency) usually appears around 20 seconds after the aversive stimulus, peaks around the second 35, and covers to the second 40 (Figure 2). In addition, in contrast to the classical view of defence that claimed an absence of habituation of this response (e.g. 23), it has been found that the second acceleration and deceleration show a moderate to rapid decreasing, i.e., habituation, with repeated stimulation [38, 39].

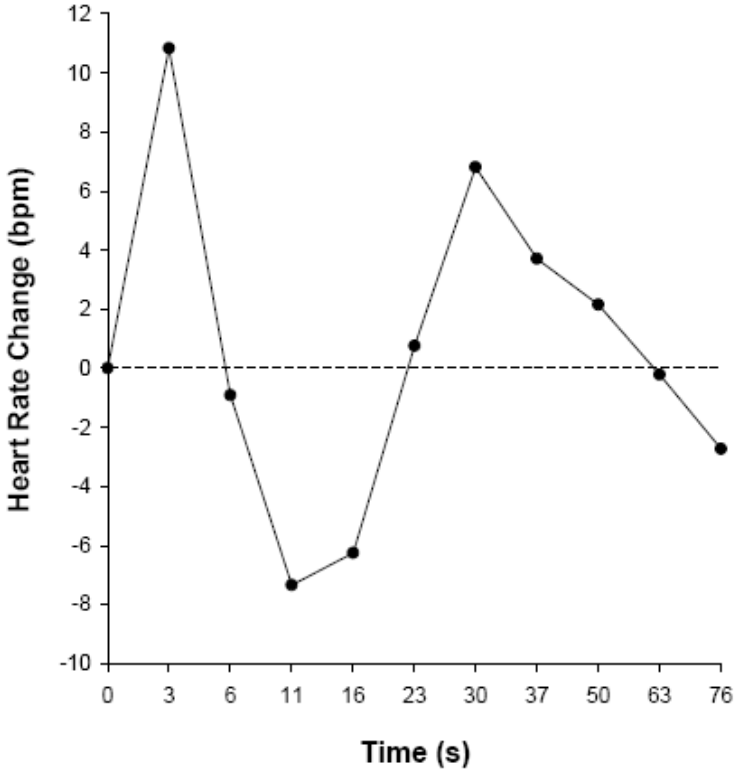

Figure 2. Cardiac defence response. The line shows the heart changes (10 medians covering 80-s poststimulus, see text) deviated from a 15-s baseline, provoked by a high-intensity white noise.

The involvement of the two divisions of the ANS in this complex cardiac pattern has been studied employing both pharmacological blockade and indirect indices of sympathetic and parasympathetic activation. In order to study the differential influences of the sympathetic and parasympathetic divisions on the cardiac response, Quigley and Berntson [40] used a parasympathetic antagonist (scopolamine) and a beta-adrenergic sympathetic antagonist (atenolol) in rats and recorded the heart rate elicited by low- (60 dB) and high-intensity (80 dB) acoustic stimuli. Low-intensity stimuli provoked heart rate deceleration, which was absent in the group treated with scopolamine, which indicates that the heart rate slowing promoted by low-intensity stimuli appears as a consequence of a transient increase in parasympathetic activity. In addition, the scopolamine group showed an acceleratory cardiac response elicited by the low-intensity stimulation, reflecting the concurrent sympathetic activation promoted by these stimuli, which was masked by the more powerful vagal response. The atenolol group, as expected, showed an increase in the magnitude of the bradycardia (heart rate slowing). These initial results pointed to the co-activation of the two branches of the ANS by low-intensity stimuli, indicative of an orienting response, but with a stronger activation of the parasympathetic division.

The cardiac component of the defence response elicited by the high-intensity acoustic stimuli showed a tachycardic pattern composed of an initial sympathetic activation followed by a reciprocal parasympathetic activation. The subjects provided with atenolol showed a marked attenuation of their heart rate acceleration, whereas those exposed to scopolamine did

not show any effect on their acceleratory cardiac pattern. Overall, the main difference between the cardiac responses to the low- and high-intensity acoustic stimuli was found in the parasympathetic division, which increases when the stimulation is of low intensity, and decreases with high intensity stimuli [3]. The sympathetic pharmacological blockade in humans has yielded an absence of the sympathetic mediated cardiac response, as measured by stroke volume through impedance electrocardiography, related to the secondary acceleration and secondary deceleration [41].

In humans, the involvement of both ANS branches in the cardiac defence response has also been demonstrated by means of indirect indices of sympathetic and parasympathetic activity. Fernández and Vila [42] employed the pulse transit time, an indirect index of the beta-adrenergic influences based on ventricular contractility, and found a decrease in the sympathetic activity during the first acceleration of the cardiac defence response that began to increase and reach its maximum at the time of the peak of the second cardiac acceleration. Thus, the pulse transit time coincided with the second acceleratory and the second deceleratory components of the heart response. These data pointed to a pre-eminence of the parasympathetic branch in the two first components (first acceleration and first deceleration) of the cardiac defence response [32, 37]. The parasympathetic mediation of the cardiac defence response in humans has been also studied through the respiratory sinus arrhythmia, since this measure is under parasympathetic control in the inspiration phase. Reyes del Paso et al. [43] have shown that when the cardiac defence response is provoked by an aversive stimulus, the respiratory sinus arrhythmia shows a pattern characterized by an initial decrease, coinciding with the first cardiac acceleration, followed immediately by an increase, coinciding with the first deceleration. Following the pattern of the cardiac response, the respiratory sinus arrhythmia shows a smaller decrease during the second heart rate acceleration and an increase coinciding with the second deceleration. This would indicate that the first two components of the cardiac defence response seem to be mainly under vagal control, while the two second components, although slightly mediated by vagal influences, are mainly under sympathetic control [32, 37].

The pattern of cardiac changes promoted by an aversive acoustic stimulus, like an unexpected and abrupt white noise, would reflect the two-stage reaction to threatening stimuli outlined above (i.e., orienting, attention, vigilance or preparation reaction, and alarm or defence reaction). Jaime Vila and colleagues have widely studied the cardiac defence response and have extended and reinterpreted the more classical postulates of Graham and Turpin. Recent data by Vila's group indicate that both the first short-latency acceleration, including its subcomponents, and the second, long-latency cardiac acceleration are part of the defence response and reflect both attentional and motivational processes [39]. The first acceleration and deceleration components, which are both parasympathetically mediated, would be related to the vigilance, orienting or preparation responses, characterized by an interruption of the ongoing behaviour and the focus of attention on the potential threat, and would represent the transition from attention to action [32]. The second cardiac acceleration and deceleration, which are both sympathetically mediated, would reflect a defence response and be related to defence behaviours (fight or flight) displayed to cope with the external threat.

Two works have explored the emotional modulation of the cardiac defence response under the frame of the motivational priming hypothesis proposed by Lang [34, 44]. These studies have shown an enhancement of the accelerative components of the cardiac defence response elicited while subjects are viewing unpleasant or phobic pictures [45]. Moreover, this effect is also found when the phobic picture is subliminally presented, and thus appears outside conscious perception [46]. In this case, the pattern of the cardiac response varies from that elicited in absence of an affective picture, and it is characterized by a single larger acceleration, while the first deceleration is absent. Authors have interpreted this change of pattern as an advance in time, some way a phase advance, of the defensive reactions – reflected by the second acceleration– due to the threat primed by the fear pictures [46].

Defence Response to Complex (but Symbolic) Threats

In real life, new stimuli and threatening events are usually more complex than an acoustic tone or a white noise, and the situation may represent a danger for the subject. It has been postulated, however, that complex pictures with a high interest or strong affective value are able to provoke orienting and defence responses that resemble those appearing in natural contexts [47]. Picture representations (e.g., photography), are able to evoke emotions because they have a representative or symbolic meaning for subjects [44, 48]. This symbolic information is similar or equivalent to the properties of the current object that it represents, and is able to activate those cognitive representations associated with the emotional responses, giving rise to physiological and behavioural reactions similar to those evoked by the current real stimulus [48].

The studies employing emotional pictures have found a bradychardic pattern, similar to that of the orienting response, when subjects are exposed to pictures that they rate as interesting (e.g., pleasant and unpleasant), whereas an accelerative cardiac pattern, related to the defence response, is found when they are exposed to fear pictures. In this line, it has been found that subjects with fear of spiders show heart rate acceleration and cephalic vasoconstriction, in addition to a tendency to show higher, and resistant to habituation, skin conductance responses, when exposed to pictures of spiders in comparison to neutral pictures [47]. Mutilation phobic subjects, selected by means of questionnaire ratings, have been found to show a transient heart rate acceleration followed by a cardiac deceleration when exposed to mutilation pictures, whereas non-phobic subjects usually show heart rate deceleration [49]. In addition, this defence response can be conditioned to a neutral stimulus. When a neutral acoustic stimulus, like a pure tone, is presented before the phobic picture, phobic subjects learn to anticipate the picture related to their fear, and show heart rate acceleration, while non-phobic subjects do not show this acceleratory pattern [50]. This cardiac acceleration constitutes an anticipatory response to the phobic-related stimuli whose function is to cope with the incoming aversive situation in order to reject or attenuate the threatening stimuli [50].

Recent research has shown, however, that the cardiac pattern elicited by viewing emotional pictures is more complex than a single sequence of acceleration or deceleration. Thus, viewing non-fear unpleasant pictures provokes a heart rate pattern that is basically

decelerative, which has been related to the freezing reaction that characterizes the vigilant or preparatory stage of the response to potential threats, and to the characteristics of the situation in which an active motor response is not required [34]. This cardiac deceleration takes the form of a triphasic wave pattern, composed by a brief initial deceleration, followed by a short heart rate increase and, finally, by a second moderate decrease [8, 34, 48]. The average heart rate change elicited by affective pictures is usually under base-line values, which indicates that this is an attention related response [27, 34]. This would be in marked contrast with classical research that has postulated an acceleratory cardiac pattern in response to aversive stimuli, as exposed above. However, according to Lang and co-workers [34] the response elicited by complex, emotional pictures, is conceived as a chain of reactions that start with an attentional response, i.e. a heart rate deceleration, elicited by both new and threatening stimuli. This initial deceleration is of a vagal origin and similar to the bradycardia promoted by fear-related stimuli in animals [51]. However, it is accompanied by an increase in the sympathetic activity, which is compatible with the results showing an influence of both branches of the autonomic nervous system in the orienting response [29, 30]. This fear bradycardia, in comparison with the heart rate deceleration related to orienting, is characterized by a greater deceleration, lower rate of habituation, and greater responsiveness to high intensity stimuli [52]. The defence, acceleratory response does not appear at this moment, in which the intake of information is taking place, but later, when the subject perceives the stimulus as threatening. This change occurs because attention is directed to the more salient stimuli, i.e., those with a motivational significance for the subjects. Hence, if the aversive stimuli persist, the subjects perceive them as threatening. But it may also occur that the activation level increases, and this deceleration pattern evolves to an acceleration one [53]. This acceleratory component of the response to aversive pictures has the function of preparing the organism for a motor response to the stimulus. An exception would occur, however, in fearful subjects, who show only a short latency accelerative cardiac pattern when they are exposed to pictures related to their phobias [47, 49, 54, 55].

The pattern of the cardiac response has been related to the attributes of the stimulus that provokes the reaction, namely affective valence and arousal. A relationship has been found between the affective valence of pictures and the heart rate they promote, with a more marked heart rate deceleration elicited by unpleasant pictures, followed by a less marked heart rate deceleration promoted by pleasant ones [56] (Figure 3). However, the low correlation appearing between the affective valence and the heart rate has led some authors to speculate that heart rate reflects several influences; for example, it may be determined by the affective valence of the eliciting stimuli, as well as by cognitive factors, like attention, or by those related to energy mobilization, like arousal or activation –with the latter being independent of the affective valence of the emotional stimuli. In this line, a relationship between heart rate and the arousal level of the eliciting stimuli has been found, in addition to a relationship between this autonomic index and the affective valence [e.g., 57, 58, 59]. Other studies have shown a relationship between heart rate and arousal, but not between heart rate and affective valence, suggesting that pictures that are more emotionally arousing promote higher orienting responses and demand greater processing resources (i.e., attention) [60,61,62].

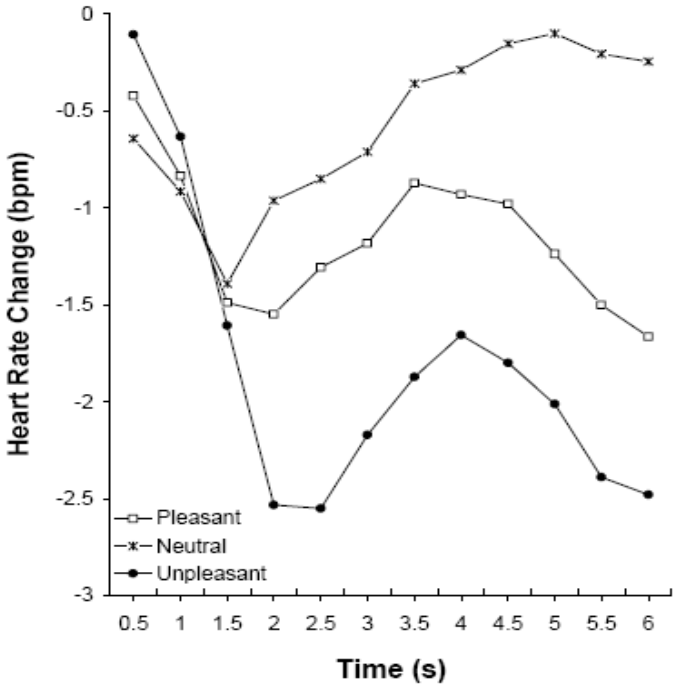

Figure 3. Cardiac response to affective content. The figure shows the decelerative heart rate promoted by unpleasant, neutral and pleasant pictures during 6-s of picture presentation (deviated from a 1-s baseline).

The studies employing fearful subjects have shown a heart rate acceleration promoted by phobic stimuli. Cook et al. [63] found a higher cardiac acceleration to imagined unpleasant material in fearful subjects. Several studies that have employed visual stimuli, have found higher heart rate acceleration to spiders and snakes in fearful subjects whose phobic fear was related to one of these two types of stimuli, which also promoted higher startle responses and skin conductance responses [55,64]. As noted by Globisch et al. [64], these data support the hypothesis of the existence of a fear network in the brain which can be quickly activated. This network would be associated to the activation of the sympathetic branch of the autonomic nervous system and related to the triggering of the defence response. An exception appears to occur, however, in blood or mutilation phobic subjects. When exposed to their feared objects, these subjects do not show the typical pattern of response found in other phobic subjects, but a transient sympathetic reactivity followed by a strong vagal response. This pattern has been clearly demonstrated in studies employing phobic pictures, which have obtained a marked heart rate deceleration [49, 55]. The only increase in heart rate promoted by phobic pictures appears in the first trial (the first phobic picture) of a sequence of several pictures, whereas the remaining pictures elicit heart rate deceleration [49, 55]. The nature of this reactivity pattern is not well known, although recent research could be starting to delineate the origins of this type of response. In non-phobic subjects, the cardiac defence response to an abrupt, acoustic stimulus has been used to classify subjects as high- and low-accelerators, depending on their cardiac response [53]. When these subjects look at pictures of different affective value, those classified as high-accelerators show a higher heart rate

acceleration promoted by unpleasant pictures in comparison to pleasant and neutral ones, and also in relation with the low-accelerators, who show the typical heart rate deceleration found in previous studies. Moreover, when pictures are reclassified in emotional categories, the mutilation and body damage pictures promote less initial heart rate deceleration and a marked and higher final acceleration only in high-accelerators, in comparison with the other types of pictures and also in relation with the low-accelerators. These data could be indicating that, in an unselected sample, those subjects that show a cardiac defence response to an acoustic aversive stimulus also show a tendency to respond to unpleasant pictures with a defensive pattern rather than an orienting one. These subjects would share some characteristics with phobic subjects, like, for example, a lower threshold of their brain fear system, which would activate an immediate defence response to specific stimulus categories [53]. Convergent findings from cellular recordings in the human amygdala in neurosurgery subjects give support to these data [65]. When the intracranial field potentials of the amygdala are recorded by means of depth electrodes while viewing emotional pictures, greater response changes have been reported in the high gamma band to pictures depicting mutilations and body damage than to positive and neutral contents, suggesting that there are neurons into the amygdala responding in a selective way to this type of aversive content –while other cells within this structure respond to other type of unpleasant stimuli, as observed by the response changes in the low gamma band to disgusting pictures [65].

The Brain Fear System

It has been proposed that emotional responses depend on two motivational systems of the brain [34, 66, 67, 68]: the appetitive system, related to approximation behaviours (like food intake, copula, etc) and the aversive or defensive one, related to avoidance, withdrawal and defensive behaviours (like flight or fight). We will focus on the second, the defensive system, since the first is outside the scope of this chapter. Studies carried out on animals and more recently on humans, have pointed to the cerebral amygdala as the core of the so called brain fear system.

The amygdala plays an important role in the elicitation of both emotional and defensive responses, and especially supports the processing and response to fearful or threatening stimuli [69]. This is a limbic structure located in the medial side of the anterior section of the temporal lobe. The amygdala is not a unitary structure but is composed of an array of neural nuclei which contribute to different functions related to emotions [70].

The amygdala has been considered a key region involved in the processing of the emotional value of sensory signals, since it receives inputs from all the sensory association areas, including visceral inputs [69, 71, 72]. The amygdala also receives neural projections coming from the orbitofrontal cortex, the CA1 sector of the hippocampus, subiculum, hypothalamus, olfactory structures, nucleus of the solitary tract and substantia innominata [71, 73]. The amygdala is a key region for the formation of association between stimuli and rewards, given the convergence of anatomical projections that it receives [70, 74, 75].

In addition to the cortical projections noted above, the amygdala also receives thalamic inputs [72, 76]. The sensory information that reaches the thalamic nuclei is sent to cortical

regions for a complex, perceptual analysis. However, the more simple features of these stimuli reach thalamic cells that also communicate with the amygdala. This thalamus-amygdala projection is involved, therefore, in the processing of the affective significance of simple sensory characteristics of the stimuli, whereas the cortical-amygdala projections are related to the complex processing of the stimuli [72, 74, 77]. It has been suggested that the more simple features of the stimuli would activate the emotional circuits of the amygdala through the thalamus-amygdala pathway, preparing the amygdala cells to receive the more complex and elaborated information coming from the cortex [77].

The amygdala performs also an affective processing of the visceral-sensory information [78, 79, 80]. The central nucleus of the amygdala receives nocioceptive inputs coming from both the parabrachial areas and the spinal cord [81]. Although the pathways that lead interoceptive information to the brain are not well known, research has shown that interoceptive inputs coming from the abdominal cavity, intestine, heart and blood vessels reach the nucleus of the solitary tract, which, in turn, sends afferent inputs to several regions of the basal brain, including the hypothalamus and the amygdala [82, 83]. In addition, neurons of the central nucleus of the amygdala respond to the activation of baroreceptors and chemorecpetors, whose stimulation activates the cells of the solitary tract nucleus [84], and the electrical stimulation of the vagus nerve alters the activity of the cells of the amygdala [80]. The central nucleus of the amygdala projects to different regions of the brain, modulating autonomic and behavioural components of the defence response. For example, through its projections to the lateral hypothalamus, periaqueductal gray, nucleus ambiguus, nucleus of the solitary tract, dorsal motor nucleus of the vagus, rostral ventrolateral medulla and paragigantocullar nucleus [85, 86], the amygdala would be involved in the modulation of the cardiovascular responses in emotions, like fear. Hence, the amygdala may have a general homeostatic function through both the evaluation of exteroceptive and interoceptive inputs, and the elicitation of visceral and behavioural responses to emotional stimuli [72].

The study of the involvement of several nuclei of the amygdala in emotion and conditioning has been widely explored employing a fear-conditioning paradigm. In this paradigm a conditioned stimulus, e.g. a pure tone, is associated with an unconditioned stimulus, e.g. an electric shock. In these studies it has been proved that the conditioning of responses related to fear depends on the connections between the thalamus and a region of the amygdala that includes the lateral nucleus, the dorsal sector of the central nucleus and the amygadalostriatal transition area situated dorsally in relation to the central nucleus [72]. In the case of auditory stimuli, the lateral nucleus receives these sensory inputs. Lesions to the lateral and central nuclei of the amygdala disrupt fear-conditioning, suggesting that this process depends on the projection from the lateral nucleus to the central nucleus (87). In addition to these sensory, thalamic, and cortical inputs, the lateral nucleus of the amygdala also receives thalamic inputs coming from the spinothalamic tract, and its cells also respond to nociceptive stimulation [88]. In the case of auditory fear conditioning, the sensory projections from the auditory cortex to the lateral nucleus of the amygdala are needed when the stimulus is complex, but not when the stimuli are simple [89].

In fear conditioning, in addition to establishing an association between the conditioned and unconditioned stimuli, a contextual effect has also been found, since the unconditioned stimulus is associated with the environment where the conditioning has taken place [90]. In

this type of conditioning, in addition to the participation of the amygdala, the hippocampus is also involved, since lesions to this last structure disrupt the contextual conditioning, with the conditioning of discrete stimuli remaining unaltered [76, 91, 92, 93]. The ventral hippocampus, CA1 and subiculum, send inputs, related to contextual keys, to the basal and accessory basal nuclei of the amygdala, which, in turn, send projections to the central nucleus of the amygdala, where they acquire an emotional meaning as a consequence of the inputs that reach the accesory basal nucleus of the amygdala related to the unconditioned stimulus [81, 90].

Hence, the amygdala is involved in the cardiac and respiratory responses related to vigilance and defence, by means of its interactions with other subcortical regions such as the hypothalamus and the periaqueductal gray.

Functional neuroimaging studies conducted in humans have also found an involvement of the amygdala in fear and in the processing of emotional stimuli [94, 95, 96]. Several studies employing functional magnetic resonance imaging (fMRI) have found that pictures rated as negative promote a greater activation in the amygdala, which, as mentioned above, is the core of a brain fear system that processes and responds to threatening stimuli [97, 98, 99].

A study employing positron emission tomography (PET) has shown differential amygdala activation depending on the type of emotion displayed by faces. Left amygdala is more active when subjects view faces expressing fear, which has led researchers to postulate that those responses promoted by aversive stimuli are mediated by this structure without the involvement of the cerebral cortex [96]. When words have been employed to elicit emotions, unpleasant words have promoted greater amygdala activation than neutral ones, as measured by fMRI [100]. Some authors have noted that the differential activation of the amygdala to unpleasant stimuli would suggest that this structure is necessary to respond in a stereotyped and universal manner to threatening stimuli or to those signalling danger, without carrying out a complex cognitive processing, and this structure could provide a quick preparation for action [101]. Other authors have been interested in the brain regions involved in heart rate changes occurring during the processing of emotional stimuli. These studies have found that cardiac changes related to the affective valence of the stimuli are supported by different neural structures, in such a way that heart rate changes evoked by negative pictures depend on the activity of the amygdala [98,102]. We must note that it has also been postulated that the amygdala might respond to the stimulus salience and not to its affective valence [103], since some research has found activity in this structure to both pleasant and unpleasant stimuli [104, 105]. However, it has been found that heart rate is faster and amygdala activity is greater to sad and angry pictures than to happy ones [98].

The involvement of the amygdala in the fast processing and response to threatening stimuli has been demonstrated in normal and brain damage patients. In a subject presenting cortical blindness as a consequence of unilateral brain damage in the primary visual cortex, the presentation of fearful faces to the blind cortex promoted higher activation in the right amygdala (as measured by fMRI) than the neutral faces did, therefore signalling the involvement of this structure in the processing of aversive stimuli, even when these appear outside the conscious of the subject, and presumably supported by the thalamus-amygdala connections [106]. A greater right amygdala response has also been obtained in normal subjects using subliminal presentation of threatening faces and in a PET scanning situation,

whereas supraliminal presentation of these stimuli evoked greater left amygdala responses [107]. Other fMRI data obtained by means of subliminal and supraliminal presentation of fear faces show a tendency of the left amygdala to respond to supraliminal fear, and a greater right amygdala activity promoted by subliminal fear [108]. Moreover, a dissociation into the amygdala has been found depending on the consciousness of the subjects of the threatening stimuli and their anxiety level, in such a way that the dorsal portion of the amygdala has been found to be dependent on the conscious perception of the stimuli, whereas the basolateral amygdala activity was related to the unconscious, masked presentation of the stimuli; the activity of this last region was related, in addition, to the trait anxiety of the subjects, while the dorsal amygdala activity was not [109]. Some authors have linked the brain activity and the cardiac activity by using fMRI to measure both central and peripheral activity [110]. Results have shown that the left amygdala, the right prefrontal cortex and the right insula are related to the sympathetically mediated cardiac changes promoted by threatening events, like the anticipation of an electric shock. In addition, those subjects who showed greater activation in these affective-related brain structures to threat cues versus safety cues, were those who also showed greater cardiac contractility and reported more subjective anxiety [110].

It has been proposed that the amygdala plays a key role in processing phobic stimuli and provoking the fear responses related to them [111]. In animal phobic subjects, greater amygdala activation appears when subjects are exposed to pictures of their feared objects than when they look at other unpleasant pictures [105]. This activation is also greater than that found in non-phobic subjects and seems to be independent of the awareness of the phobic object, since it appears even when subliminal stimuli are employed [112, 113]. In addition, it has also been found that the activation of the amygdala develops faster in phobic subjects exposed to their feared object than in non-phobic subjects [114]. Some authors have also found that amygdala activation is not only involved in phobic-relevant stimuli, but also in disgust ones, which has been interpreted as an indicator of the increased disgust-related sensitivity of phobic subjects, and in non-phobic fear stimuli [115]. It appears, that the amygdala is particularly involved in the automatic processing of phobia-relevant threat, with a special role in the rapid detection of and responding to the phobic stimulus rather than in the maintenance of such a fear [116].

Conclusions

In addition to its vital homeostatic functions, the cardiovascular system is also influenced by cognitive and emotional factors. The presentation of novel or significant stimuli evokes bodily changes –the orienting response - that manifest themselves in the cardiovascular system mainly as a heart rate deceleration. This cardiac deceleration is composed of three phases purportedly related to different stages of the processing of the stimulus: an initial deceleration (related to the registration of the stimulus), followed by an acceleration (related to the aversiveness and intensity of the stimulus) and a final deceleration (related to the level of attention received by the stimulus).

When environmental stimuli are threatening, the orienting response changes to a defence response, whose physiological, behavioural and cognitive components may protect the organism against the threat. The cardiac defence response elicited by aversive acoustic stimuli shows a pattern that covers around 80 seconds and is composed of two accelerative and two decelerative waves that appear in an alternating order. The first accelerative wave appears immediately after the stimulus onset and peaks around 3-s later, while the second accelerative wave appears around 20-s post stimulus. It has been shown that the first acceleration and deceleration are under parasympathetic control and have been related to orienting and preparation behaviours, while the second acceleration and deceleration are under sympathetic control and have been related to defence behaviours. This defence response is affectively modulated, since its accelerative components are enhanced when it is evoked while viewing unpleasant and phobic pictures, and its topography changes to a single larger acceleration, which might be interpreted as a phase advance of the second acceleration.

When exposed to more complex threats, like pictures, the cardiac changes they promote are characterized by a deceleration that takes the form of a triphasic wave composed by an initial deceleration, followed by a short acceleration (although under the baseline) and a second moderate deceleration. This deceleration is vagally mediated and seems to be a reminiscent of the fear bradycardia in animals elicited by threatening stimuli. However, this response changes when phobic subjects are exposed to pictures depicting their feared object, and the cardiac pattern is now clearly accelerative. In addition, it is an open question if the cardiac changes promoted by complex affective stimuli, like pictures, depend on the affective valence or the arousal that these stimuli elicit in the subjects.

At a central nervous system level, the amygdala has been proposed as the central core of a so called brain fear system prepared to the rapid detection of and the reaction to threatening stimuli. The amygdala modulates the cardiac reactions to threatening stimuli through its efferences to hypothalamus, midbrain and brain stern nuclei related to cardiac changes, in addition to its role in promoting other autonomic and motor reactions. Modern neuroimaging techniques have shown the participation of the amygdala in the processing of fear stimuli, and also a left-right dissociation depending on the degree of conscious perception of the threatening stimuli. In addition, a greater and faster amygdala response has been found in phobic subjects exposed to pictures of their feared object.

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Chapter 7

Biosocial Synergy: Stress, Cardiovascular Disease, and High Risk Populations

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Abstract

Our primary objective in this chapter was to review work regarding the association between stressors and cardiovascular disease (CVD) and examine scientific rationale behind this proposed link. Stress is a heuristic term often overused to describe many psychological anomalies. We attempt to narrow this definition of stress to one of biosocial synergy, encompassing various types of chronic and traumatic stressors, individual perception, and physiological responses. Given this conceptual basis, we describe relevant physiological pathways associated with stress and subsequent disease, focusing on the hypothalamic-pituitary-adrenal axis (HPA) and cortisol. A further specific discussion of stress, trauma stress (e.g., posttraumatic stress disorder), and CVD is provided. Lastly, we provide a discussion of the cardiovascular consequences of exposure to stressors in populations considered at high risk: caregivers, medical professionals, air traffic controllers, firefighters, and police officers.

Introduction

The term “stress” is generally used to describe a process brought about by environmental stimuli, individual psychological mediation, and physiological change. The difficulty in conceptualizing stress accurately can be attributed to its subjective quality. The manner in

which an individual reacts to a stressor depends to a great degree on perception of the event, experiences with similar events, culture, and genetic makeup. Individual perception and appraisal appear to play a part in what specific environmental demands initiate the stress process [1]. To gain a better understanding of how stress may be associated with disease outcome, one needs to consider both psychological and physiological factors. Conceptualizing stress as a biosocial process allows for a systemic assessment of environmental stimuli, undue strain on an organism, and resultant psychological and biological changes that increase the risk for disease [2]. Seyle [3] was among the first to develop a model of stress based on physiological responses to external environmental stimuli. He proposed that disease states occur when the body can no longer adapt to external stressors and remains in a state of chemical imbalance. Stress was believed to produce a neuroendocrine response which, through nervous and endocrine systems, affected all body organs [3].

There is disagreement regarding characteristics of events or stimuli that place people at risk for disease. Such characteristics include change created by the event, loss or threat of loss, the amount of control a person has over the event, and event duration. [2]. There are also various types of stressful events examined in the literature; three will be discussed here. One type involves major life changes over a specific time period. Individuals exposed to high levels of life event stressors experience "greater degeneration of overall health, more diseases of the upper respiratory tract, more allergies, a greater incidence of hypertension and a greater risk of sudden cardiac death and coronary diseases than do people who have been exposed to a low degree of life stress" [4]. The significance of life stress has also been reported in relation to tuberculosis, diabetes, arthritis, and cancer [5]. Another type of stressor measures daily events or “daily hassles” over a specified period of time [6]. Early initial work demonstrated associations between measures of daily events and psychological distress [7]. Progress has also been made on understanding the relationship between daily events and physical symptoms [8].

The third type of stressor is a severe form brought about by exposure to a traumatic event. Table 1 outlines the criterion for posttraumatic stress disorder (PTSD) as set forth by the American Psychiatric Association Diagnostic and Statistical Manual- Fourth Edition (DSM-IV) [9].

PTSD is a significant mental health issue and can be debilitating. The National Comorbidity Survey (NCS), a representative sample of 5,877 people in the United States aged 15 - 54, found a 7.8% lifetime prevalence of PTSD. Approximately 14% of people in the sample who had been exposed to trauma developed PTSD (10). Individuals with history of PTSD have demonstrated higher lifetime rates of endocrine disorders, major depression, medically explained and unexplained somatic complaints, and eating disorders. Neurobiologically, PTSD represents a dysregulated stress response and is characterized by neurochemical and neuroanatomic abnormalities. The impact of PTSD on health and CVD will be discussed in a subsequent section of this chapter.

The remainder of this chapter will discuss the impact of stress and trauma stressors on health outcomes, and specifically on CVD. Figure 1 suggests pathways for stress and disease and will serve as a general guide for discussion.

Table 1. DSM-IV-TR Diagnostic Criteria for PTSD (American Psychiatric Association, Washington, DC, 2000)

Criterion A: Traumatic Stressor	An event, or events, in which an individual experiences, witnesses, or is confronted with life endangerment, death, or serious injury or threat to self or others; and the individual responds to the experience with feelings of intense fear, horror, or helplessness
Criterion B: Reexperiencing Symptoms (one or more)	Intrusive recollections; distressing dreams; flashbacks; dissociative phenomenon; psychological and physical distress with reminders of the event.
Criterion C: Avoidance or Numbing Symptoms (three or more)	Avoidance of thoughts, feelings, or conversations associated with the event; avoidance of places, situations, or people that are reminiscent of the event; inability to recall important aspects of the event; diminished interest; estrangement from others; restricted range of affect; sense of a foreshortened future.
Criterion D: Hyperarousal symptoms (two or more)	Sleep disruption; impaired concentration; irritability or anger outbursts; hypervigilance; exaggerated startle reflex.
Criterion E	Minimum symptom duration of 1 month.
Criterion F	Symptoms cause distress or functional impairment.

In addition, we will review recent research on populations that are at high risk for exposure to stressors. These include caregivers, health care workers, air traffic controllers, and first responders (firefighters and police officers).

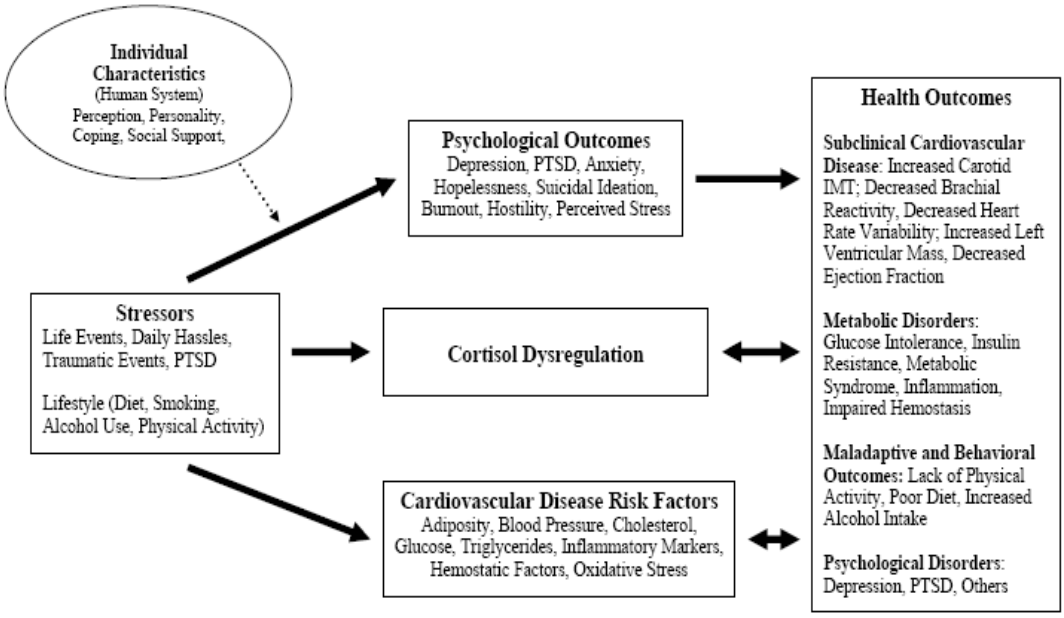

Figure 1. Stress Exposure: Psychological and Health Outcomes.

Stress and the HPA Axis: Pathways to Disease

The most commonly studied physiological systems that respond to stress are the HPA (hypothalamic-pituitary adrenal axis) and the autonomic nervous system. The severity and impact of the stress response can be viewed by gauging physiological disruption and dysregulation of these systems [11, 12]. The stress response is considered “adaptive” when it is in reaction to an acute situation and is of limited duration. It is considered “maladaptive” when the physiological reaction is not brought under control by the usual regulatory mechanisms. If a person cannot remove him/herself from the stressful encounter, the physiological response may become chronic and dysregulated [13].

The concept of “homeostasis” (steady state) is somewhat limited in describing the scope of physiological systems that activate during the stress response [14]. Homeostasis applies to a limited number of systems, such as body temperature and oxygen regulation, that are essential to life and are controlled within a narrow range. These systems are not activated or varied in order to help the individual adapt to the environment. In contrast, systems that show variation to meet perceived/anticipated demands characterize the state of the organism in a changing world and reflect the operation of most body systems in meeting environmental challenges. Such stress mediators are not held constant and they lead to adaptation as well as damage when they are produced insufficiently or in excess, that is, outside of the normal range [14].

Sterling and Eyer [15] formulated a concept to account for the more holistic nature of the stress response as it relates to stabilized bodily states -“allostasis”, which refers to the maintenance of physiological stability through change. The concept of “allostatic load”, refers to the wear and tear that the body experiences due to repeated cycles of allostasis as well as the inefficient turning on, or shutting off of physiological responses to stress [14, 15]. Seeman, McEwen, Rowe, and Singer [16] reported an operational measure of allostatic load that reflects information on levels of physiologic activity across a range of important regulatory systems, including the HPA axis and sympathetic nervous systems as well as the cardiovascular system and metabolic processes. Over this 2 ½ year follow-up study, higher baseline allostatic load scores were found to predict significant increased risk for incident CVD, for decline in physical and cognitive functioning, and mortality.

Allostatic load thus appears to be a more holistic way to describe stress as producing "wear and tear" on the body, across a variety of stressors which activate physiological systems [14]. Hormones protect the body in the short run and promote adaptation, but in the long run, allostatic load causes changes in the body that lead to disease. Lifestyle factors such as diet, exercise, substance abuse, and social developmental experiences may also be involved in this process. All of these factors influence the turning on and off of the physiological mediators of stress [16].

Cortisol and the HPA Axis

Cortisol is a primary hormone released by the adrenal glands as a result of the HPA axis response to stress, and is a frequently used biomarker of stress [17, 18]. Cortisol levels that

are chronically elevated and hyper-reactivity of the HPA axis are associated with an increased risk for diabetes, hypertension, and CVD. Researchers have found cortisol levels to be 21.7% higher in persons reporting high job strain [19]. In addition, lower levels of cortisol output have been associated with higher psychological well-being [20]. If prolonged stress suppresses immunity, more infectious diseases could result because of the longer cortisol secretion, which suppresses immunity below where it is effective. This impairs defense against disease and results in more illness [21].

Stress and CVD

Cardiovascular effects of the HPA axis and sympathetic nervous system activity are diverse [22, 23]. Both systems can potentially lead to harmful effects such as increased blood pressure (BP) and decreased insulin sensitivity [24, 25]. Some evidence suggests that both systems might precipitate endothelial dysfunction—an important early manifestation of atherosclerosis [26, 27]. During stress, these systems interact to form a complex pattern of cardiovascular adjustments involving neural, endocrine, and mechanical factors. Changes in any one component of the system necessarily affect other components of the system [10]. Stressors mentioned earlier in this chapter may affect the cardiovascular system in different ways. Studies conducted on the rate of defibrillator firings among a sample of New York City residents during the month after the 2001 terrorist attacks on the World Trade Center in New York resulted in rates that were two to three times higher than normally observed [28, 29].

Chronic daily stress can also increase risk of cardiovascular events. In a study of work-related stressors, upcoming deadlines were associated with a six-fold increase in myocardial infarction [30]. Other studies suggest that chronic work-related stress carries as much as two to three times higher risk of cardiac events, especially when employees perceive little control over their work environment [31]. In women with CVD, marital stress was associated with a risk of recurrent cardiac events that was three times higher than in women with no marital stress [32]. By contrast, with acute stress, which can trigger acute thrombotic, arrhythmic, or mechanical cardiovascular events, chronic daily stress seems to affect cardiovascular risk mainly by acceleration of the atherosclerotic process [33].

Exposure to Traumatic Events and CVD

PTSD may promote poor health through a complex interaction between biological and psychological mechanisms. Those who report PTSD symptoms are more likely to have a greater number of physical health problems. PTSD also has been found to be associated with greater medical service utilization for physical health problems [34]. Much of the research on the pathophysiology of PTSD has focused on dysregulation of the HPA axis. Evidence suggesting a role for HPA axis dysregulation in the development of PTSD is supported by clinical studies demonstrating decreased 24-hour urinary cortisol levels in subjects with PTSD. For example, Yehuda et al. [35] examined 22 Holocaust survivors with PTSD and 25 without PTSD. Subjects with PTSD had an average cortisol level of 32.6 pg in their 24-hour

urine sample, compared to a level of 62.7 pg of cortisol in those without PTSD. This finding has been replicated in other studies [36, 37].

Individuals with a history of PTSD have demonstrated higher lifetime rates of endocrine disorders, major depression, medically explained and unexplained somatic complaints, and eating disorders. Evidence linking exposure to trauma with CVD has been found across different populations and various types of traumatic events. Military veterans diagnosed with PTSD, for example, were significantly more likely to have had abnormal electrocardiographic results, including a higher prevalence of myocardial (Q-wave) infarctions and atrioventricular conduction defects [38, 39]. Civilian populations exposed to traumatic events also report increased cardiovascular health problems. A recent meta-analysis of cardiovascular status in persons with PTSD indicates that they have a higher resting heart rate (HR) and elevated BP compared to individuals without PTSD. A subset analysis revealed that the effect sizes for comparisons of basal HR were greatest in studies with the most chronic PTSD samples [40]. It has been suggested that lower cortisol levels in PTSD are associated with a down-regulated glucocorticoid system that may result in elevations in leukocyte counts and other immune inflammatory activities associated with CVD. Physiologic arousal during intrusive memories of traumatic events has been associated with alterations in neuroendocrine functions related to changes in the HPA axis [41].

Biological Mechanisms

Studies suggest that biological mechanisms might mediate the effects of PTSD on cardiovascular disorders such as sympathoadrenal hyperactivity, diminished heart rate variability, and platelet aggregation. These studies document substantial evidence of excessive sympathoadrenal activity in PTSD [41]. There appears to be two major areas relative to PTSD in which disturbances of the HPA axis could lead to CVD - platelet activation and heart rate variability [42]. Platelets may affect both atherogenesis and acute thrombus formation on top of existing atherosclerotic plaques. Platelets contain adrenergic, serotonergic, and dopaminergic receptors, which suggests a mechanism for how depression might also influence platelet function [43]. Heart rate variability reflects the balance between sympathetic and parasympathetic tone in relation to the cardiac pacemaker [44]. Most studies have found that depressed patients have lower heart rate variability [45], perhaps reflecting decreased parasympathetic tone.

Behavioral Mechanisms

Although PTSD has substantial effects on physical health even if the effects of behaviors such as smoking are statistically controlled, these behaviors are also an important part of the pathway from traumatic exposure to poor health. Health is also affected by personal characteristics such as age, gender, and genetic makeup; social factors such as socioeconomic status, social support, and proximity to sources of preventive care; and ethnic and cultural background [46].

CVD in High Stress Populations

Allostatic Load in High Stress Populations

When persons are subjected to stressful situations on a constant or regular basis the HPA regulatory system may be in a continuous elevated state of activation. Four types of allostatic load have been identified which appear to be related to different types of exposure to stress [16]:

(1) When a person experiences too much stress in the form of repeated, novel events that cause repeated elevations of stress mediators over long periods of time. High stress populations and occupations live in a milieu of unexpectedness. Every day, a new or novel experience may occur.
(2) A second type involves failure to adapt to the same stressor. This leads to an overexposure to stress mediators because of the failure of the body to dampen, or eliminate the hormonal stress response to a repeated event. Lack of control over events at work is an example. This is a continuous and ubiquitous stressor that pervades the high stress lifestyle.
(3) A third type involves failure to shut off the physiological response to the stressor. Since stressors may be continuously present in high risk populations, the physiological system may never have the opportunity to shut down.
(4) A fourth type involves an inadequate hormonal stress response that allows other systems, such as the inflammatory cytokines, to become overactive. When regulatory systems fail to shut off due to heavy exposure to stressful encounters, other systems become overactive. This may precipitate disease states.

In this section, we describe associations between stressors and CVD in populations at increased risk for stress: caregivers, health care workers, air traffic controllers, and first responders (firefighters and police officers). These groups are exposed to a variety of stressors during their services.

Caregivers

Changes in the health care system now place much of the responsibility of the care of patients with mental and physical disabilities on the shoulders of family or friends, usually untrained, who must also contend with other household and work responsibilities. Caregiving can be both physically exhausting and psychologically stressful. Besides the potential physical demands of having to dress, bathe, or feed the patient, caregivers are frequently exposed to depression, anger, aggression, agitation, and paranoia from the patient. Research has found that caregivers, due to demands on their time, have poor self-care habits such as not getting enough exercise, eating a healthy diet, and getting adequate rest [47, 48]. This, along with the stress, may come at a great cost to the mental and physical health of the caregiver [49-55]. Caregiving may contribute to pathophysiologic changes that lead to

elevated levels of BP, cholesterol, triglycerides, and insulin. These risk factors along with other psychological and behavioral characteristics may increase the caregiver's risk of poor health outcomes [47, 49, 52, 53, 56-64]. There is an extensive literature evaluating potential health risks that caregivers face; those that address potential risk factors associated with CVD will be highlighted here.

Heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were examined in three different populations to determine if caregiving resulted in higher cardiac reactivity compared to non-caregiving [50, 64, 65]. These studies found that caregivers were more likely to have increased HR, SBP, and DBP. However, these elevated levels were influenced by a number of factors other than caregiving. Uchino [65] found that caregivers with high social support had typical age-related decreases in HR reactivity, but those with low social support had atypical increases. Vitaliano [66], who used caregiving as a marker for stress, found that cardiac reactivity was the result of a combination of factors including personality type, expressed emotions, hostility, anger expression, and avoidance coping [66]. Furthermore, only those caregivers that were already hyper-reactive were found to be more reactive than the non-caregiver control population. King [54] found no difference in ambulatory BP between the caregivers and non-caregivers during their regular working hours; however SBP was significantly elevated while caregiving occurred. These results indicate that caregivers have higher levels of cardiac reactivity, but also show that reactivity is affected by other factors.

The perturbation of certain biological markers as a result of chronic stress experienced by caregivers may indicate pathophysiologic changes involved in CVD. These include markers such as fibrin D-dimer (DD), von Willebrand factor (vWF), and thrombin-antithrombin III complex (TAT), as well as the more traditional markers known to play a role in the pathology of CVD such as triglycerides (TG), high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, insulin, and glucose [66, 67]. Changes in DD, vWF, and TAT may predict coronary events in apparently healthy individuals and those with prevalent coronary artery disease (CAD). Von Känel [64, 67] hypothesized that "added life stress beyond chronic caregiving distress would promote hypercoagulability" as measured by DD, vWF, and TAT. What they found was that while life stress did not predict TAT or vWF, life stress together with body mass index (BMI), hypertension, gender, and depression status were significant predictors of DD. These results indicate that added life stress on top of the chronic stress caregivers experience may elicit a hypercoagulable state that might contribute to CAD [64, 67].

It has also been hypothesized that caregivers will be more likely to have high levels of TG, LDL cholesterol, insulin and glucose and low HDL cholesterol compared to non-caregivers [62, 63]. Vitaliano [64], using caregiving as a stressor, found that caregiving along with different measures of anger expression, Type A personality, and avoidance coping were associated with variability in TG, HDL cholesterol, and LDL cholesterol. For example, male caregivers had higher TG and lower HDL than the male non-caregiver controls [64]. In a separate study, they also found that chronic stress or "distress" among caregivers was positively associated with insulin and glucose levels [65]. Caregiving alone was found to be associated with higher insulin levels, and while caregiving was not associated with higher glucose levels, stress was. Distress was also associated with elevated insulin levels.

These results indicated that caregivers may also be at risk for metabolic syndrome. Metabolic syndrome is a constellation of risk factors that include elevated waist circumference, elevated TG, low HDL cholesterol, elevated fasting glucose or treatment for diabetes, and elevated BP or treatment for hypertension. Metabolic syndrome may be associated with increased CVD risk, therefore, it has been hypothesized that caregivers will be more likely to have more metabolic syndrome components than non-caregivers [68, 69]. Vitaliano [68] found that caregivers with coronary heart disease (CHD) did have more metabolic syndrome components than non-caregivers with CHD. A follow-up study [69] found that among men, caregivers had higher rates of CHD than non-caregivers. CHD was affected by caregiving distress, which was also associated with metabolic syndrome. Among women, caregiving was not associated with CHD. In women not on hormone replacement drugs, distress was associated with metabolic syndrome, which in turn was associated with CHD. This distress-metabolic syndrome-CHD relationship was not seen in women on hormone-replacement therapy [69]. These results indicate that distress experienced by caregivers was associated with metabolic syndrome, which in turn predicted CHD. In both of these studies, it should be noted that poor health habits (lack of exercise, poor diet) significantly contributed to metabolic syndrome, which also suggests that caregiving may interfere with self-care.

Two studies have evaluated caregiving and incident CHD. Both used prospective data from 54,412 women participating in the Nurses' Health Study. The first study evaluated the association of caregiving for an ill or disabled spouse, disabled or ill parent, and disabled or ill other, with incident CHD in a cohort of middle-age and older women [49]. After four years of follow-up, there were 321 incident cases of CHD. The age-adjusted relative risk (RR) of total incident CHD among women who cared for an ill or disabled spouse nine or more hours per week compared to no caregiving responsibilities was 1.93 (95% confidence interval (CI) = 1.16, 3.20). When a range of risk factors associated with CHD (e.g., smoking, alcohol intake, hypertension, diabetes, menopausal status, physical activity, marital status, education etc.) were controlled for, the multivariate RR remained significant (RR = 1.82; 95% CI = 1.08, 3.05). Caregiving for someone other than a spouse was not associated with CHD [49]. This work was later extended to evaluate caregiving to non-ill children or grandchildren, while controlling for the care of an ill or disabled spouse, disabled or ill parent, and disabled or ill other [70]. In this case, the age-adjusted RR of CHD in women who reported providing care to children $\geq$ 21 hours per week compared to those providing no care was 1.77 (95% CI = 1.08, 2.89). Multivariate adjustment for all CHD risk factors (e.g. smoking, alcohol intake, hypertension, diabetes, menopausal status, physical activity, marital status, education etc.) attenuated this risk slightly (RR = 1.58; 95%CI = 0.96, 2.67). In women who reported taking care of grandchildren, compared to those who did not provide care, the age-adjusted RR of CHD in women reporting nine or more hours of care per week was 1.86 (95% CI = 1.3, 2.59). Multivariate adjustment attenuated the RR of CHD, but it remained significant (RR = 1.55; 95% CI = 1.10, 2.18). When these women were stratified according to employment status, the risk of CHD was higher in non-working women caring for grandchildren nine or more hours per week compared to women who were not working nor providing care (RR = 1.69; 95% CI = 1.1, 2.6). However, these studies did indicate that high levels of caregiving burden among these women may increase their risk of CHD. It is interesting to note that, regardless of who

was being cared for, neither reported caregiver stress nor reward was associated with CHD in this population [59, 70].

Overall the literature supports the hypothesis that caregivers are at an increased risk of CVD. It has been theorized that it is the stress caregivers experience that is the main cause of poor health outcomes. This is supported by Schultz [48], who reported that adverse psychological and physical effects were greatest among those caregivers who reported being "strained". It must also be noted, however that many of these studies, particularly those of Vitaliano [47, 52, 66, 71, 72], Schulz [47], and Moritz [73] indicate that factors other than stress, or in combination with stress, including age, race, gender, disposition, health history, income, education, and self care, contributed to the risk of CVD. With this in mind, future research would need to consider these moderating factors along with stress as the relationship between caregiving and CVD continues to be evaluated. Furthermore, it may be through these modifiers that stress and poor health outcomes of caregivers may be addressed.

Health Care Workers

Health care is the largest industry in the United States, providing 14 million jobs [74]. Numerous studies have identified health care workers as a group with high levels of workplace stress. Evidence is more limited concerning the link between the stress of medical caregiving and health outcomes, including CVD.

Health care workers are routinely exposed to various types of stressors. Among these are both organizational stressors, such as overtime, shift work, paperwork; and traumatic stressors, including patient suffering, dealing with upset family members and ultimately death. A 1977 study by the National Institute for Occupational Safety and Health looked at hospital admissions for mental health disorders among occupational categories. Six of the 22 occupations with the highest admission rates were health care occupations, including nurses, practical nurses and licensed practical nurses [75].

Nurses

Registered nurses are the largest health care occupational group with 2.4 million jobs [76]. The majority of research on stress and CVD among health care workers has been focused on nurses specifically. Among the numerous stressors nurses routinely encounter are life-threatening health situations, work overload, dealing with difficult patients, role conflict, lack of supervisor and coworker support, and physical and verbal abuse. Results from the 2004 National Sample Survey of Registered Nurses show that besides career change the top reasons nurses left the profession were burnout, scheduling/too many hours, inadequate staffing, and the need to take care of home and family [77].

Numerous studies have observed associations between work stress and CVD among nurses. Goldstein and colleagues found increases in catecholamines, BP and HR on work days compared to non-work days [78]. SBP, HR and epinephrine were higher on work than non-work days during waking time, and DBP and HR were higher during daytime than

during evening hours [78]. Nurses who reported high job demands had higher SBP during daytime compared to evening hours, higher daytime HR on work days, and greater difference in epinephrine levels between work and non-work days [78]. A study of Swedish female hospital workers showed that both systolic and DBP during work hours were positively associated with job strain [79]. Among female health care providers working rotating shifts, Fujiwara and colleagues found an association of job strain with high noradrenaline levels and low cortisol levels on the day shift [80]. Women with high job strain had higher noradrenaline excretion during night sleep on their day off and workdays [80]. Participants in the Nurses' Health Study who reported short ($\leq$ 5 hours/day) and long ($\geq$ 9 hours/day) sleep duration had an increased prevalence of diabetes mellitus, hypertension and hypercholesterolemia, and a higher incidence of CHD than those nurses who slept between six and eight hours each day [81].

Brown and colleagues observed significant correlations between epinephrine and norepinephrine excretion rates in the workplace and BP variability throughout the day, but no associations were found with job strain [82]. They concluded that sympathetic responses, not job strain, contributed to elevated BP and thus, CVD risk [82]. Similarly, Lee and colleagues observed no association between job strain and incidence of CHD in a four-year follow-up period of the Nurses' Health Study [83]. Riese and colleagues also found no association of job strain with BP and HR among female nurses in the Netherlands [84].

Comparison studies have examined differences between nurses and school teachers, and nurses working in the emergency department (ED) versus the general floor. A recent study found that nurses had lower decision latitude scores, higher BP, norepinephrine and epinephrine levels than teachers [85]. The authors concluded that nurses have a greater physiological response to stress and that this response was present during work and non-work settings [85]. In a study by Yang and colleagues, ED nurses perceived their work as more stressful citing patient-related difficulties, organizational structure, lack of resources and conflict with other professionals as top stressors [86]. Those ED nurses with high perceived stress had lower morning and morning-afternoon difference in salivary cortisol levels [86].

In addition to the stressors that nurses face on the job, some have suggested that female nurses are further stressed with handling household responsibilities that accompany marriage and children, referred to by Hochschild as the "second shift" [87]. Goldstein and colleagues found that 85% of married nurses received "a great deal of enjoyment from their home life" and observed no relationship between marital status and BP [78]. However, unmarried nurses had significant decreases in norepinephrine on non-work days compared with work days and nurses with no children had a greater decrease in HR from daytime to evening hours [78].

Physicians

Early research has shown that compared to other professions, physicians report having the highest workloads, greatest responsibility for others, and highest job complexity levels [88]. Physicians who work in the emergency department (ED) may be particularly vulnerable to more stressful situations, such as routine exposure to severe trauma and life and death situations, than primary care physicians [89]. According to Doan-Wiggins and colleagues, the

consequences of work in the ED could be significant: as many as one-quarter of emergency department physicians experience burnout and 20% plan to leave emergency medicine within the next five years [90].

Other research concerning physicians and work-related stress has focused on physicians-in-training, who may be vulnerable because of inexperience and role confusion, and the uncertainty about the best course of medical action [91]. Specifically, female physicians-in-training are subjected to more work-related stress and higher depression scores than men [92]. As previously mentioned regarding female nurses, this stress has been attributed to competing work and home demands, including childbearing and childrearing, and more pressure in their social lives [91, 92].

In terms of potential health outcomes associated with physician stress, del Arco-Galan and colleagues found higher DBP and HR during waking and sleeping hours when physicians were on call compared to days off [93].

Emergency Medical Technicians

Emergency medical technicians (EMTs) and paramedics share similar exposures to stressful and often life-and-death situations with nurses and physicians. However, they have the added responsibility of working under dangerous conditions, such as maneuvering through traffic, contending with severe weather, and performing in uncertain or hostile conditions, while being underpaid and working long hours [94, 95]. Paramedics have high burnout and job turnover and reported the highest level of job stress, even when compared to firefighters [94, 96, 97].

EMTs who reported both low supervisor and coworker support had higher work-related stress [95]. One example of such stress is the relationship between paramedics and hospital personnel. Shapiro and colleagues found that paramedics identified having a negative interpersonal relationship with emergency room physicians and nurses and that this was a major predictor of burnout [98]. Often paramedics felt challenged by the hospital staff compared to feeling in control in the ambulance [97]. These relationships have been shown to impact the health of paramedics. Paramedics had higher levels of epinephrine and norepinephrine on work versus non-work days [96]. Examining cynicism and defensiveness, Jamner and colleagues found that male paramedics with high cynical hostility and defensiveness had greater HR reactivity and significantly higher DBP in the hospital setting compared to being in the ambulance [97]. Goldstein and colleagues found male paramedics had higher SBP when at the scene of an accident and at the hospital, compared to non-work day activities [94]. Additionally, SBP was higher when riding in the ambulance versus riding in a car on a non-work day [94]. However, they found no overall differences between a 24-hour work-day versus a non-workday [94].

Health care workers are an obvious occupational group in which to study the effects of work-related stress. While much research has been completed to establish that nurses, physicians and EMTs, as well as other health care group, are exposed to both organizational and traumatic stress, the link between this stress and future health outcomes has been less studied, particularly among physicians and EMTs. Future research examining particular

aspects of health care work and its relationship with subclinical CVD and CVD events is warranted.

Air Traffic Controllers

Air traffic control (ATC) is a very demanding and stressful job due to the need for rapid decision-making based on multiple sources of information and the potential disastrous consequences of a mistake or error in judgment [99-101]. Research evaluating if ATCs are more likely to experience heart disease risk factors or are at an increased risk of CVD are relatively rare and tend to be inconsistent. A few studies have found that rates of hypertension or CHD for ATCs are no greater than would be expected for the general population [102-105]. Other studies however, have found that ATCs are more likely to suffer from illnesses that contribute to CVD such as hypertension and diabetes [99, 101, 105-107].

Maxwell et al., [104] evaluated CHD risk factors in ATCs to determine if they were more likely to experience CHD compared to a matched control. They found that there were no statistical differences in the frequency of the risk factors between the two groups [104]. Similarly, when Booze examined the 10 year morbidity experience (1967-1977) of 28,086 ATCs, it was found that rates were no different than that observed for other occupations [102]. Booze and Simcox using computer records maintained by the Aeromedical Certification Branch of the Civil Aeromedical Institute and the airman health data file, evaluated the prevalence of hypertension in ATCs compared to the general population as reported in the 1971-75 Health and Nutrition Examination Survey (HANES) [103]. Prevalence of hypertension, as defined by a SBP $\geq$ 160 mm Hg, a DBP of $\geq$ 95 mm Hg, or use of hypertension medication, was found to be higher in the ATCs when compared to the other airmen, but lower than that reported in the general population. Age-adjusted hypertension prevalence for all airmen, airline pilots, ATCs, and the U.S. population were 2%, 0.6%, 5.5%, and 16.8% respectively. If borderline hypertension (SBP between 140-159 mm Hg and/or DBP between 90-94mm Hg) was also included these prevalence estimates increased to 16.8%, 10.1%, 24.0%, and 35.3% respectively. Hypertension in the ATCs and general population was most likely higher than in the other airman categories due to health restriction in licensing experienced by the airmen, resulting in a healthy worker effect. These results, along with those reported by Booze [102] and Maxwell et al. [104], imply that despite the high stress ATCs experience on the job, their risk of heart disease may be no higher than that experienced by the general population. This result, however, has not been supported by other studies.

In 1973, Cobb and Rose examined the medical records of 4,325 ATCs and 8,435 second class airmen for comparison to determine if ATCs were at increased risk of illnesses [101]. The results from two different exams were evaluated in order to obtain both prevalent and incident data. The prevalence of hypertension (SBP >140 mmHg or a DBP of > 90 mm Hg) in ATCs was nearly four times higher than that in the second class airmen. However, some of this difference was thought to be a result of the fact that the second class airmen were denied licensing if they suffered from hypertension. This explanation along, however, could not account for the difference in incidence of hypertension, which was nearly six times greater

among the ATCs compared to the second class airmen. The mean age for hypertension was also found to be lower in the ATCs compared to the second class airmen (41 years vs. 48 years). Interestingly, when traffic density was used as a surrogate for level of job stress, rates of hypertension were significantly higher in ATCs in the high traffic density group compared to those who usually worked in low traffic density airports [101].

In this same report, the ATCs were also two times more likely to have diabetes than the second class airmen. Although the numbers were too small to evaluate incidence, the rates were again found to be higher in the ATCs. Rates of diabetes were not as high as those for hypertension, but the presence of both imply that ATCs are at an increased risk for some diseases [101]. A longitudinal study conducted by Rose et al., [99, 105, 107] confirmed these findings.

Rose et al., studied 388 ATCs over the course of three years [99, 105, 107]. BP measurements and blood from clinical measurements were taken every 20 minutes while the ATCs worked. In this case, stage 2 or 3 hypertension was defined as having a systolic SBP $\geq$ 160 mm Hg or a DBP of $\geq$ 100 mm Hg. Information regarding aircraft number and altitude-transitioning aircraft was also recorded. Both the prevalence and incidence of hypertension were significantly higher in the ATC group than that of comparable men from other occupations. They also found that the development of hypertension correlated with the BP response to controlling air traffic. Overall, BP levels were found to be higher in those workers who eventually developed hypertension compared to those who did not [99, 107]. Based on these results, a 20 year follow-up study of the original normotensive and stage I hypertensive participants was conducted. It was found that increased SBP reactivity to work stress was associated with long-term hypertension [106].

These results would indicate that ATCs, having higher prevalence of hypertension, may be more likely to experience higher risk of CVD; in sharp contrast to the findings of Maxwell (1983) and Booze (1979, 1985). The differences between these studies however must be looked at in light of their limitations, which include their cross-sectional nature and dependence on medical records in contrast to the longitudinal reports. The lack of appropriate comparison groups may also have compromised the results. For example, airmen were frequently used as a comparison group, yet their licensing restrictions precluded them from entering the workforce if they suffer from hypertension or other chronic diseases [99, 102]. In another study, hypertension data from the 1971-1974 HANES population was compared to the hypertension data of ATCs in 1980. General population prevalence of hypertension may have changed between 1974-1980 making the earlier HANES data a poor comparison group [107]. Furthermore, because CVD is the result of multiple risk factors, the presence of hypertension alone may not notably increase risk of CVD in ATCs. Further prospective research evaluating level of stress, other health and lifestyle factors such as shift work and sleep also needs to be conducted to determine how they might also contribute to risk of CVD.

Firefighters

Risks involved in firefighting include exposure to the following: shift work; carbon monoxide, smoke, particulate matter and other toxic chemicals; irregular extreme physical

demands; heat stress; and psychological stress [101-110]. Psychological stress and trauma have been highlighted as occupational health issues for firefighters [110-113]. In a comprehensive review of literature on risk factors in firefighting, Guidotti [111] points out that both acute and chronic psychological stressors have been related to exposure to traumatic events, the inherent unpredictability of firefighting, high performance expectations, and career advancement. Exposure to incidents involving serious injuries, particularly to children, or child fatalities, are further event-related factors that cause many firefighters to experience distress [114]. Findings for psychological stress response in firefighters from Finland have shown lower levels of depression, anxiety and psychological avoidance than in the general population. However, in firefighters these symptoms were correlated with sleep deprivation, physical and time demands, the need for constant vigilance, personal risk, unsatisfactory interactions with the public, rigid working conditions, unforeseen situations, and inconsistent instructions [111]. Firefighters in Germany were found to have high levels of perceived stress from conflicts related to the job, time pressure, and responsibilities on the job [111]. Research involving the cardiovascular response to alarm has shown increased HR, separate from that related to physical exertion, from responding to a fire alarm [111].

Objective measures of PTSD symptoms in firefighter populations have led to PTSD prevalence estimates ranging from 5% to 37%. Much of this variation can be explained by the use of different measurement instruments and associated diagnostic cut points. Use of the more complete PTSD checklist (PCL) instrument along with the standard cut point (PCL > 44) has been shown to reduce PTSD prevalence estimates from a high of 17%, with one widely used instrument and cut point, to around 8%, and adding restrictions to include the DSM-IV criteria for immediate response to a traumatic event (e.g., fear, helplessness, or horror) and functional impairment further reduced the prevalence to 5% [115]. This result is not higher than estimates of the prevalence of current PTSD in the general population, which range from 5% to 9% [116]. The prevalence of PTSD for firefighters involved in the World Trade Center disaster and Hurricane Katrina was much higher with estimates of 14% to 17% for the World Trade Center disaster [117] and 22% for Hurricane Katrina.

CVD in Firefighters

The study of CVD in firefighters as a group is complicated by the presence of a strong “healthy worker effect”. This effect is thought to explain why studies of CVD mortality in firefighters have not shown consistent evidence of increased risk over that of the general population, even though firefighting is a high risk occupation [111, 113]. However, CVD accounts for a much higher percentage of deaths among firefighters on duty (45%) than among other high risk occupations (e.g., 22% for police officers on duty), and firefighters show a significantly increased risk of cardiovascular related death during or shortly after emergency duties when compared to non-emergency duties [117, 118].

The presence of chronic and acute psychological stressors, mediated through activation of the HPA axis and stimulation of the sympathetic nervous system, has shown strong associations with prevalent CVD [119]. Since physical stressors and psychological stressors activate the same systems, it may be somewhat more difficult to separate the effects of

psychological stress from physical stress, particularly in an occupation like firefighting that has significant levels of both, when compared to occupations that tend to be only psychologically demanding. Much of the research on cardiovascular risk for firefighters, although mentioning psychological stress, has focused primarily on the physical and environmental demands or on lifestyle risk factors [112, 118, 120-122]. In the most recent of these studies, Kales [118] found that the risk of CHD mortality during alarm response duties (not including fire suppression) was sevenfold higher than during non-emergency duties. This is suggestive of CHD risk independent of the extreme physical exertion (e.g., physical stress response) that is involved in fire suppression and instead may be due to the psychological stress response. In view of these results and the limited evidence to date, further research focusing on isolating the independent effects of psychological stress from other forms of stress on CVD risk in firefighters is warranted.

Police Officers

It has been suggested that police officers are at increased risk for CVD [123-124]. Police work is routine in nature with episodic moments of intensive danger and stress. Officers are often placed in situations of severe emotional stress [125]. There is an ever-present perception of danger which leaves officers in a state of constant hypervigilance [126]. Previous research has identified two distinct sources of stress in police work [127]: (1) the inherent aspect, which involves danger and job risk; and [2] the police organization [128, 129].

In addition to daily routine stress, police officers are also exposed to traumatic work events. Such events may involve shootings (by oneself or other officers), riots, hostage situations, and other threatened or actual violence. PTSD risk factors among police officers include excessive difficulty in expressing emotions, lack of an outlet to vent feelings outside of work, and lack of diversion from the police role [130]. Other trauma risk factors include inadequate social support networks, emotional exhaustion at the time of the traumatic event, and prior experience of traumatic incidents. Certain PTSD risk factors, such as insufficient time allowed for coping with traumatic incidents, dissatisfaction with the support provided, uncertain career prospects, and discontent about work, can also be present within the work environment of police officers [131, 132, 133]. Stephens, Long, and Flett [134] discussed the impact of previous life trauma for those entering police work. Police recruits who have already suffered traumatic stress are, following exposure to subsequent distressing experiences, at increased risk of mental health problems and more likely to retire from police service early. Paton, Violanti, and Schmuckler [135] discuss the long-term implications and consequences of repetitive exposure to high risk and duty-related traumatic incidents. Here they explore its implications for behavioral addiction and separation from active police duties. Figley [136] developed a model of "police compassion fatigue", where he suggests that if police officers are empathic, have sufficient concern for others, and are exposed to traumatized people on a continuous basis, they may develop a debilitating psychological fatigue.

CVD in Police Officers

Persons who enter police work are generally part of a healthy work population, but appear to deteriorate physically and psychologically as years of police service increase [124]. Few studies have looked at police cardiovascular health. A 22-year prospective study of the Helsinki Policemen [137] hypothesized that complex clustering of risk factors related to insulin resistance could be predictive of CHD and stroke risk. Factor analysis of 10 risk variables produced three underlying factors: an insulin resistance factor, which comprised BMI, subscapular skinfold, insulin, glucose, maximal oxygen uptake, mean BP, and triglycerides; a lipid factor, which comprised cholesterol and triglycerides; and a lifestyle factor, which comprised physical activity and smoking. In this prospective study the insulin resistance factor proved to be a statistically significant predictor of CHD. While metabolic syndrome was not specifically determined in this population, analysis of the 22-year risk of CHD by tertiles of insulin resistance showed that excess risk was confined to the highest tertile [137]. A cross-sectional study of metabolic syndrome in a sample of 84 adult male police officers in Texas found that prevalence of metabolic syndrome in male police officers may be higher than the American male population, and thus law enforcement officers may be at increased risk for future CVD morbidity and mortality [138].

Similar patterns of CVD have historically been observed in other police cohort studies. Guralnick [139] found mortality rates for policemen, sheriffs, and marshals to be significantly elevated for arteriosclerotic heart disease. Milham [140] found increased rates for arteriosclerotic heart disease and pulmonary embolism in Washington state police officers. Age-specific proportionate mortality ratios for arteriosclerotic heart disease were highest for younger officers. Violanti, Vena, Marshall and Feidler [141] found city of Buffalo police officers had increased rates for arterioslcerotic heart disease. Feuer and Rosenman [142] reported that police and firefighters in New Jersey had significant increased proportionate mortality ratios for arteriosclerotic heart disease. An inverse relationship was noted between arteriosclerotic heart disease and latency, indicating that police officers most susceptible to heart disease were affected early in their careers. Demers, Heyer, and Rosenstock [143] compared police and firefighters in three cities in the United States and found police to have higher rates for all causes of death combined. Forastiere, Perucci, DiPietro, Miceli, et al [144] studied a cohort of urban policemen in Rome, Italy and found increased rates for ischemic heart disease in officers less than 50 years of age. Additional studies have found police to have higher rates for heart disease, homicide, and suicide [145-148]. A somewhat unexpected finding was that arteriosclerotic heart disease rates were higher in officers with fewer years of service. The average age of death for police officers in a mortality study was 66 years [148], compared with the general population average of 75 years. Officers also died from heart disease at earlier ages than the general population. This is infrequently found in a healthy worker population [149].

The low physical fitness level found among police officers may also be an indicator of the impact of stress. Williams et al, [150] found that a substantial number of officers in their sample were at elevated risk for atherosclerotic heart disease; 76% had elevated cholesterol, 26% had elevated triglycerides, and 60% elevated body fat composition. Price et al [151] concluded that middle-aged police officers had CVD risk above that of the general

population. Franke and Anderson [152] found that public safety officers had a higher probability of developing CHD than did the Framingham Heart Study population. Steinhardt, Greehow, and Stewart [153] found an inverse association between cardiovascular fitness and medical claims among police officers.

PTSD and Metabolic Syndrome among Police Officers

In a recent study conducted by the Violanti and colleagues [154], we examined associations between PTSD symptoms and metabolic syndrome in 115 police officers. This study utilized data obtained from the Buffalo Cardio-Metabolic Occupational Police Stress (BCOPS) baseline health study [155]. The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) [156] put forth guidelines for the proposed clinical definitions of the metabolic syndrome in adults to aid in diagnosis and recommended preventive interventions for this syndrome. The ATP III guidelines defined metabolic syndrome as abnormalities in any three or more of the following clinical measures: waist circumference (obesity), triglycerides, HDL cholesterol, BP, and fasting glucose level [157]. Elevated waist circumference was defined as $\geq$ 102 cm in men and $\geq$ 88 cm in women, elevated triglycerides as $\geq$ 150 mg/dL, reduced HDL cholesterol as < 40 mg/dL in men or < 50 mg/dL in women, elevated BP as DBP $\geq$ 130 mmHg or SBP $\geq$ 85 mmHg, and glucose intolerance as fasting blood glucose $\geq$ 100 mg/dL. The authors measured PTSD symptoms with the Impact of Event scale (IES) [158], divided into categories of subclinical, mild, moderate and severe symptom levels. This scale identifies symptoms of PTSD. The metabolic syndrome was considered present if three or more constituent parameters of metabolic syndrome were present in each officer (obesity, BP, high density lipoprotein cholesterol, triglycerides, and glucose levels).

Table 2. Prevalence estimates and ratios for metabolic syndrome by PTSD severity category among police officers

			Unadjusted		Age-adjusted		Multivariable-adjusted*	
PTSD category	N	Prevalence (%)	PR	95% CI	PR	95% CI	PR	95% CI
Sub-clinical	59	15.1	1.00	referent	1.00	referent	1.00	referent
Mild	19	21.1	1.39	0.47 - 4.11	1.48	0.50 - 4.42	1.82	0.59 - 5.62
Moderate	23	4.4	0.29	0.04 - 2.17	0.28	0.04 - 2.14	0.37	0.04 - 3.17
Severe	6	50.0	3.31	1.19 - 9.22	3.12	1.15 - 8.50	2.69	0.79 - 9.13

Abbreviations: PTSD = Posttraumatic stress disorder; PR = prevalence ratio; CI = confidence interval
*Adjusted for age, education, smoking and alcohol intake.
Source: Violanti, J, Fekedulgen, D, Hartley, T, Andrew. M, Charles, L, Burchfiel, C: Police trauma and cardiovascular disease: Association between PTSD symptoms and metabolic syndrome. Int. J Emerg Mental Health 2007; 4: 227-238.

Results indicated a slightly increased risk of metabolic syndrome for officers in the mild PTSD category (prevalence ratio (PR) = 1.39, 95% CI = 0.47-4.11) and a significantly increased metabolic syndrome prevalence among those officers in the severe PTSD symptom category (PR = 3.31, 95% CI = 1.19-9.22; p = 0.021). Adjustment for age decreased risk in the severe category somewhat but the risk remained significantly elevated (PR = 3.12, 95% CI = 1.15-8.50, p = 0.0261). Adjustment of a combination of lifestyle factors (age, education, smoking, alcohol intake) reduced the prevalence ratio in the severe PTSD category (PR = 2.69, 95% CI = 0.79-9.13, p = 0.113), indicating the possible influence of these lifestyle factors. Table 2 provides prevalence estimates and ratios for metabolic syndrome by PTSD severity category. Future work is planned with a larger sample of police officers to further assess this relationship.

Conclusions and Future Directions

Evidence reviewed in this chapter suggests a biosocial synergy between psychosocial stress, physiological adaptation, and disease. The presence of CVD in high stress populations discussed in this chapter also suggests that stress may be an important factor in the development of CVD. Yet, despite such research, assessing psychological and health outcomes in fragmented domains and scientific disciplines has resulted in a lack of translational integration, predictive validity, and successful intervention strategies. Doubts continue to exist about the scientific validity and/or clinical relevance of this evidence (159-160). Scheidt (160) describes some of the reasons for such doubts including (1) that the literature contains many studies with various design limitations, such as small or selected samples among studies reporting positive (or negative) results, or lack of appropriate control groups; (2) inconsistent results among studies; and (3) doubts about the actual relevance of behavioral variables and interventions. There are also inconsistencies in defining and measuring various psychosocial measures (e.g., stress, hostility, anger), and gaps in knowledge regarding the applicability of various psychological risk factors in different demographic and health groups. Inconsistencies in psychosocial research might result from the use of convenience samples or nonvalidated versions of psychological scales in some studies. Studies may also use different measures of psychological risk factors (e.g., anger or hostility), perhaps with differing results [161].

Further research in the area of stress and CVD should consider possible protective factors as well. Resiliency is an example - an ability to “bounce back” from adversity, stress and trauma. Persons high in resiliency, who are marked by a strong sense of commitment, control, and challenge, tend to remain healthy under stress compared to those low in resiliency [162-165]. Maddi [163] outlined the hardy personality type, describing the person who lives a vigorous and proactive life, with a strong sense of meaning and purpose, and an abiding belief in his/her own ability to influence things.

Also to be further considered in playing a role in CVD are the biological aspects of resiliency. Dehydroepiandrosterone (DHEA), for example, has adrenal gland products that are secreted in response to adrenocorticotropic hormone. DHEA appears to have an antagonistic relationship with cortisol. Whereas cortisol is a glucocorticoid, DHEA has anti-

glucocorticoid properties that appear to protect neurons [166-167]. Given this antagonistic relationship of DHEA(S) with cortisol, it may antagonize enhanced negative memories of the trauma, resulting in decreased PTSD symptoms of re-experiencing traumatic events [168-169]. Neuropeptide Y (NPY) is another resilient factor. Individuals with PTSD have been found to have lower NPY levels at baseline and a blunted NPY increase [170]. NPY may exert a stress-buffering effect by inhibiting norepinephrine release.

Some of these issues may be addressed on a larger scale with carefully designed prospective studies that measure morbidity and mortality outcomes [171]. This progress has been further facilitated as behavioral research begins to incorporate relevant methodologies and an increasing knowledge base [172]. Continued progress in this area is dependent on multidisciplinary research that incorporates the knowledge in both the medical and behavioral sciences. Such progress will ultimately lead to better evaluation and treatment of mental difficulties associated with stress, and thus reduce their impact on the risk for CVD.

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Chapter 8

Cardiovascular Risk as a Paradigm of the Negative Consequences of Stress at Work: A "Conflicting Evidence"

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Abstract

The relation between stress and coronary diseases is controversial. Positive and null or negative results are almost equally obtained. An explanation of this can be that the most widely used stress questionnaires are not able to collect all the factors that constitute stress perception in different socio-cultural contexts. Indeed, from a clinical and experimental perspective the relation between breakdown in adaptation and cardiovascular disorder is a fact. More consistent results on the social, cultural and psychological determinants of an increased cardiovascular risk are obtained when stress is studied in relation to the socio-economic condition of groups and individuals. To better embrace and describe the social factors, a new theoretical contribution has been introduced: social capital. This is a more sophisticated version of social cohesion, social integration and social support. For the future, an interdisciplinary approach is recommended in health surveillance of life and work environmnent.

Introduction

The great Canadian doctor, Sir William Osler, more than one century ago (1897) considered the "pressure of modern life" as a factor of "arterious degeneration" [1]. Hans Selye (1907-1982), on the basis of the homeostasis concept developed by Claude Bernard and of the studies of Walter Cannon on the emergency role of adrenaline, identified the response to stress as a "general adaptation syndrome", in which cardiovascular modifications were central [2]. Many other findings have been added over time. Selye [3] himself noted in

1976 that, since his first letter to Nature, forty years before, on *A syndrome produced by diverse nocuous agents*, 110,000 papers were published. If the keywords *stress* and *cardiovascular disease* are introduced for a search through PubMed, about 10.000 papers, with more than 3000 reviews, can be found in the last five years. Now biological effects of stress are related not only to the activation of neurovegetative system and hypothalamic adrenal axis, as Selye thought, but also to inflammatory [4], oxidative [5], coagulation [6] processes and gene environment interactions [7]. In the same PubMed search only 178 papers are devoted to occupational stress and cardiovascular disease. Most of these papers restrict the investigation on occupational stress to the concept of job strain, a subjective perception measured with, essentially, two instruments: the questionnaires derived from the model of Karasek [8] – *demand/control* – and Siegrist [9] – *effort/reward* – are the more commonly used.

The disproportion between an apparently wide biological awareness and the paucity (in the sense of "a few" and "a little") of psychological assessment depicts the problem of "stress and disease", particularly occupational stress and cardiovascular disease. The findings are controversial and the main problem of research is to standardize subjective measurement.

Epidemiology

In a recent (2004) accurate review, the authors [10], who themselves are involved in occupational stress research and hence advocate of the relationship between stress and cardiovascular diseases, cannot but cite a number of negative or non significant results equal to the positive ones. An even more recent meta-analysis reports uncertain findings [11]. Negative or controversial results [12-15] – in the sense that job strain effects are higher in managers than in workers or viceversa; job strain is observed to be produced by low control, high demand or both - and positive results [16-19] continue to alternate in the studies published in the last 3 years. In addition most of the cited papers reports that the cardiovascular system of men is more affected by workstress, but some papers report worse influences in women [15, 20].

Our personal experience also shows positive and negative findings, obtained with exactly the same methods, albeit in different population samples [21]. However, negative findings cannot abolish the positive ones, which "persist" and are repeatedly observed in the same and very distant research groups. It may be that the dissimilar characteristics of the samples make the differences in the results. The most widely used questionnaires, just because of their necessary standardization, may not be able to collect all the factors which in different contexts constitute and graduate the stress perception; this impression is growing as the same instruments are used more and more times. The insufficiency of single time exposure measures has been also evidenced [22]

On the other hand, the clinical and experimental evidence of the influence of stress on the cardiovascular system and on the evolution of cardiovascular disease is a fact [23]. The psychophysiological concept of stress has been introduced to describe the person-environment interaction that modifies heart rate, blood pressure and their metabolic correlates. Stress prolongs the recovery from a coronary event, can aggravate it or even bring

about a heart attack. No guidelines on prevention or treatment of cardiovascular diseases ignore the counseling about the importance of controlling major tensions in life and work [24, 25]. Intolerable emotions can be a cause of disability in a coronary patient [26, 27].

Unfortunately, the accurate observation which is possible in a clinical and experimental setting, is not possible in epidemiological field studies. In the chain which links occupational stress to cardiovascular disease – *occupational discomfort→ stress→ biological mediators→ risk factors→ disease* – each step is only an etiological fraction of the subsequent one. Too many variables can intervene altering the hypothesized causal passages, and actually in field research results are not absent, but diverse; sometimes in opposite directions [2].

More stable results on the relation of cardiovascular disease with psychosocial factors are reported for socio-economic status, or SES, usually defined by education, occupational level, neighborhood area or income, taken singularly or together [28-32]. Stress is not excluded by the definition of SES, because it may alternatively represent the synthetic or partial index of the adaptation difficulties, considered respectively as a whole or as a specific emotional hazard. In any case, the hypothesized biological mechanisms are the same mentioned above. Cardiovascular disease (CVD) appears to show a higher incidence and gravity in lower social classes and the difference is claimed to increase in all western societies. Evidence for this relation has been derived from prevalence, prospective and retrospective cohort studies. A good review of the early works done on SES and CVD mortality can be found in Kaplan and Keil [33] with articles dating back to 1949. Now major studies on incidence are also available [in addition to the above references, see 34, 35]. Higher incidence may simply mean that the "western" decrease in cardiovascular disease is less manifest as the social condition deteriorates. The phenomenon has been observed also in low incidence Mediterranean countries, where the opposite was true until a few decades ago [36, 37]. This change over time must however remind that the relationship between social factors and disease is complex and mobile, with unexpected displacements, although within a rather constant trend [38]

Recently, a strong debate has been initiated among the epidemiologists on the connotation of social class and in particular of its biopsychological counterparts. The concept of "social capital" has been introduced with the aim to better embrace and describe the factors which the human existence is confronted with in the societal organization and so exposed to the ineludible "wear and tear" of life.

A Novel Theoretical Contribution

The concept of social capital has long existed in economics, but it is only in 1996 that it makes its appearance in public health [39]. It has been launched under the perspective of a more sophisticated version of social cohesion, social support, social integration and civic society [40]. The theory has been then developed in more detail. In their paper Szreter and Woolcock [41] identify three different views: the social support perspective, the inequality thesis and the political economy approach. The social support school believes that health outcomes are strongly connected to social relations and norms of reciprocity, as chronic and degenerative conditions decrease when there are good social networks. The second school of thought sees social capital issues as part of the psychosocial effects that widen level of social

economic inequalities [42, 43]. Marmot, in particular, links this idea to the concept of stress seen as the absence or loss of autonomy over one's life course, recalling and expanding the job strain construct of Karasek. Finally for the political economy approach social capital is confined to the access to material resources as these are the roots of inequalities in health and induce political and ideological decisions [44, 45].

Szreter and Woolcock introduce a new approach to try to unify the three assumptions. They differentiate social capital in the forms of bonding, bridging and linking. Bonding social capital refers to the relations of trust and cooperation between members of a network who see themselves as being similar. Bridging social capital refers to the relations of respect and mutuality between people who know they are not alike in social identity or socio-demographic sense. Finally, linking social capital refers to the norms of respect and networks between people interacting with explicit, formal power or authority. The social support perspective and the inequality thesis are compatible both with bonding and bridging, while the inequality thesis and the political economy approach are "unified" through linking

Szreter and Woolcock contribution is considered very valuable as their attempt to reconcile all the different explanations provides a starting point for working on a common ground [46, 47]. However, there are some issues that need to be solved. First, it needs to be decided if social capital should be interpreted as an individual or a collective property [48]. Second, there is the need for measuring instruments which could distinguish between bonding, bridging and linking. Third, models integrating social structures and psychological exposures should also be introduced in order to better understand the determinants of morbidity and mortality. The discussion on how and whether integrate stress theories to social capital develops from here. Fourth, there are still people like Putnam and Navarro [49, 50] who are not entirely convinced with Szeter and Woolcock definition of social capital. Putnam states that health should not be considered a direct outcome of social capital. Things may be more complex and tautological definitions (e.g. a good government produces good health changes) should be avoided. He claims, for example, that adding the category of linking social capital is not a valid, reliable, or substantively important feature. Indeed, even though, in principle, networks interacting through formal power are essential in any civic society, distinction between "responsive" and "exploitative linking" should be made, as not all vertical networks have pro-social consequences

So, the debate is on whether social circumstances should be understood and tackled to determine health outcomes. A big discussion, just on stress and CVD, was reported in the 2002 December issue of the International Journal of Epidemiology. Two of the contributors were Marmot and Beaglehole [51, 52]. Marmot, on the basis of his long experience of stress studies on British civil servants, emphasized that healthy behaviours should be encouraged across the whole of society and that more attention should be paid to the social environments, job design and the consequences of income inequality. Beaglehole, as a "pure" epidemiologist, claimed that, as the traditional risk factors explain at least 75% of new cases of CHD, it would makes more sense to identify and reduce them increasing the proportion of people at low risk. In Beaglehole's opinion, acting on the social factors would not produce much benefit as its contribution for population health is limited and unclear.

What is still really discussed is whether social epidemiology, i.e. the science that studies the link between social environment and the development and distribution of disease in

population, is a useful tool or not. This has obvious consequences also for occupational stress research.

Generally speaking, no one is truly denying the importance of sociology and psychology in the understanding of health phenomena, but the disagreement is more on how much "shopping in neighbouring fields without thorough subject matter knowledge" should be allowed [39]: lack of good knowledge of both fields may only lead to statistical results without relevant meaning. Indeed epidemiology and psycho-sociology rely on very different backgrounds and so on very different methods and measures. The first discipline is based on experimental science and human biology, the second one, although professed as a scientific approach, is strongly influenced by philosophical and cultural beliefs.

Krieger [53] claims that ignoring the social determinants of disparities in heath precludes adequate explanations for actual and changing population burdens of disease and death. Other authors [54, 55] also do not believe in the need of drawing boundaries around epidemiology to only include the biological side. These authors are very much in favour of social epidemiology as some of the greatest achievements in epidemiology have been possible thanks to the cooperation of other disciplines. For example, the malaria distribution was studied thanks to entomology and ecology, the spread of HIV/AIDS with a detailed ethnology of human sexuality [56]. Also, these authors believe that intellectual development can be achieved by different means and it is not necessarily a specialization that determines proper knowledge.

Conclusions

It is acknowledge by most of the medical community that the social gaps – between the poor and the rich, the stressed and the adapted, the worker and the manager – in the very same society are a cause of health disparities. Such differences are observed especially in relation to cardiovascular diseases: should we concentrate on social theories to reduce it "uniformly" or should we act directly on the risk factors? According to the previous discussion, the answer is obvious and is "both" [57-59]. But it is not a one man job. An interdisciplinary approach is necessarily required.

The most important international health institutions have been fostering this kind of approach since the WHO, in 1946, defined health not only as the absence of disease, but as a physical, psychological and social wellbeing. What needs to be avoided is the presumption to explain everything, i.e. the so called "umbrella theory". This ends up confounding the real results that have been objectively achieved.

Indeed the studies investigating social capital are really looking at the fact that, whatever we take social capital to mean, having "a lot" of it seems without any doubts something positive [60]. What we can do is to proceed by studying the influence on health of the lack or the shortage of social capital, i.e. low education, support, income, working conditions that cannot simply be characterised as someone's choice, and so on. As Kornhauser [61] said in 1965, "The unsatisfactory mental health of the working people consists in no small measure of their dwarfed desires and deadened initiative, reduction of their goals and restriction of their efforts to a point where life is relatively empty and only half meaningful".

Shopping too much into neighbouring fields without really knowing the other disciplines can bring to very serious interpretation mistakes. Probably, a thorough knowledge of sociology and psychology may not be essential, but a good enough knowledge of them is [62]. This is a recognized exigency and a collaboration issue of modern clinical medicine. Occupational and, more generally, environmental medicine should rediscover its clinical origin and method and apply it not only to individuals, but also to the investigation of groups. Stress is not a disease, but a symptom. Its relation with the disease is multifaceted in individuals as well in groups. It is the clinician, who, by carefully observing the patient and for enough time, can understand the true reason of the discomfort and the better therapy, which may be different for the same symptom. This process put into operation in the work and life environment is called health surveillance and it is the most appropriate context in which the consideration of stress and disease is worthwhile through a progressive and never ending approximation.

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Chapter 9

The Role of Self-Involvement in the Development of Cardiovascular Disease: A Motivational Analysis

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Abstract

Elaborating the reactivity hypothesis about the development of cardiovascular disease we posit that performance conditions having strong consequences for individuals' self-definitions and self-esteem can provide a severe health risk. Based on a recent application of motivational intensity theory to self-relevant performance conditions we argue that such performance conditions justify the mobilization of high resources for active coping. The result is high effort when self-relevant demands are difficult or individuals try to do their best in active coping. Given the systematic link between resource mobilization and cardiovascular reactivity, this leads to strong cardiovascular reactivity under these conditions, which in turn promotes the development of hypertension and cardiovascular disease. The results of a recent series of studies are discussed.

Cardiovascular Reactivity and Disease

The World Health Organization estimates that 17 million people die of cardiovascular disease worldwide every year [1]. Research has identified a number of well known factors that are associated with the development of cardiovascular disease. Among them are elevated blood pressure, elevated cholesterol level, smoking, diabetes mellitus, obesity, a family history of heart disease, an inactive lifestyle, a low vitamin diet, aging, and gender [1]. The present analysis focuses on the role of psychological variables (i.e., self-involvement) in the development of hypertension—that is, chronically elevated blood pressure above the

population's norm—as a main risk factor for the development of cardiovascular disease. Main parameters of blood pressure are systolic blood pressure (SBP)—the maximal pressure in the blood vessels after a heartbeat—and diastolic blood pressure (DBP)—the minimal pressure between two heartbeats.

For individuals under the age of 50 years, a resting SBP higher than 140 millimeters of mercury (mmHg) and/or a DBP exceeding 90 mmHg over an extended period of time are classified as *hypertension* (for older individuals, a resting pressure exceeding 160/95 mmHg is diagnosed as hypertension) [2]. Because high blood pressure causes the heart to permanently work with high intensity, both the heart and the arteries are more prone to injuries. As a result of permanent overload, the heart muscle may thicken and become weak over the years. The arteries narrow, become less elastic, and may fail to supply enough oxygen and nutrients for a proper functioning of the body's organs and tissues. Later consequences are arteriosclerosis, myocardial infarction, stroke, and impairments of the eyes and kidneys.

Interestingly, in most of the cases the biological causes of diagnosed hypertension are unknown. This type of chronically elevated blood pressure is thus termed *essential hypertension*. Researchers have not yet completely understood the causes of this disease, but they have identified several variables that can contribute to the development of essential hypertension. One of these variables is cardiovascular reactivity under *stress*—that is, conditions under which the organism is urged to respond to a discrepancy between the normal, steady state of the person and some change in the environment [3]. Cardiovascular reactivity is the change in activity of the cardiovascular system in response to situational factors compared to cardiovascular activity under rest. Evidence for the significant role of this variable in essential hypertension stems from studies with both humans and animals [4, 5, 6, 7]. According to this line of research, high cardiovascular reactivity is both a *characteristic* [8, 9, 10] and a *predictor* of hypertension [11, 12, 13]. This perspective is called the *reactivity hypothesis*.

One research example that has impressively demonstrated the significant role of cardiovascular reactivity in the development of hypertension is a longitudinal study by Light, Dolan et al. [11]. These researchers assessed participants' blood pressure and heart rate (HR) values twice with an interval of 15 years between both measures. The first time, blood pressure and HR were assessed in an experiment on cardiovascular reactivity during coping with acute mental stress. The second time, cardiovascular parameters of the same individuals were measured again. This study revealed that participants with greater cardiovascular reactivity in the initial testing showed higher cardiovascular values 15 years later–both under conditions of acute stress and at resting conditions. Specifically, SBP reactivity during acute stress in the first experiment statistically predicted SBP and DBP levels. HR reactivity predicted SBP, DBP, and HR; DBP reactivity was only a predictor of DBP. Recent studies found similar results in support of the reactivity hypothesis [13]. In summary, the existing evidence suggests that psychological mechanisms underlying cardiovascular reactivity are of great importance for the etiology of essential hypertension and cardiovascular disease.

Psychological Variables and Cardiovascular Reactivity

Based on the current state of research, psychological factors that promote strong cardiovascular reactivity are significant for explaining the development of essential hypertension. Physical activity is directly related to the activity of the cardiovascular system: the higher the physical demand, the stronger the activity of the cardiovascular system [14]. Moreover, most relevant to the topic of this chapter, mental engagement is also systematically linked to the activity of the cardiovascular system. However, the association between mental engagement and cardiovascular activity applies only to *active coping* settings, that is, when the outcome of coping with a stressor or a demand is under the individual's control [15, 16]. This condition leads to cardiac-somatic uncoupling: the mobilization of bodily resources exceeds the actual metabolic needs, and the cardiovascular system works harder than necessary. In *passive coping*—that is, when people have no control over the outcome of a situation—the cardiovascular system does not react to differences in demand and only shows a modest response.

Regarding psychological variables, one large part of the literature has focused on affective states, like anger [e.g., 17, 18], or the role of positive and negative moods [19] as predictors of cardiovascular reactivity. Another part has highlighted stable personality traits as for instance negative affectivity and defensiveness as predictors of cardiovascular reactivity and essential hypertension [20, 21]. In the present paper, we introduce a specification of these approaches by a motivational variable. We posit that the frequent or chronic personal involvement in performance settings is a critical variable in developing hypertension.

Self-involvement refers to situations in which behavior has implications for people's self-definition, self-esteem, and personal interests [22]. Self-involving performance conditions can be distinguished from conditions under which people strive for the *proximal* goal to attain concrete material (e.g., money) or physical (e.g., avoidance of pain) incentives, which have *no* direct implications for their self-definition, self-esteem, or personal interests. Performance settings differ in the degree to which people's proximal goals are concrete physical incentives versus more abstract entirely self-related goals like experiencing competence [23] or satisfying personal interests [24, 25]. Referring to proximal self-relevance, Greenwald (26) has proposed three performance settings under which the self is involved. These are (1) *social evaluation* of one's abilities, (2) *self-evaluation* under self-awareness, and (3) personal importance or attraction of behaviors by means of their relation to personal *interests and values*. Based on the reactivity hypothesis, we argue that self-involvement promotes the development of hypertension and cardiovascular disease, because self-involvement systematically increases cardiovascular reactivity in active coping with mental demands, as we will outline in more detail below. To support this argument, we will discuss the findings of a series of experimental studies that have demonstrated that people who perform difficult self-involving tasks experience strong cardiovascular reactivity. If such performance settings are frequently encountered or created by an individual, self-involvement becomes a risk factor for the development of hypertension and cardiovascular disease.

As the core idea of this chapter, we posit that performance conditions having high implications for individuals' self-definitions and self-esteem justify the mobilization of high resources to accomplish high demands. As we will outline in more detail below, especially self-relevant tasks that are difficult bear the risk of the development of hypertension and cardiovascular disease due to high resource mobilization and cardiovascular reactivity, respectively. The predictions about the link between self-relevant performance conditions and cardiovascular reactivity are based on motivational intensity theory [27] and its integration with the active coping approach [16] to cardiovascular reactivity by Wright [28].

Motivational Intensity Theory

Recently, we have applied motivational intensity theory [27, 29] to challenges that involve the performer's self [22]. Motivational intensity theory builds on two premises. The first postulates that the direct function of effort is to cope with deterrents in the goal pursuit process. The second posits that effort mobilization follows a resource conservation principle. Consequently, effort rises proportionally with the extent of subjective difficulty until the demand level exceeds a person's abilities (i.e., the task is too difficult) or until the amount of necessary effort is no longer justified by the value of success—which defines the level of "potential motivation" (i.e., the hypothetical maximum of justified effort). That is, engagement rises with task difficulty until a task is too difficult or does not justify the necessary resources.

Respecting the resource conservation principle requires that performers have an idea about the level of actual demand. Whenever individuals face tasks with a *fixed* performance standard (e.g., "memorize these 6 items within 2 minutes"), difficulty is relatively clear and the necessary resources can be adjusted to the level of experienced task demand. But when task difficulty is *unfixed* because no clear fixed performance standard is provided (e.g., "memorize as many items as possible"), motivational intensity theory predicts that people will strive for the highest possible performance level that is justified to be accomplished in order to assure goal attainment.

Consequently, when persons face an unfixed task, effort intensity should be determined by the value of success (i.e., the level of potential motivation). It follows that under the same level of value of success, task-engagement in the face of an unfixed performance-standard should correspond to engagement in the face of the highest fixed performance standard for which effort is mobilized. When the value of success is relatively low, effort should be modest in unfixed and fixed standard conditions, because more engagement is neither justified nor necessary.

As presented in Figure 1, individuals are willing to expend more effort when self-involvement is high than when self-involvement is low. However, whether they do so depends on the level of subjective task difficulty. Consequently, individuals should generally mobilize low effort when self-involvement is low, because high effort is not *justified* under this condition. People should also mobilize low effort when task difficulty is low, because performing easy tasks *requires* only low effort regardless of the magnitude of self-involvement. When task difficulty is unfixed, the level of potential motivation determines

effort directly. Thus, high effort should only be mobilized when task difficulty is high or unfixed under self-involving performance conditions.

According to the present analysis, self-relevance refers to the level of potential motivation in Brehm's model. Thus, with regard to effort mobilization, there is no qualitative difference between self-involving and non self-involving performance conditions. In either case, effort mobilization will be determined by the interplay between potential motivation (defined by the extent of self-involvement) and task difficulty.

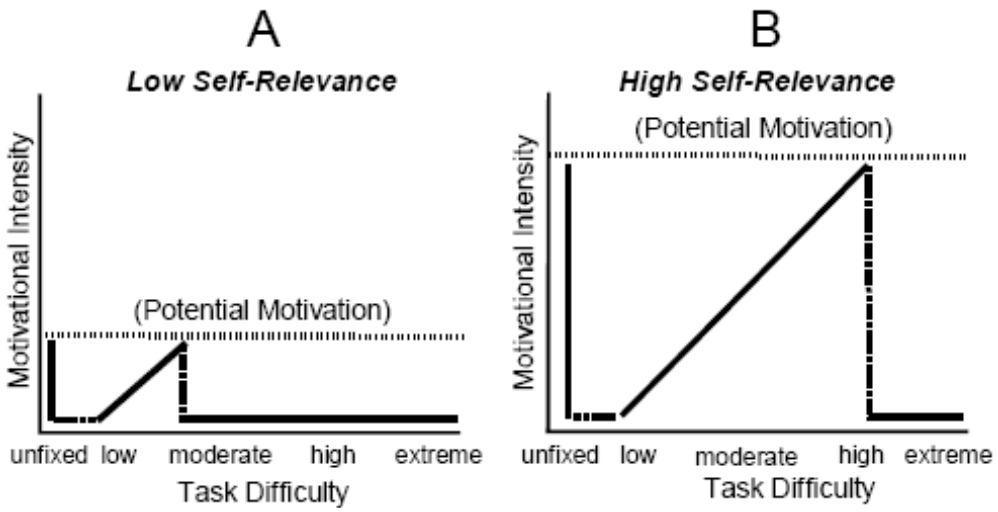

Figure 1. The joint impact of self-relevance and task difficulty on motivational intensity according to Gendolla (22). Panel A shows the condition of low self-relevance. Panel B shown the condition of high self-relevance. Motivational intensity is reflected in cardiovascular reactivity in the context of task performance.

Based on Obrist's demonstration that task engagement in active coping is mediated by beta-adrenergic activity [16], Wright applied motivational intensity theory to cardiovascular psychophysiology [28]. According to this perspective, any cardiovascular measure that reflects beta-adrenergic impact on the heart should be sensitive to differences in effort and, thus, follow the predictions of motivational intensity theory. Furthermore, Wright postulated that especially SBP should be sensitive to differences in effort mobilization since it is strongly determined by the force of myocardial contraction—which is mainly determined by myocardial beta-adrenergic impact. Other classical cardiovascular measures—which are only loosely connected to myocardial contraction force—as for instance DBP or HR should be less systematically associated with effort.

Self-Involvement and Effort-Related Cardiovascular Response: Empirical Evidence

The theoretical predictions of Brehm's motivational intensity theory have been supported by numerous studies that have used cardiovascular reactivity as a measure of effort

mobilization [28, 30, 31, for reviews]. The vast majority of these studies involved concrete material and physical operationalizations of potential motivation. However, some studies also assessed cardiovascular reactivity under self-involving performance conditions and supported the present argument that the principles of motivational intensity theory apply well to this behavioral realm.

Social Evaluation Effects

Wright and colleagues have shown that the explicit information that individuals' performance will be evaluated by a panel of experts increases the level of maximally justified effort (potential motivation) [32, 33, 34]. A recent experiment from our laboratory found additional evidence for the effects of implicit social evaluation [35]: After assessment of cardiovascular baseline values, participants performed an either easy or difficult version of a computerized letter detection task. Participants had to decide if presented letters conformed to a defined criterion (targets, yes response) or not (non-targets, no response). In the easy condition the stimuli were presented for 3000 ms, whereas the presentation time in the difficult condition was 700 ms. Half the participants worked in a private condition (i.e., they worked alone). The other half worked in a public condition and was observed by the experimenter who took a seat next behind the participants. Systolic reactivity (i.e., the difference between the task and the baseline period) is depicted in Figure 2. As expected, social observation, which was anticipated to induce a state of social evaluation in the observed participants, led to higher SBP reactivity in the difficult condition. In the easy condition, social observation had no effect. These effects corroborate the predictions depicted in Figure 1 and support the idea that social evaluation justified the mobilization of relatively high effort. However, high effort mobilization became evident only in the difficult condition. In the easy condition high effort was not necessary and therefore not mobilized.

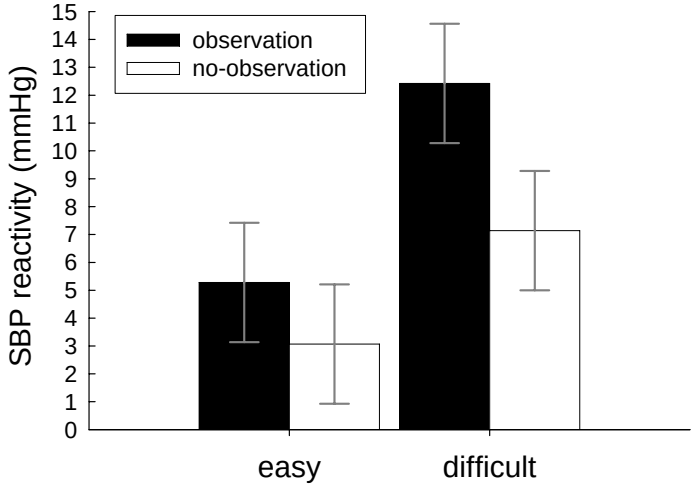

Figure 2. SBP reactivity in dependence on task difficulty and observation condition in the study by Gendolla and Richter [35].

Another series of experiments by Gendolla and Richter [36] examined cardiovascular reactivity under another condition supposed to lead to self-involvement: ego-involvement—that is, an attempt to demonstrate the possession of an important ability making success on a task highly valuable [37]. Participants were university students who learned that a forthcoming memory task was either a test that reflected an important ability predicting academic success, namely learning under time pressure (high ego-involvement), or believed that the memory task was only a filler without diagnostic significance (low ego-involvement). Task difficulty was manipulated on four levels. Participants were asked to memorize 2 (very easy), 6 (moderately difficult), or 15 (very difficult) letter series within 5 min, or were instructed to memorize as many as they could from a list of 15 series (unfixed difficulty). As presented in Figure 3, the results for SBP reactivity during task performance with respect to previously assessed baseline values clearly supported the predictions.

In the low ego-involvement condition, no significant differences emerged between the four difficulty cells. But under high ego-involvement, SBP reactivity was high in the unfixed difficulty condition where participants were instructed to correctly memorize as many items as they could and increased, as anticipated, from the very easy to the very difficult condition. The unfixed and the difficult conditions did not differ, suggesting that participants in these conditions mobilized effort up to the level of potential motivation, which was defined by the extent of self-involvement. Thus, SBP reactivity exactly described the function predicted in Figure 1.

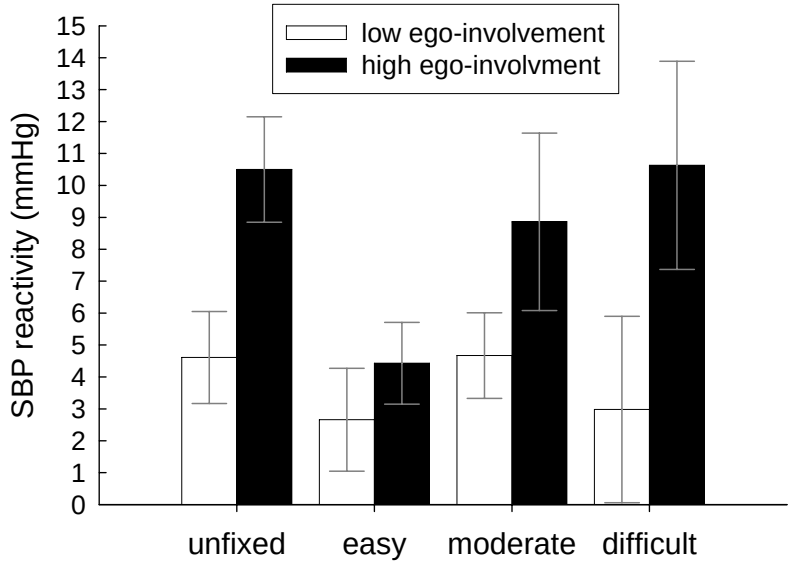

Figure 3. SBP reactivity in dependence on ego-involvement and task difficulty in the study by Gendolla and Richter [36].

A second experiment by Gendolla and Richter [36] tested if an impossible task leads to disengagement and thus to low cardiovascular reactivity when ego-involvement is high. The ego-involvement manipulation was the same as in the previous study. Task difficulty was either unfixed or extremely high. Participants were asked to correctly memorize a list of letter

series within 5 min. In the extremely difficult condition, participants were asked to memorize the whole list—which was impossible. In the unfixed difficulty condition, they were asked to memorize as many items as they could. As expected, systolic reactivity was stronger in the ego-involvement/unfixed condition than in the remaining three cells, which did not differ from one another. That is, when task difficulty was so high that success was obviously impossible, participants disengaged even though ego-involvement was high, resulting in low SBP reactivity.

Self-Evaluation Effects

After investigating effects of social observation and ego-involvement, two recent experiments [38] examined the impact of self-evaluation on cardiovascular reactivity. These studies were based on the notion of objective self-awareness theory stating that attention focused on the self induces a state of self-evaluation, in which individuals compare their actual behavior with salient behavioral standards [39]. As a result, self-aware individuals seek to reduce existing discrepancies between standards and behavior by trying to comply with the standards as long as it is possible to do so. This principle of self-regulation has received ample empirical evidence [40]. Applying motivational intensity theory to self-relevant performance conditions, one can predict that the state of self-evaluation induced by self-focused attention justifies relatively much effort in achievement situations in which the behavioral standard is succeeding on the task. Thus, self-evaluation should have the same effect as social evaluation in the studies discussed above. Up to the level of maximally justified effort, actual effort-related cardiovascular response should be determined by task difficulty (see Figure 1).

In the experiments by Gendolla et al. [38], participants performed a computer-based letter-detection task with manipulated task difficulty levels after their cardiovascular baseline values had been assessed at the beginning of the experimental session. In the high self-focus condition of each experiment, participants were exposed to their face on a video monitor during the task. Participants were told that the video camera would record facial expressions during task performance. The camera filmed participants' face from the left hand side perspective and transmitted it to a video monitor that was placed next to participants' computer monitor. Thus, participants were exposed to a picture of their own face during task performance. In the low self-focus condition, participants were not filmed. They were told that the camera was out of order and consequently saw the blank video monitor.

In Experiment 1, participants performed the same letter detection task as presented above, either with an easy standard (stimulus presentation time 3000 ms.) or with no fixed performance standard (participants could work on their own pace). As expected, participants in the self-focus/unfixed condition showed significantly stronger SBP reactivity than those in the other three experimental cells, which did not differ from one another. Thus, self-focus justified high effort that was, however, not mobilized when the easy task did not necessitate high resources for succeeding. Experiment 2 involved the same unfixed difficulty condition as the first study but additionally a difficult (stimulus presentation time 600 ms) and an extremely difficult (stimulus presentation time 350 ms), actually impossible, condition of the

letter detection task. For the high self-focus condition, where relatively much effort should be justified, SBP reactivity was anticipated to be high in both the unfixed and the difficult conditions, whereas it should be low in the extremely difficult condition due to disengagement. In the low self-focus condition, where only low effort should be justified, reactivity was anticipated to be low in general. As depicted in Figure 4, the results confirmed the predictions.

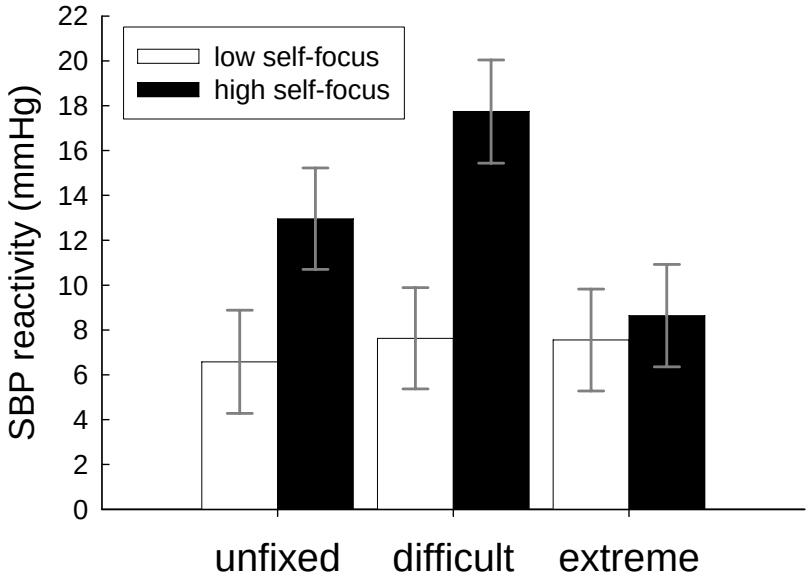

Figure 4. SBP reactivity in dependence on self-focused attention and task difficulty in the second study by Gendolla, Richter, and Silvia [38].

Important Personal Goals

An earlier experiment by Gendolla [41] examined a further aspect of self-involvement—the extent of instrumentality of successful task performance for achieving an identity-related personal goal. According to an analysis by Baumeister [42], people in modern Western societies have to actively create their identities on their own. Unlike previous epochs, in which individuals' place in society was automatically determined by factors like gender, social status, and the father's profession, people nowadays have to decide which identity goal they want to pursue and must invest effort for goal attainment. The experiment focused on the second process—effort mobilization.

Participants were freshmen in psychology who attended the experiment immediately before beginning their first term. All participants had already decided for a professional goal in the psychology realm (e.g., clinician, researcher etc.). After habituation and assessment of cardiovascular baselines, participants performed a memory task—they were asked to correctly memorize a list of names within 5 min. For half of the participants, successful performance was relevant for attaining their pursued professional identity goal. In these conditions, participants learned that the list consisted of the names of prominent

psychologists that had to be learned in order to pass necessary exams for a degree in psychology. That is, success in the experimental task brought participants closer to their identity goal—professional psychologist. The other half of the participants was not informed about the names' connection to psychology. Additionally, task difficulty was manipulated on two levels. The list comprised 8 names in the easy and 40 names in the difficult condition.

The results supported the present application of motivational intensity theory to self-involving performance conditions: Performance-related responses of SBP and HR were high only when high identity relevance was bound up with high task difficulty. They were low in the easy task condition independent of self-involvement. Thus, although success in the identity-relevant condition had implications for an important life goal, participants did not mobilize more effort than necessary in the easy condition.

Empirical Evidence: Summary

Drawing on Greenwald's [26] analysis, we have proposed that especially three variables may lead to strong involvement of performer's selves into the performance setting: social evaluation of own abilities, self-evaluation under conditions of self-awareness, and personal importance of performance through its relation to personal interests and values. The above discussed studies have corroborated the impact of all of these variables. They clearly support the assumption that the cardiovascular system reacts proportionally to the extent of subjective task difficulty and that self-involvement justifies relatively high task engagement. That is, high self-involvement justifies the mobilization of high resources and leads to strong cardiovascular reactivity when task difficulty is high or when people are asked to do their best (unfixed task difficulty). In contrast, low self-involvement does not justify high effort mobilization and thus leads to less task engagement, especially under difficult or unfixed task conditions.

Outlook and Conclusions

We interpret the here discussed findings as supportive for the argument that self-relevance can have a significant impact on high cardiovascular reactivity and thus on the development of hypertension and cardiovascular disease. However, we acknowledge that a more conclusive test of our hypothesis would be a longitudinal study like that by Light, Dolan et al. [11]. Nevertheless, the studies we have discussed in this chapter provide clear evidence how self-involvement interferes in the development of hypertension and cardiovascular disease: Self-relevant performance settings that have implications for individuals' self-definition and self-esteem justify the mobilization of high resources for succeeding. Therefore, they have a significant impact on cardiovascular reactivity in active coping. When tasks are difficult or have no fixed performance standard, high resources are mobilized. Given that there is already replicated evidence that cardiovascular reactivity to behavioral challenges is a predictor of essential hypertension and cardiovascular disease [see 4], we believe that the beginning of the chain of events in this process is the critical and

central part that has to be more closely investigated. Although a longitudinal study that tests all steps of the posited process is not available yet, we think that the existing experimental evidence for our assumption is promising. Accordingly, high self-involvement can foster the development of cardiovascular disease, especially when settings that call for active coping are combined with frequent or permanent high involvement of the self.

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Chapter 10

Drained: Studies of Fatigue Influence on Engagement and Associated Cardiovascular Responses

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Abstract

A long-standing research program in my laboratory has concerned the determinants and cardiovascular (CV) consequences of task engagement in people confronted with performance challenges. One focus has been on the manner in which ability perceptions impact engagement and CV response outcomes and this has evolved recently into an interest in how fatigue impacts these outcomes. Our ability reasoning implies that fatigue should have potential for augmenting engagement and CV responses, retarding them, or leaving them unchanged, depending on the difficulty of the challenge at hand. The implication is supported by data from a variety of studies and suggests that chronic fatigue may increase health risk under some performance conditions.

Introduction

For a couple of decades now, my students and I have conducted experiments concerned broadly with the determinants and cardiovascular (CV) consequences of task engagement (effort or active striving) in people confronted with performance challenges. We have been interested in CV response as an engagement outcome in large part because CV responses are believed to be linked to risk for negative health outcomes, including hypertension and heart disease [1, 2]. Although mediating mechanisms are not fully understood, there is compelling

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evidence that people who evince chronically pronounced CV responses in their daily lives are at greater risk than people who evince relatively diminished responses.

A persistent focus over the years has been on the manner in which perceptions of *ability*, or self-efficacy [3, 4], impact engagement and associated CV responses. Recently, this focus has evolved into an interest in fatigue. The fatigue interest followed from the straightforward assumption that perceptions of ability should decline to the degree that resources are depleted within a performance system, that is, to the degree that there is fatigue in the system [5,6]. If this is the case, then our guiding ability analysis implies that fatigue (resource depletion) should have different engagement and CV effects depending on the difficulty of the performance challenge at hand. More specifically, the analysis implies that depending on difficulty conditions, fatigue should have potential for augmenting engagement and CV responses, retarding them, or leaving them unchanged.

My central purposes in preparing this chapter are twofold. One is to review our ability perception analysis and spell out its implications for fatigue influence on engagement and associated CV responses. The other is to provide an overview of evidence that bears out the analysis' fatigue implications. Once I have accomplished these purposes, I will comment briefly on health implications of our ideas and findings. I also will point to some fatigue issues that either have not been addressed empirically or need to be addressed further.

Ability Perception, Engagement, and CV Response: Traditional Conceptions

There is a history in psychology of interest in the relation between ability perception and engagement in performance circumstances. Perhaps not surprisingly, there also is a history of debate on the issue. Some theorists have suggested that there may be no relation [7]. However, most have assumed that there is and taken one of two positions concerning its character. One character position has been that engagement increases with the perceived capacity to perform [3, 8, 9]. Those taking this view have tended to assume that striving is driven by expectations of success. It stands to reason that success expectations should rise as performance capacity improves. If this is so, it follows that striving should also rise with performance capacity improvement.

The second character position has been the polar opposite of the first, that engagement *de*creases directly with the perceived capacity to perform [10, 11]. Those taking this view have tended to focus on the compensatory function that engagement can play in performance circumstances. Performers regularly "make up" for a reduced performance capacity by expending themselves to an extra degree. Consider, for example, a modestly gifted athlete. She might make up for her limited ability by working harder in practice and at game time. If it is true that people exert effort to the degree that they need to, given their ability, it follows that striving should be inversely proportional to performance capacity.

Just as psychologists have been interested in and disagreed about the relation between perceived ability and engagement in performance circumstances, they also have been interested in and disagreed about the relation between perceived ability and CV response in those circumstances. Once again, two contrary views have been dominant, (a) that CV

response increases as perceived ability increases, and (b) that CV response decreases as perceived ability increases. Here, the contrariness is somewhat of an illusion because the dominant views generally have been applied in different *types* of performance circumstances. Whereas the first generally has been applied in appetitive performance circumstances (in which people can attain attractive outcomes by doing well), the second generally has been applied in aversive performance circumstances (in which people are likely to incur harm or loss if they do poorly).

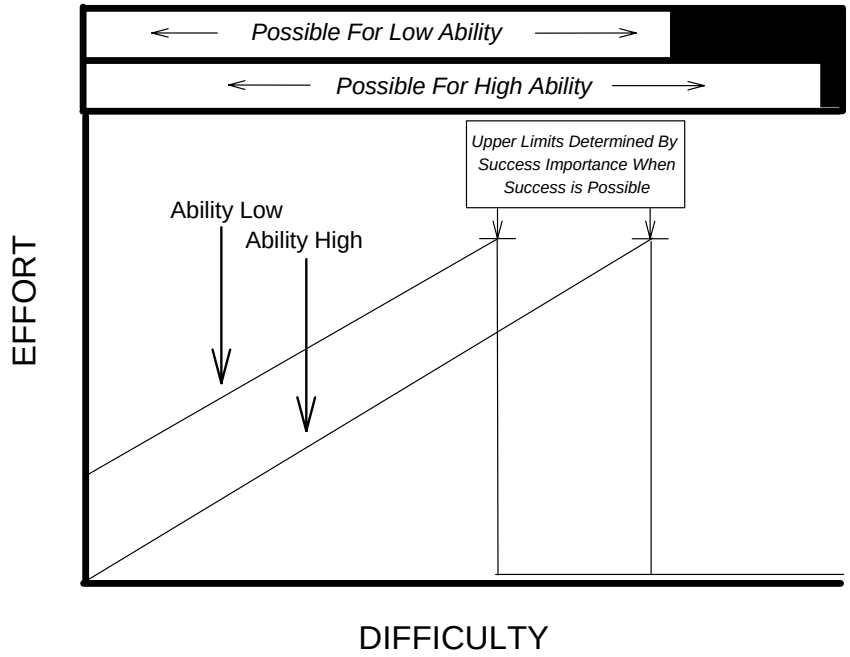
The different applications "clean up" some of the inconsistency between the dominant perceived-ability/CV-response views. However, they do not make the dominant views entirely consistent because the views differ markedly in terms of the assumptions they make pertaining to mechanism. Assumptions underlying the first view are (a) that engagement rises with ability perception [e.g., 3], and (b) that CV response rises with engagement [12]. Contrasting assumptions underlying the second view are (a) that subjective threat rises as ability perception falls [e.g., 13], and (b) that CV response rises with subjective threat [e.g., 14, 15]. Thus, whereas one dominant view considers engagement to be the critical mediator of CV response, the other dominant view considers threat appraisal to be the critical mediator.

Our Ability Analysis

The ability analysis that has guided work in my laboratory has elements in common with most of the effort and CV response arguments above. However, it differs from these arguments in crucial respects and – in our view at least - presents a more integrated image of relations among the constructs of interest. Others and I have discussed details of the analysis elsewhere [16-18]. Consequently, I will present it here only in summary:

- Sympathetic nervous system influence on the heart and vasculature rises and falls with momentary engagement, that is, effort at a given point in time [12, 19].
- Effort expended to meet a performance challenge corresponds to the difficulty of that challenge so long as success is viewed as possible and worthwhile; when success is viewed as impossible or excessively difficult, given the strength (importance) of the motive driving behavior, effort is low [20].
- People with low perceived ability with respect to a performance challenge should view the challenge as more difficult than people with high perceived ability with respect to the challenge [e.g., 21, 22].

Together, the preceding propositions have a number of intriguing implications, three of which have received primary emphasis to date. First, people low in perceived ability should be more engaged and display stronger CV responses in attempting to meet a performance challenge than people high in perceived ability so long as both groups view success as possible and worthwhile. Second, Low Ability people should withhold effort at a lower level of challenge difficulty than should High Ability people, because they should conclude at a lower difficulty level that success is impossible or too costly.



Wright and Franklin, 2004.

Figure 1. Relation between challenge difficulty and engagement (effort) for people low- and high in perceived ability.

This means that as difficulty rises, a difficulty level should be reached at which Low Ability people try less and are less CV responsive than High Ability people. Third, as challenge difficulty continues to rise, a difficulty level should be reached at which engagement and CV responsiveness bear no relation to ability perception. If difficulty is high enough, even High Ability people should conclude that success requires more than they can or will do. At and beyond this difficulty level, their engagement and CV response levels should be low and equivalent to those of Low Ability people.

One "big picture" suggestion from our ability analysis is that ability perception should not have a single effect on engagement and CV response, as some traditional views have held. Rather, it should have different effects depending on the difficulty conditions involved. This is illustrated in Figure 1, which plots engagement (and, thus, sympathetically-mediated CV response) against difficulty for people who view themselves as more or less capable. Another big picture suggestion is that relations among ability perception, engagement, and CV response may not vary with the appetitive or aversive quality of the situation, as some theorists have argued. Rather, they should be the same whether one is striving to attain or avoid an outcome.

Implications for Fatigue

As noted earlier, our interest in fatigue followed from the assumption that perceptions of ability should decline to the degree that resources within a performance system are depleted. In combination with the ability analysis, this suggests that fatigue (resource depletion)

influence on engagement and CV response should depend on challenge difficulty. Specifically, when fatigue causes success to appear impossible or excessively difficult, it should retard engagement and CV responsiveness. That is, it should lead performers to withhold effort and show minimal CV responsiveness as a result. By contrast, when fatigue leaves unaltered a perception that success is possible and worthwhile, it should augment engagement and CV responsiveness. That is, it should lead performers to expend themselves in a compensatory fashion and experience heightened CV arousal as a result. Finally, when fatigue leaves unaltered a perception that success is impossible or excessively difficult, it should have no impact on engagement and CV responsiveness. That is, it should leave unchanged performers' disposition to withhold effort and experience minimal CV arousal as a result. To visualize the implied relations among fatigue, engagement, and CV response, one needs only to replace the low ability label in Figure 1 with the label "high fatigue" and the high ability label in the figure with the label "low fatigue".

Evidence

Evidence for the preceding fatigue implications comes chiefly from two types of studies. One type includes experiments that have examined ability perception effects on engagement and CV responses under different challenge difficulty conditions. These studies provide indirect support for the fatigue implications because they bear out the relations among ability perception, engagement, and CV response that the implications assume. The other type of study from which evidence for the fatigue implications comes includes experiments that have examined CV effects of fatigue directly. In the subsections that follow, I will discuss each type of study in turn.

Ability Studies

Numerous studies have examined ability perception effects under different challenge difficulty conditions and provided indirect support for the fatigue implications. The specific character of these studies has varied considerably. Whereas some studies have involved CV response measures, others have involved alternative dependent outcomes that may reasonably be linked to engagement. Similarly, whereas some have manipulated ability perception, others have studied ability perception as a measured variable.

An example of a non-physiological study in this group is an early experiment by Kukla [23] that classified participants in terms of resultant achievement motivation construing that variable in terms of perceived ability. Participants low and high in resultant achievement motivation (ability) were assigned to conditions in which they were given arithmetic problems to solve with instructions that solutions would be easy or moderately difficult. For the low need-achievement (i.e., ability) participants, performance (taken as an index of striving) proved to be better where the task was described as easy. For the high need-achievement (i.e., ability) participants the reverse was true.

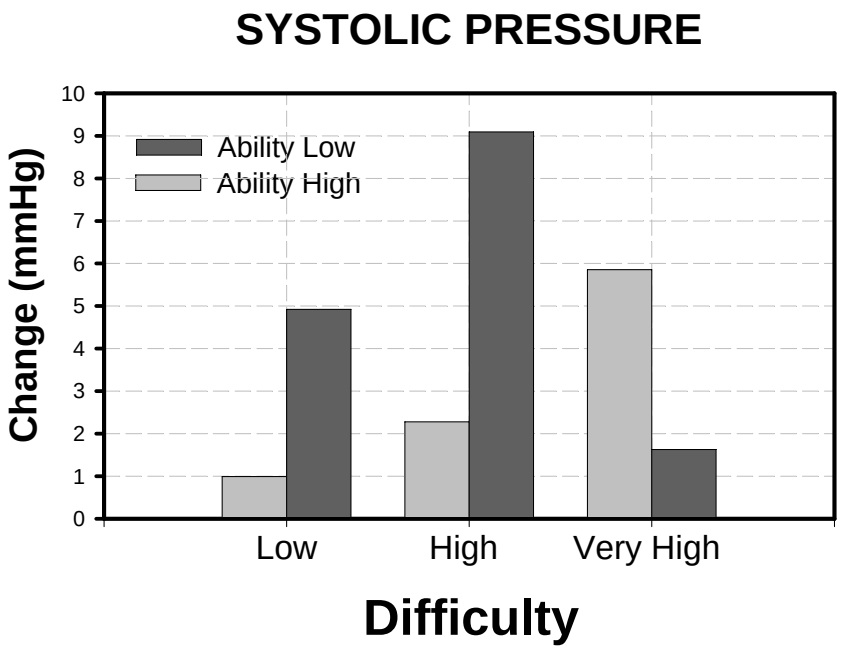


Figure 2. Systolic blood pressure change scores for Low- and High Ability participants presented the math problems described as easy, difficulty and very difficult to solve.

An example of a study that involved CV response measures is a later experiment from my laboratory [24]. Investigators first manipulated ability perception by urging participants to do their best on a visual scanning task and then telling the participants that they had performed well (87th percentile) or poorly in comparison to others (12th percentile). Subsequently, the investigators presented a second scanning task and told the participants that they could earn a prize by attaining a high (85th percentile) or low (15th percentile) standard. As expected, analysis of CV responses assessed just before and during the second performance period revealed an interaction between ability (i.e., performance feedback) and difficulty for systolic blood pressure (SBP) response, with means in a crossover pattern. The crossover pattern reflected relatively greater responsiveness for Low Ability (i.e., negative feedback) participants than for High Ability (i.e., positive feedback) participants when the standard was low, but the reverse of that when the standard was high. The interaction was expected for SBP responses because SBP is partially determined by heart contraction force, which is determined chiefly by sympathetic nervous system arousal [25, 26]. Analysis of diastolic blood pressure (DBP) responses yielded the same interaction and crossover response pattern.

A further example of a study that involved CV response measures is an experiment from my laboratory that examined ability as a measured, rather than a manipulated, variable [27]. Investigators in this case first formed high- and low ability groups by administering in advance a screening questionnaire that included an item that assessed respondents' perceived math ability (0 = low; 10 = high). They then invited to participate in the study proper individuals with relatively high- and low ability ratings (values of 7-10 and 0-3, respectively). When participants arrived, they were presented a set of math problems described as easy, difficult, or extremely difficult and told they could avoid a blast of noise

by solving them. Immediately prior to the point at which participants were to commence work, the investigators took CV samples, including blood pressure and heart rate.

Once again, analysis of SBP responses produced an ability x difficulty interaction. Figure 2 shows that High Ability participants tended to evince greater anticipatory SBP responsiveness as difficulty increased; by contrast, Low Ability participants evinced more pronounced anticipatory SBP responses in the high difficulty condition than in the low- and extreme difficulty conditions. Whereas Low Ability participants had or tended to have stronger anticipatory SBP responses where difficulty was low and high, they tended to have weaker anticipatory SBP responses where difficulty was extreme.

Some of the most recent ability studies in this group have been conducted as part of an ongoing program of research by Gendolla and his colleagues at the University of Geneva [28-32]. The program is concerned directly with the role that mood plays in determining engagement and associated CV responses. However, it is has ability implications because it assumes that mood effects on engagement and CV response are mediated by ability appraisals. A core assumption is that ability appraisals tend to be lower in negative moods. This suggests that mood can be viewed as a proxy for ability perception and should interact with challenge difficulty to produce the outcomes of interest.

Findings have consistently supported Gendolla's reasoning. Consider, for example, those from a study by Gendolla and Krüsken [30]. The study induced mood with happy or sad music and presented participants an easy or difficult version of the d2 letter-cancellation task [33]. Easy participants were told they would have to attain a performance standard 20% slower (easy condition) than one they had attained in practice; Difficult participants were told they would have to attain a standard 20% faster than one they had attained. As expected, there were no CV mood effects during the mood induction (i.e., music) period, indicating that mood *per se* has no CV effect. However, during performance there were mood x difficulty interactions for SBP and DBP responsiveness. When difficulty was low, pressure responses were relatively greater for the negative mood group. When difficulty was high, pressure responses were relatively greater among positive mood participants, presumably because the negative mood participants viewed the difficult task as impossible or excessively difficult.

To summarize, numerous studies have examined ability perception effects under different challenge difficulty conditions and provided indirect support for the fatigue implications that derive from our ability analysis. Some of the ability studies have involved CV response measures. Others have involved alternative dependent outcomes that may reasonably be linked to engagement. Some of the studies have manipulated ability perception; others have studied ability perception as a measured variable. Data from these studies support the fatigue implications because they bear out the relations among ability perception, engagement, and CV response that the implications assume.

Studies of Fatigue

Although the preceding ability studies provide the strong suggestion that fatigue *should* produce different engagement and CV outcomes under different challenge difficulty conditions, they by no means confirm that it does. Confirmation that fatigue does produce the

different outcomes requires investigations of fatigue itself, which has led my students and me to undertake a number of fatigue projects in the past several years. All of our fatigue studies have not "worked", that is, produced interpretable fatigue results. However, most have yielded findings compatible with the fatigue implications that inspired them and, thus, supported directly those implications.

Our Initial Experiments. Our earliest fatigue study was an experiment that involved a motor challenge [34]. Purposes of the study were twofold. First, we wanted to examine the implication that CV responsiveness should be proportional to fatigue under conditions where a performance challenge can and will be met. Second, we wanted to investigate the idea that motor fatigue effects should be – to a degree at least - challenge-specific, that is, confined to related performance systems. Regarding the latter, it seemed reasonable that fatigue in one motor performance system (e.g., the legs) should impact powerfully engagement and CV responses to challenges highly relevant to that system (e.g., dunking a basketball), but impact minimally engagement and CV responses to challenges mildly- or unrelated to the system (e.g., bench pressing a barbell).

Participants in the study first performed left- or right handedly a set of easy (low fatigue) or difficult (high fatigue) dynamometer grips. They then made and held with their right hand a modest grip while CV measures were taken. As expected, SBP responses were stronger under high fatigue conditions among participants who gripped initially with their right hand. By contrast, these responses were unrelated to fatigue among participants who gripped initially with their left hand.

A follow-up study aimed to partially replicate the gripping study's CV findings using a mental challenge and determine whether mental fatigue influence varies with challenge difficulty [35]. Our main reason for investigating mental fatigue effects was to establish the generality of fatigue influence. However, we also were interested in these effects because they could have stronger health implications than motor fatigue effects [2, 12].

The experiment first required participants to perform for five minutes an easy or difficult counting task. More specifically, it required participants to either count forward from zero in increments of one at five second intervals (fatigue low) or count backwards from 375 in increments of three at the same pace (fatigue high). After the counting period, experimenters presented participants mental arithmetic problems with instructions that they could earn a prize if they attained a low (30^{th} percentile) or high (80^{th} percentile) performance standard.

Analysis of CV data collected during the work periods indicated fatigue x difficulty x period interactions for SBP, DBP, and mean arterial pressure (MAP, the average pressure over a heart cycle). As anticipated, High Fatigue participants showed, or tended to show, stronger responses during the initial (fatigue induction) period. Also as anticipated, the fatigue groups showed different response patterns in the second period, depending on the standard assigned. Responses for Low Fatigue participants were relatively stronger when the standard was high than when it was low. By contrast, those for High Fatigue participants were relatively stronger when the standard was low than when it was high. Further comparisons indicated that responses were or tended to be greater for High- than Low Fatigue participants when the standard was low, but were or tended to be greater for Low- than High Fatigue participants when it was high.

Later Studies: The Domain Specificity of Mental Fatigue Influence. Having obtained evidence that motor fatigue effects are – to a degree at least – challenge-specific and that mental fatigue produces CV effects comparable to those of motor fatigue, we decided to explore the possibility that mental fatigue effects also may be challenge-specific. That is, we decided to explore the possibility that resource depletion in one mental system (e.g., that involved in quantitative performance) impacts powerfully engagement and CV responses to highly relevant cognitive challenges (e.g., balancing a checkbook), but impacts minimally those responses to mildly- or unrelated cognitive challenges (e.g., writing a poem). We explored this possibility in a series of four studies, three of which yielded clearly interpretable results.

Typical of the specificity studies that "worked" is an experiment that (a) required participants to perform easy (fatigue low) or difficult (fatigue high) counting tasks similar to those in the first mental fatigue study, and then (b) presented the participants either an arithmetic challenge (fatigue relevance high) or a letter scanning challenge (fatigue relevance low) with instructions that they would avoid a noise if they attained a modest (50^{th} percentile) performance standard (36, Experiment 1). Analysis of the CV data indicated fatigue effects for SBP, DBP, and MAP reflecting stronger responses for High Fatigue participants across periods and regardless of the second challenge presented.

Also typical is an experiment that employed a similar procedure but included a high (90^{th} percentile) performance standard instead of a modest one and provided participants the chance to win a prize instead of the chance to avoid noise (36, Experiment 2). Analysis of the CV data in this case revealed fatigue x period interactions for the blood pressure measures. Once again, pressure responses were relatively elevated for High Fatigue participants in period 1. However, they were relatively *diminished* for High Fatigue participants in period 2, presumably because these participants tended to withhold effort in the second period, whereas the Low Fatigue participants did not. As in the earlier extension study, fatigue effects were unaffected by the fatigue relevance manipulation, suggesting that mental fatigue influence was not challenge-specific.

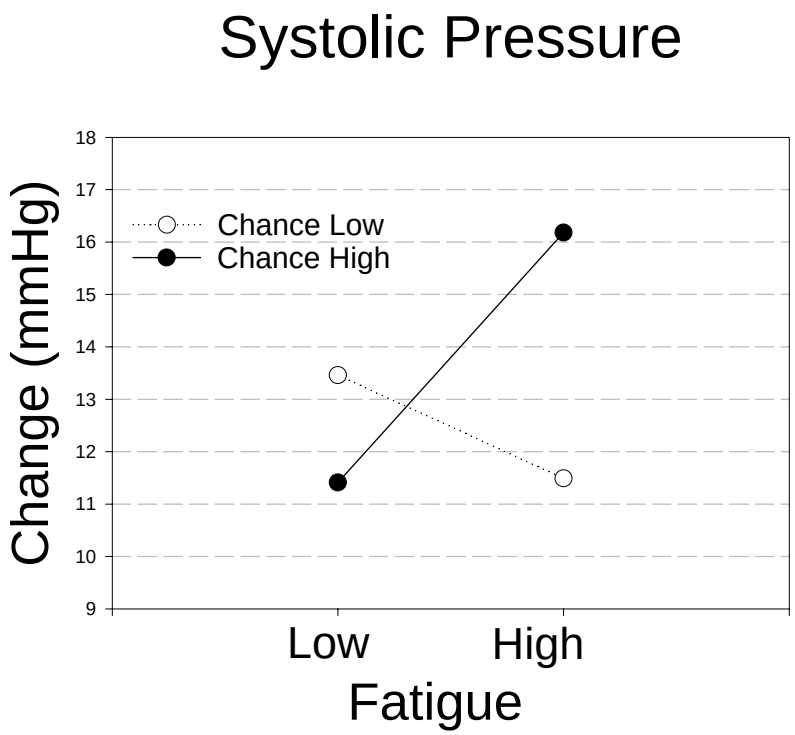
Our Most Recent Studies: Effects of Success Importance and Naturally Occurring Fatigue. Our most recent fatigue studies had, between them, two goals: (a) to examine success importance as a possible moderator of fatigue influence, and (b) to evaluate the degree to which natural (i.e., spontaneous) fatigue effects on CV response compare with manipulated fatigue effects on CV response. The interest in success importance followed from the ability analysis idea that when success is perceived as possible, motive strength (importance) should determine the difficulty level which Low- and High Ability people withhold effort (review Figure 1). If this is true, success importance should determine the difficulty level at which low- and high fatigue groups withhold effort as well. The interest in natural fatigue followed from a desire to establish the external validity (i.e., generalizability) of our fatigue findings.

The Importance Study. In the importance study [37] we manipulated mental fatigue somewhat differently than did the other mental fatigue studies I have described. Specifically, we had participants perform initially an easy (fatigue low) or difficult (fatigue high) version of the d2 letter-cancellation task mentioned in relation to the mood study by Gendolla and Krüsken [30]. The difficult version of the d2 presented on a series of pages arrays of d and p

letters paired with one, two, three, four, or no apostrophes. Participants were required to circle at 3 second intervals d letters linked to two, and only two, apostrophes. The easy version of the d2 did the same except that it allowed participants to circle d letters without the two-apostrophe restriction. Participants receiving this treatment were directed to circle d letters ignoring the apostrophes associated with them.

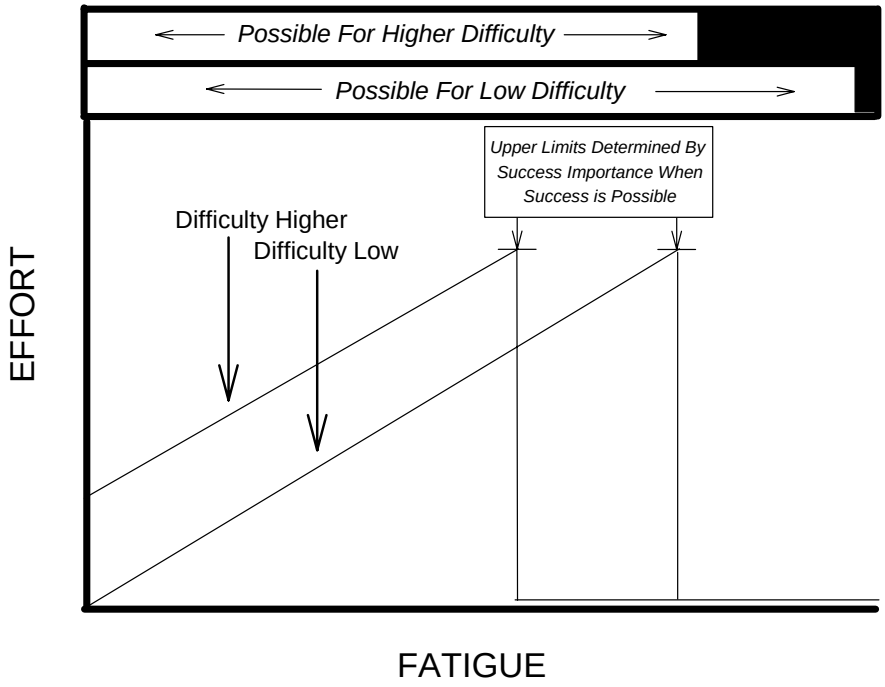
Shortly after the fatigue induction period, we presented participants an extended set of single-digit multiplication problems with instructions that they would earn a strong (51 out of 52, i.e., 98%) or weak (1 out of 52, i.e., 2%) chance of winning an attractive prize if they attained a moderate (50^{th} percentile) performance standard. We manipulated the chance of winning, given success on the task, on the assumption that success importance would be greater when the chance was high than when it was low [38]. Drawing from the logic of the ability analysis, we predicted that fatigue would augment engagement and CV responsiveness during the second period where the chance of winning (and, thus, success importance) was high, but – if anything – lead to diminished engagement and CV responsiveness where the chance of winning (and, thus, importance) was low.

SBP responses assessed during the second period were supportive (Figure 3). Whereas they were proportional to fatigue for the High Chance (Importance) participants, they were low regardless of fatigue for the Low Chance (Importance) participants. Analyses on the DBP and MAP data indicated the same interactional response patterns.

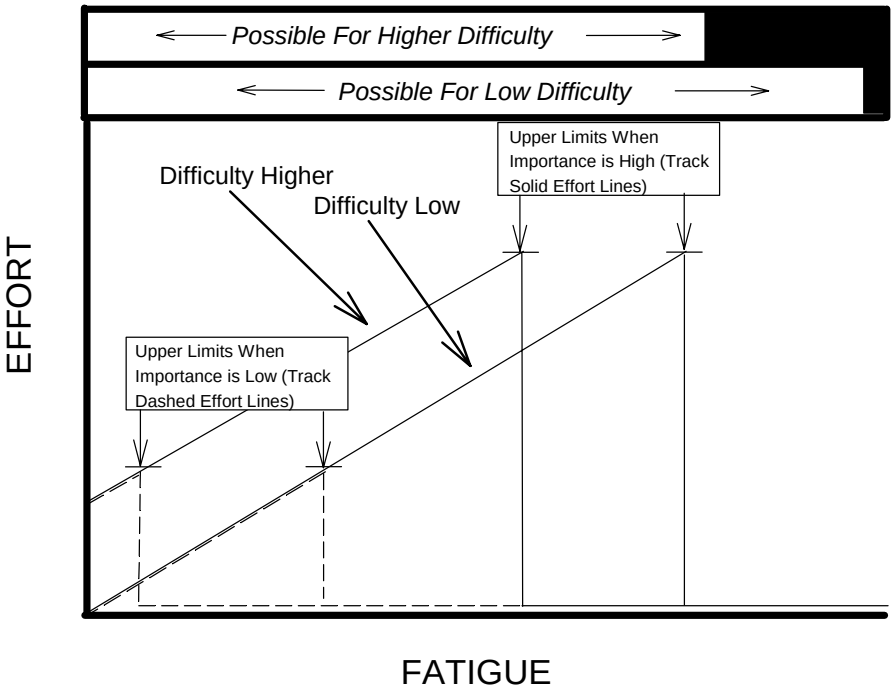


Wright et al., 2008.

Figure 3. Systolic blood pressure change scores for Low- and High Fatigue participants under low- and high chance conditions.



Panel A.



Panel B.

Nolte et al., 2008.

Figure 4. Relation between fatigue and effort (1) for people confronted with low- and higher difficulty challenges (panel A), and (2) for people confronted with low- and higher difficulty challenges under low- and high importance conditions (panel B).

The Natural Fatigue Study. Comprehension of our natural fatigue study [39] is facilitated by reflection on three points. First, our reasoning assumes that the proximal determinant of engagement is the subjective appraisal of task difficulty. Second, subjective difficulty appraisals are determined in part by the character of the challenge at hand and in part by the performer's perceived capacity to meet the challenge. Third, fatigue is only one factor that determines the perceived capacity to perform.

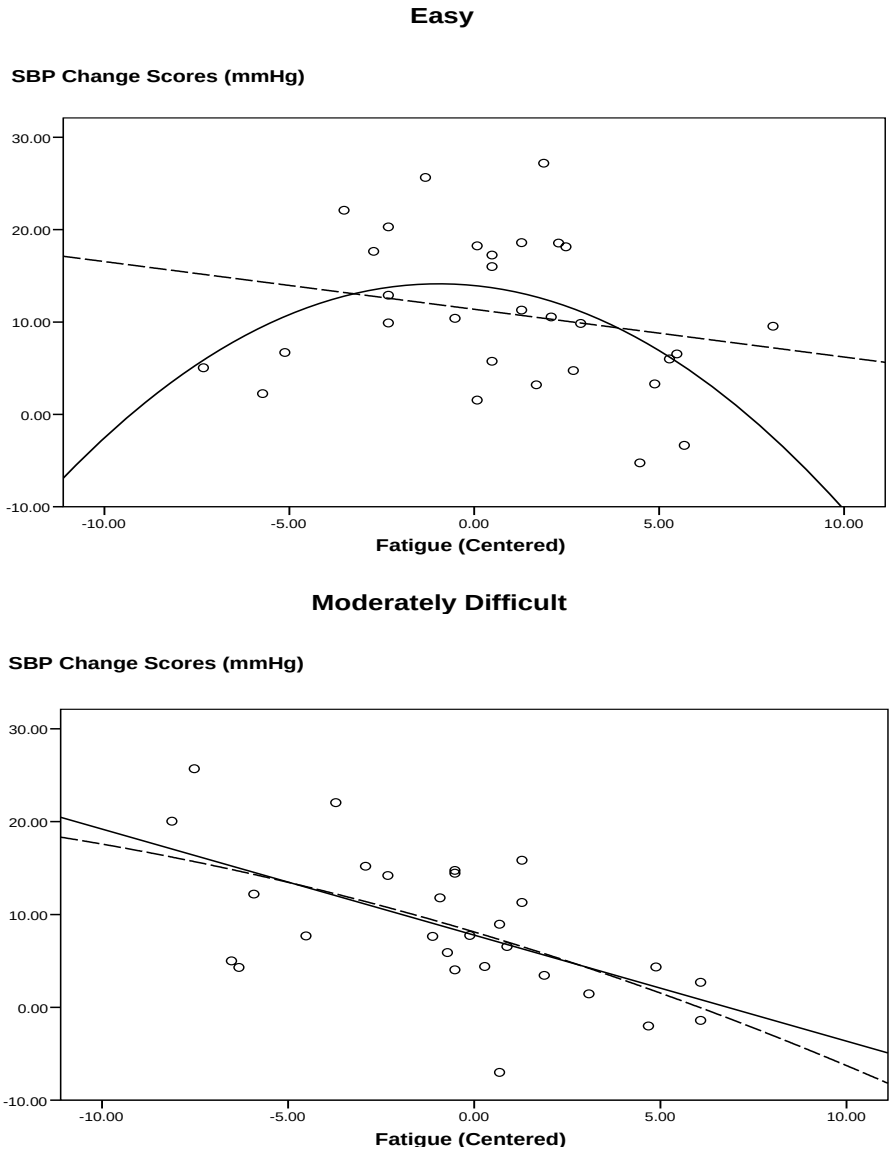
Because fatigue is just one personal determinant of difficulty, one can plot engagement against it directly, constructing different engagement functions for challenges low- and higher in (objective) difficulty. Inspection of such a figure (Figure 4, Panel A) shows that regardless of difficulty, engagement should first rise with fatigue and then drop. Inspection also shows that as fatigue rises, engagement should initially be higher for people confronted with more difficult challenges, then be lower for these people, and then be low for both difficulty groups. Still another indication is that so long as success is possible, success importance should determine the points at which low- and high difficulty groups withhold effort, with the groups withholding at higher fatigue levels if importance is high than if it is low. Of course, all of these relationships can be grasped through careful inspection of my original ability/effort figure (Figure 1). However, certain ones are more apparent when one takes this alternative visual perspective.

Our natural fatigue study was not designed with fatigue as a central focus. However, it included state fatigue measures and, thus, provided the opportunity to evaluate natural fatigue influence, construing fatigue as a continuous variable. The study also included more and less challenging performance conditions and consequently provided the opportunity to evaluate moderating effects of challenge difficulty. Participants were assigned two (easy condition) or six (moderately difficult condition) nonsense trigrams (i.e., meaningless three letter sequences) with instructions that they would earn a small chance of winning an inexpensive spiral notebook if they memorized them in two minutes. The chance of winning, given success, was 1 in 12 or about 8%. In combination with the modest value of the prize, this low chance should have caused participants to view success importance as low.

Prediction of continuous fatigue effects in a study of this type is no small task. Much should depend, for example, on the character of the fatigue distribution. However, if one assumes a full distribution and low importance appraisals, it is reasonable to expect effects along lines of those depicted under low importance conditions in the B panel of Figure 4. Specifically, it is reasonable to expect (a) Easy participants to show minimal CV responsiveness at the low end of the fatigue distribution followed by a rise in responsiveness to a point and then a decline, and (b) Moderately Difficult participants to show pronounced CV responses at the low end of the fatigue distribution followed by a decline. Considering the groups together, one should first find greater responsiveness for Moderately Difficult participants, then find greater responsiveness for Easy participants, then find low responsiveness for both.

With the preceding in mind, we examined relations among the fatigue, difficulty, and CV response variables using multiple regression procedures in which fatigue was represented as a continuous predictor and manipulated difficulty was represented as a two-level categorical predictor (using dummy codes). The panels in Figure 5 show that results for SBP were broadly consistent with the suggestions above. Analysis of the SBP data for Easy participants

yielded a reliable quadratic trend for fatigue; by contrast, analysis of the data for Moderately Difficult participants yielded a reliable linear trend for fatigue. Whereas responses for Easy participants first rose and then fell with fatigue, those for Moderately Difficult participants were pronounced at the lowest fatigue level and then declined. Considering the groups together, responsiveness was first greater for Moderately Difficult participants, then somewhat greater for the Easy participants, then low for both difficulty groups. Findings for DBP and, especially, MAP were similar to those for SBP.



Nolte et al., 2008.

Figure 5. Systolic blood pressure change scores as a function of (centered) fatigue under easy and moderately difficult task conditions. Functions depicted with solid lines are reliable at $p = .01$ (quadratic, easy condition) and $p = .002$ (linear, moderately difficult condition). Functions depicted with dashed lines do not approach significance.

Summary. To sum up, my students and I have carried out various studies in the past several years to examine directly fatigue implications of our ability analysis. The studies have not all generated interpretable findings. However, most have yielded findings compatible with the implications. Our studies have shown fatigue effects in response to both motor and cognitive challenges. They also have indicated that the effects (a) vary with difficulty, (b) are moderated by success importance under conditions where success is perceived to be possible, and (c) are in evidence when one measures fatigue as well as when one manipulates it. Our initial gripping study indicated that motor fatigue effects are – to a degree at least - challenge-specific. By contrast, our specificity studies involving mental challenges produced only fatigue main effects.

General Summary and Concluding Comments

A long-standing program of research in my laboratory has been concerned broadly with the determinants and CV consequences of task engagement. The program has examined CV response as an engagement outcome in part because CV responses are believed to be linked to negative health outcomes, including hypertension and heart disease. A persistent focus has been on the manner in which ability perceptions impact engagement and CV response outcomes and this has evolved recently into an interest in how fatigue impacts these outcomes.

Application of our ability reasoning to fatigue followed from the assumption that ability perceptions should decline to the degree that resources are depleted within a performance system. It implies broadly that fatigue (resource depletion) influence on engagement and CV response should depend on challenge difficulty. More specific implications are: (a) When fatigue causes success to appear impossible or excessively difficult, it should retard engagement and CV responsiveness; (b) When fatigue leaves unaltered a perception that success is possible and worthwhile, it should augment engagement and CV responsiveness; and (c) When fatigue leaves unaltered a perception that success is impossible or excessively difficult, it should have no impact on engagement and CV responsiveness. Indirect support for these implications comes from studies that have examined ability perception effects under different challenge difficulty conditions and borne out the assumed relations among ability perception, engagement, and CV response. Direct support comes from a set of fatigue studies my students and I have carried out in the past several years.

Fatigue and Health

An obvious suggestion from the ability and fatigue studies above is that fatigue could be instrumental in producing poor health outcomes under some performance conditions. That is, if chronically elevated CV responses are associated with undesirable endpoints such as hypertension and heart disease, it follows that fatigue could produce those endpoints under conditions where it augments CV responsivity. One of the values of our conceptual analysis is that it provides direction for anticipating what those conditions might be. In theory, they

should be conditions under which fatigued individuals are confronted with challenges that they can and will meet. The exact magnitude of CV responses in these circumstances should depend on the (objective) difficulty of the challenge at hand and the degree to which the fatigued individuals are depleted. The higher the difficulty level and the lower the level of performance resources, the harder the individuals should strive.

It might be argued that fatigue is of little concern from a health standpoint because people will tend to withdraw effort once they become fatigued. The problem with this view is that it fails to recognize that people do not always have the luxury of withdrawing effort or perhaps the wisdom to do so. Consider, for example, a single parent with a small child who must maintain his performance level at work despite extreme and persistent fatigue. Alternatively, consider an upwardly mobile administrator who sets increasingly difficult performance goals for herself despite the chronic fatigue that she experiences as a result of poor nutrition and sleep habits. To be sure, fatigue should sometimes be so compelling that it demands effort withdrawal. However, in many instances it will be below this threshold and merely amplify the effort that people expend.

Unresolved Issues

Although our fatigue studies have, to date, addressed a number of important issues, they have not addressed all issues conclusively. One issue that has not been addressed conclusively is whether mental fatigue effects are challenge-specific. Findings from our specificity studies involving mental challenges suggest that they are not. However, those studies included a limited number of challenges and depletion methods. They also may have included hidden confounds that blunted or blocked the emergence of challenge-specific outcomes. Thus, it is possible that specificity in some form will be documented in future investigations.

Another issue that has not been addressed conclusively pertains to the natural fatigue effects that we observed [39]. Careful review of the data in Figure 5 shows that they were broadly compatible with the fatigue implications, but not perfectly so. Engagement lines in the panels of Figure 4 suggest that CV responsiveness should have declined abruptly beyond certain fatigue levels (higher for Easy participants, lower for Moderately Difficult participants). However, the data show gradual declines following CV response peaks. It presently is not clear why declines associated with fatigue were gradual rather than abrupt and additional research attention is warranted.

Our fatigue studies also have not provided evidence relevant to all important fatigue questions that might be posed. An example here is the question of whether fatigue will impact engagement and associated CV responses when it leaves unaltered a perception that success is impossible or excessively difficult. A further, and in some ways more interesting, example is a question that has been raised increasingly in recent discussions of our fatigue work. The question is whether engagement and CV response outcomes follow from *perceptions* of ability or actual ability levels. My assumption for years has been that it is ability perceptions that are important and that actual ability levels are of concern only insofar as they impact those perceptions. However, it is possible that this is not always true.

Consider, for example, elderly people suffering from dementia. They could show compensatory engagement and CV response effects despite having limited or no awareness of their memory impairment.[2] Empirical investigation of this question would likely be difficult, in part because ability appraisals may sometimes be non-conscious or "implicit" [e.g., 40]. Nonetheless, it would be well justified in my opinion.

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2 I am grateful to Chris Stewart for drawing this case to my attention.

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Chapter 11

Indigenous Views of Heart, Health, and Disease: A Medical-Anthropological Study

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Abstract

Cardiovascular diseases are strongly linked to adverse lifestyle behaviors, psychosocial stress, and some mental disorders associated with modern Westernized societies. These diseases are accompanied by obesity, diabetes, and cancer in developing societies and among indigenous peoples "transitioning" into modern urban centers. This chapter explores pathogenic cultural influences which engender psychosocial dysfunction (e.g., chronic stress, constant time pressure, anxiety, depression, hopelessness) and increase cardiovascular disease and coronary artery disease risk factors (e.g., inactivity, unhealthy diet, tobacco use). Because overt signs of cardiovascular disease show up late—in advanced stages—and since research indicates that such degenerative disease first begins developing in adolescence, comprehensive prevention programs aimed at children and implemented at the national level are strongly advocated by the World Health Organization. To implement such programs at the national level is to engage in cultural change: therefore solid prevention planning can benefit from medical-anthropological and critical ethnographic investigation into the role of culture-syntonic (i.e., what seems normal but is pathogenic) influence on disease process in modern Western societies, bringing them into more explicit awareness and thereby rendering them culture-dystonic (i.e., perceived as pathogenic and needing to be changed).

Introduction and Plan

Medical anthropology is a multidisciplinary field examining the relationships between culture and healthcare systems, and the way disease is engendered, shaped, managed, diagnosed, and treated within a given society. This chapter will briefly review recent epidemiological data on cardiovascular disease in context with other non communicable diseases associated with modern Westernized societies (including "developing societies"), and then review the call for nationwide cardiovascular disease (CVD) prevention programs in light of recent research into the relationship between psychosocial factors in the pathogenesis of coronary artery disease (CAD). This will be followed by an ethnographic description of the conception of heart, health, and sickness in several indigenous societies in the Americas, in contrast to the biomedical understanding of the cardiac organ and in contrast to biomedical assumptions about the heart. The intention is to take a closer look at culture-syntonic sources of psychosocial stress within Western societies by looking at modern Western culture from an indigenous perspective. This ethnographic exposition will be followed by a "cultural diagnostic" involving four indigenous American healers from North, Central and South America who attempt to assess what they see as central pathogenic signs and factors within modern Western society, and in particular in the United States. The heart-based, instinctual-intuitive way of life of these indigenous peoples comes up against the modern Western way of life that has a number of features that are now found to be pathogenic psychosocial factors in cardiovascular disease. Finally we shall examine some of the cultural sectors where "risk factors" are identified: diet, exercise, and psychosocial factors making comparisons of indigenous diet and correlate physical activity levels, and reviewing the biomedical data on these indigenous (and hunter-gatherer) peoples.

Biomedical Context of Cardiovascular Disease and Culture

The rapidly increasing burden of non-communicable diseases such as CVD and CAD, cancer, diabetes, and obesity associated with the spread and development of modern Westernized societies is well documented by the World Health Organization (WHO). By 1999 60% of deaths in the world and 43% of the global burden of disease was accounted for by noncommunicable diseases. Of these, approximately half, 30%, are attributed to cardiovascular disease (CVD).The WHO projects that by 2020 the death rates will rise to 73% and the burden of disease to 60% [1]. Most Western countries face high and increasing rates of CVD, and each year heart disease kills more people in the USA than cancer. While in the USA and many European countries rates of death from CVD are still very high, there have been slightly declining deaths presumed as due to educational prevention programs and pharmacological and surgical methods of treatment: but the rates of death by CVD disease are sky rocketing in previously non-Westernized societies which are now considered "developing" [1, 2].

In China and India the burden of CVD is greater than in industrialized countries as a whole [1]. Indigenous non-western peoples from around the world rapidly begin showing a

rise in these non-communicable diseases once they enter the major urban centers and begin adopting Westernized life styles. Studies of enculturation and epidemiology in the USA show that Japanese immigrants who resist enculturation also resist these diseases, but those Japanese immigrants who thoroughly acculturate themselves develop the same rates of these noncommunicable diseases as the rest of the population [3]. This is evidence that there are cultural influences engendering life-style related risk factors.

An *American Heart Association* report by Rozanski, Blumenthal and Kaplan [4] in which 279 recent studies are reviewed, concludes there is clear and very convincing evidence that psychosocial factors contribute to the pathogenesis of CAD and cite evidence from 5 domains: 1) Depression, with its related symptoms of demoralized feelings, hopelessness, despair, discouragement, 2) Anxiety, with its associated hyperactive sympathetic nervous activity, and associated chronic and acute forms, 3) Personality Factors and Character Traits, citing Type A behavior with its time pressure, exaggerated commitment to work, aggressiveness, and particularly lethal risk factor: hostility involving anger, cynicism, and mistrust; 4) Social Isolation; and 5) Chronic Life Stress. Mechanisms underlying these relationships manifest either through modifiable risk behaviors such as poor diet, tobacco use, inactivity; or through direct pathophysiological mechanisms, such as platelet activation and neuroendocrine surges.

Extensive animal-model research (primate) establishes that chronic psychosocial stress leads to transient endothelial dysfunction and even necrosis associated with excessive sympathetic nervous system (SNS) activity, and exacerbation of coronary atherosclerosis. Animal model research (primate) also shows that psychosocial stress induces hypercortisolemia, excessive SNS adrenergic activation, and ovarian dysfunction in premenopausal women [5]. In animal models acute stress has been shown to increase a variety of physiological abnormalities including increases in platelet over-activity [6], and increases in blood viscosity through hemoconcentration, leading to vasoconstriction. [6] These studies suggest the strong pathogenic influence of acute and chronic stress.

Chronic hopelessness (including deep sadness and discouragement) has been linked to sudden cardiac death in observational and animal studies of males, and the experience of hopelessness has more than doubled the risk for CAD in men [7]. Anxiety, including panic reactions, has been linked to sudden cardiac death, but not to myocardial infarction [8].

The WHO proposes that because CVD begins early in life, prevention must begin early. The prevention proposal of the WHO cites the well known evidence that the major causal risk factors for CVD are also the same for other diseases associated with modern Western societies (diabetes type 2, obesity, osteoporosis, and cancer). The major three areas targeted are unhealthy diet, tobacco use, and insufficient physical activity. The Executive Board of the WHO documents the example of North Karelia, Finland, where the mortality rate of the 34-64 year old population was reduced by 73% over 25 years during a community based and national program [1]. It was concluded that more than half this decline could be accounted for in terms of dietary changes in the population [1]. Such studies are encouraging in showing that national programs of prevention can work. However, the WHO proposal for prevention does not address the culture-syntonic influences on lifestyles and behaviors that engender CVD risk and other non-communicable diseases in the first place. According to Rozanski, et.al. [4], psychosocial factors engendering unhealthy risk factors must be addressed.

Programs to eat right, stop smoking, and get sufficient exercise do not address the cultural influences in society that are giving rise to psychosocial pathologies and the closely related dangerous life-style choices. To open up research and inquiry into the role of culture in the formation of psychosocial risk behavior and CVD, leverage is needed to examine our own culture and assumptive world from without and thereby render unseen pathogenic influences as culture-dystonic. Only when seen culture-dystonically (i.e. as pathogenic rather than as normal) can prevention strategies to change those pathogenic influences become possible.

By "culture," in this study, we shall mean a system of symbols and norms that structure and guide the life of a society and its individual members, providing general images of the nature of life, and ideals of how it should be lived (including norms for dietary, social and hygienic behavior). From within the purview of medical anthropology, we add that each culture has an *assumptive world* not entirely conscious, shared by each member of the society, and that each culture has a way of establishing notions of health and sickness, and culture-specific modes of diagnosis and treatment rooted partly in natural observation, and partly in traditional norms, symbols, and values [9, 10]. Health care systems are rooted in the history of a people, its religions, rites, philosophies, and laws. Explanatory Models, (EMs) for diagnosing sickness and illness are shaped out of these cultural resources. [9,10]. One justification for anthropological and medical anthropological understanding is not to just enlarge the fields of human discourse, but to increase research into preventive and prevention program development via investigation into the cultural roots and shaping of illness and its care and possible prevention.

Indigenous American Conception of the Heart and Health

The indigenous peoples of North, Central, and South America include a multitude of tribes or nations, and these are part of a number of cultures and cultural systems that are quite diverse. It is difficult to specify shared beliefs and practices that apply to all or most of them. However, across cultural and linguistic boundaries there are certain shared assumptions and outlooks, particularly when it comes the nature of the human heart and the related conceptions of health and sickness.

The Indigenous Americans hold to a shared set of assumptions concerning the heart that has always included psychological functioning, in healthful and unhealthful forms. By "indigenous peoples" we mean a society and the culture of peoples native to a specific geography, such as the Alaskan Inuit, the Southwestern Pueblo, the Quechua (Kichwa) people of the high Andes in Ecuador. In their indigenous way of life, prior to any Western influence, they have lived in terms of the symbolic, normative, and spiritual traditions of their culture, generally in ways that are in instinctual and intuitive resonance with the surrounding landscapes on which they depend.

The conception of the heart in these cultures is two-fold. On the one hand there is recognition of the cardiac pumper at the center of the enclosed circulatory system. This physical center is seen as vital to the life of the body, and is taken up metaphorically in the mythologies and rites of some indigenous peoples, such that the "Great Spirit" which is the

source and dwells in the center of every creature in the cosmos [11]. Metaphorically, this cardiac pumper is sometimes referred to as the "heart drum", beating out the pulse of Earth Mother in all her creatures, human and non-human. A metaphor for happiness was considered a strong beating heart in Ojibway culture. However, this metaphoric understanding transfers meaning from the physiological cardiac pumper to a second kind of *central core*, which is understood without any mind-body dualism. This second kind of heart is experienced as present in the middle of the chest, and is closely related to the physical pumper. This "core of aliveness" carries much of the sense of the "psyche" in Western psychological idiom, but also the sense of it being the vital core of psychological life; a deep center of motivating energy, action and behavior.

As a *core of aliveness*, a healthy heart is one which is open, unguarded, and filled with vitality and spirit. This heart has powers of feeling and "perception", but it is not simply an emotional feeler. Although it includes emotions, it is viewed as possessing sentient, instinctual, and intuitive intelligence and percipience. To "know with the heart" is to know bodily, instinctually and intuitively and to feel that knowing concretely in the center of one's chest. This system contrasts with the psychological powers of the mind, which is viewed as the "thinker" that analyzes, plans, likes to solve problems, develop strategy, and so on. The mind is viewed as one kind of intelligence whose nourishing ground is the heart: a holistic, sentient, and instinctive intelligence of the body and of natural organisms.

The "intelligence of the heart" is considered more holistic and natural –an intelligence which in its operation is similar to the way roots know how to find a water source, and the way leaves know how to reach for and find sun light. In the indigenous view of the Americas, the heart, the "core of aliveness," is concerned with the quality, satisfaction, and purpose of one's life. In this cultural system, the direction for one's life cannot come from the mind, but must come from the heart. Once one has a vision and purpose for one's life clarified, through a rite of passage such as the Vision Quest, for example, the mind can help one figure out how to turn it into reality, remove obstacles, and so on. The mind is thus viewed as a partner of the heart --but to be in balance, the mind must become "servant" of the heart.

The normative life in indigenous American cultures, its ideal person, is one who lives from the heart, and the practice of doing so is often called the "path of the heart", and it is supported by the sacred traditions of the culture, and community. To live from the heart is to live vitally and freshly, open to the natural world and in tune with its cycles and seasons, in reciprocity with and care for the surrounding landscape and its variety of life forms. To live from the heart is to become a strong and individuated participant in the life of the community. Reciprocity is an ethical norm inculcating respect and care for "all my relations," known in the Lakotah language "*Mitakuye oyasin*". "All my relations" includes the mineral, plant, and animal peoples. "Peoples" is a term that gives equal dignity to other life forms, in the indigenous paradigm of the Lakota people.

From an early age, each person is encouraged to discover and get to know his or her own heart, and to use it for guiding their steps in living. The heart, as core of aliveness, comes equipped with its own natural and internal guidance system, or IGS. Attending inwardly in the middle of one's body --sometimes called "listening to the heart drum"-- one can notice visceral-instinctual stirrings, felt-sensings that in effect draw one toward or repel one away from something, for example, from some person, object, or course of action. In this way one

considers any course of action, any life choice from the vantage point of the heart's IGS. By trusting the instinctual wisdom of the IGS a person is enabled to walk a life-path that is naturally satisfying, even joyful.

A good path or life-course is considered any path in love, in work, and in service that "makes your heart beat strong" [12]. The health of a person is determined by indigenous healers of the Americas in terms of how well the individual is connected to and living from his or her own heart. Living from the heart, letting oneself live the life one's heart naturally draws one toward is considered "good medicine" in a cultural system that has a vastly expanded sense of "medicine" that makes for wellness. Anything that results in happiness, joy, or a sense of well being is considered "good medicine," and anything that results in unhappiness, continual stress, hopelessness, or selfishness is considered "bad medicine."

To not be able to live from one's heart is cause for great concern, as it can engender many forms of sickness and lead to death. The extensive ethnographic work on indigenous psychology by Hultkrantz documents widespread concepts correlating the heart and vital sprit or soul, and even locating them in the heart or identifying them as the heart amongst such native American cultures as the Cherokee, Paiute, Walapai, Tepehuano, the Naskapi of Labrador, Ute, and Pueblo peoples of the southwest [13]. The individual's everyday biological and social existence is believed to be powered by and given quality through a vital spirit or inner soul or psyche. An individual is considered vital, spirit-full or soul-full when he or she is connected to and living from the heart.

Through a variety of forms of physical or emotional trauma or shock it is believed this inner "vital soul" or "free soul" can leave the person [13, 14]. In such cases biological and even social life goes on, but the person's vitality is lacking. To translate this across cultures and into our modern cultural idiom, this condition is like the person whose spirit is broken, who *raison d'etre* is lost, who feels dead inside, who goes about the business of living, but without any real vigor or fire within. In short it is a condition that might be variously described, depending on the actual symptoms, as dysthymia, depression, dissociation, anxiety, or chronic grief, despair, hopelessness, or anomic mourning.

It is worth noting, here, that the cardiac pumper and the heart as core of aliveness are very intimately related in the indigenous American conception. Emotionally or psychologically devastating events caused by traumatic accidents such as the death of a loved one, love-sickness (broken heart), amongst other psychosocial traumata, are widely believed, by indigenous American healers, to be able cause cardiac death and thus cessation of biological life [13]. From the perspective of biomedical research one is reminded of correlate studies of sudden cardiac death associated with hopelessness, in animal studies and human observation [15] and with anxiety [16].

In Native North America, prior to its devastation by Euro-colonialism, ethnographic archives report Native American populations as healthy, with rare obesity or dental caries observed, and few of the "white man's" diseases [17, 18]. With the destruction of North American cultures and the assimilation of their peoples into the modern Western culture, anomic devastation leading to depression, alcoholism, high suicide rates and obesity are now well documented [19, 20]. In Central and South America some still intact indigenous cultures are vital and not yet assimilated into the modern Western culture, but are aware of it and tribal elders feel threatened by it for the sake of the physical, emotional and spiritual health of

their people, as well as their cultural integrity. As younger members of the Kichwa and Qero tribes of Ecuador and Peru abandon their mountain culture and move towards the urban centers, they begin developing, as elsewhere in the world, many of the diseases associated with the psychosocial and dietary problems of Westernized urban living-- at an alarming rate and disproportionate share of the burden of CVD. It is from within the context of the indigenous American vantage-point that listening openly to the impressions of several indigenous healers on modern Western society can be revealing.

A Contemporary Mayan Diagnostic Observation

When indigenous healers have described their views of modern Western civilization, it has often been with diagnostic eye for the condition of the heart, the core of aliveness. Perkins [21] reports that when the Mayan Elder Candelaria was a child she often dreamed of visiting the USA. When she finally had the opportunity as an adult, she was surprised to find it was quite different than she had imagined. She reported that the buildings were bigger, the stores more opulent and the material possessions, the sheer number of cars a family owned exceeded her wildest expectations. But she was deeply struck by the level of unhappiness she saw everywhere around her. With all this material wealth, she expected to see more happiness. *"Where are the laughing children working side by side with their mothers and fathers?"* [21]. And then she laid her finger on what she saw as a central cause of the unhappiness she saw: *"My people have a saying that a person's wealth is not measured by the amount of corn in the his field, but by the amount of sunshine in his heart"* [21].

A Pueblo Cultural Dianostic

In the 1920s CG Jung [22] began his ethnopsychological investigations in Africa, India, and in the Southwestern USA in order to find a leverage point for seeing more clearly the psycho-cultural features of European civilization that were invisible to him. He interviewed the Taos Pueblo medicine man Ochwiay Biano and inquired into his perspective on the "white man" [22].

Ochwiay Biano reported to Jung that the white man seemed quite mad to the Pueblos. When Jung inquired why they thought this, Biano said that the white man looked tense, restless, his jaws tight, his eyes always searching, but never knowing what they want. When Jung inquired of the Pueblo medicine man why he thought the whites were this way, he said it was because they "think with the head [meaning the mind]. Jung said, "Why of course, what do you think with?" and Biano pointed to the middle of his chest, indicating the heart [22]. Jung felt immediately that he had gotten the leverage of culture-dystonic insight he sought into his own civilization. Jung struggled to find words for this insight, but was flooded with images which circumscribed it.

> This Indian had struck a vulnerable spot, unveiled a truth to which we are blind. I felt rising within me like a shapeless mist something unknown and yet deeply familiar. And

> out of this mist, image upon image detached itself: first Roman legions smashing into the cities of Gaul. ….I saw the Roman eagle on the North Sea and on the banks of the White Niles. Then I saw St. Augustine transmitting the Christian creed to Britons on the tips of Roman lances, and Charlemagne's most glorious forced conversions of the heathen; then the pillaging and murdering bands of the Crusading armies.
>
> ….It was enough. What we from our point of view call colonization, missions to the heathen, spread of civilization, etc., has another face—the face of a bird of prey seeking with cruel intentness for distant quarry—a face worthy of a race of pirates and highway men. All the eagles and other predatory creatures that adorn our coat of arms seem to me apt psychological representatives of our true nature [22].

Biano's view that the white man lives by his great intellectual powers but no longer knows about the bodily felt and instinctual knowing of the heart [core of aliveness] is interpretively elaborated by Jung. He did not find it easy to hear, but he felt immediately that a pathogenic "blind spot" (i.e., a culture-syntonic factor) within Western culture had been identified by this old medicine man. Biano's "diagnostic impressions" refer to the effect that this primarily mind-centered way of living is disconnected from heart, body, earth, community and respect for others (human and non-human others). These characteristics in turn engender signs of unhealth in the white man: restless stress, greedy and aggressive searching for more and more, pressured by artificial clocks and ignoring natural rhythms and cycles of nature.

Jung's reflections about the Romans and the great Conquerers and Explorers can be equally difficult to listen too, for seeing our blind spots is generally emotionally painful and can be humiliating. But Jung believed the honest observations were, like empirical facts, ultimately friendly. He expressed gratitude for the way Biano had provided leverage for understanding a sector of problematic ideals and values (and thus of behavioral motives) within Western culture: driven by greed to domination, conquest, and violence against other peoples and other life forms. Correlating these observations with recent Western medical research we can note several of the CAD psychosocial risk factors are pinpointed right here within the cultural characteristics just noted: anxiety, social isolation, chronic stress, and hostility [1, 4, 5].

A Sioux Cultural Diagnostic

Erdoes [23] documents the assessment of the Sioux medicine man and holy man John Fire Lame Deer. Lame Deer felt that the "white man" does not typically live by earth-honoring values, does not develop beliefs from his own direct experience, doesn't listen to his own heart, and so does not know how to be in balance with things. Lame Deer, speaking in the spiritual idiom of his culture says:

> They have forgotten the secret knowledge of their bodies, their senses, their dreams. They don't use the knowledge the spirit has put in every one of them [i.e., in the heart].They are not even aware of this, and so they stumble along blindly on the road to nowhere—a paved highway which they themselves bull doze and make smooth so that

> they can get faster to the big empty hole which they will find at the end, waiting to swallow them [23].

This brief excerpt of a large ethnographic report may be especially hard to openly consider because it is also conveys a rather strong criticism borne by a Lakota Elder who has seen his own culture and people devastated by American colonialism and a history of broken treaties. Yet underneath this understandable layer of outrage is a sincere effort to speak honestly about what he sees as pathogenic in modern American society, and the effects on human life. From within his Lakota context (earth-honoring, heart centered and trusting of the wisdom of the body) the modern emphasis upon the use of the mind to bulldoze forests and grasslands, and pave them over with asphalt, build strip malls, devastate the ecosystem and myriad forms of life. This is not only believed to be a sacrilege, it is perceived as unhealthy for humans as it cuts us off from the elemental resources of the natural landscape that sustain, nourish, and provide "medicine" for our lives. Living without being in close contact and in accord *with* the natural world is considered by indigenous Americans to be the end of *living*, and the beginning of *existing*.

A Quechua Iachak's Disagnosis and Remedy

Smith [24] documents the theory and practice of the Quechua healer don Alverto Taxo, a contemporary Taita Iachak [shaman and elder] of the Atis Quechua (Kichwa) tribe. Don Alverto's reputation as a great healer stretches throughout Ecuador, Columbia, Peru and Brazil; he was elected a master shaman by the Shamanic Council of South America in 1989. He currently lives in the high Andes of Ecuador, in the Mount Cotopaxi region. Commissioned by the six million member Quechua tribe, he has been traveling back and forth between North and South America for nearly a decade, teaching from his tradition and healing wisdom at Harvard, University of Michigan, University of Notre Dame, and various inter-cultural exchange centers in the USA and Canada.

His reason for teaching in North America is because many of his tribe are still living their traditional and earth-honoring way of life, but he and his shamanic peers believe this situation will not last long, and the devastation currently going in with the widespread slash and burn economics of rain forests, and the encroachment of Western civilization in the urban centers of Ecuador and surrounding countries is bringing Western civilization's beneficial technologies, but also its stresses, diseases, and problematic environmental policies as well as a primarily mind-centered, heart-ignoring psychology.

His "diagnosis" of the industrial and technological North [by which he means Western civilization] is that it is over-developed mentally and under-developed feelingly. By "feeling" he doesn't simply mean emotion, although that is part of the human "capacity to feel". He means heart-open sentient perception, instinctual knowing, intuitive knowing, holistic sensing. He and his people symbolize the powers of the mind by the "Eagle," and the powers of feeling, of the heart, by the "Condor". They must "fly together to be in balance," he says [24].

The Condor, symbolically speaking, is considered a “bird of the South” [non-Western indigenous peoples]. Literally it eats carrion, and so is considered to be an environmental bird that helps clean up the environment —but it is not considered a prosperous bird, materialistically speaking. The Condor is also associated with the powers of the heart, and its prodigous “capacity to feel.” The Eagle, by contrast, is considered to be a “bird of the North,” meaning modern Western industrialized countries, symbolically associated with aggressiveness and materialistic concerns. It is also associated with the powers of the mind [i.e., the “intellect’], its capacity to create science and technology, the important capacities to analyze data and plan and theorize. The Eagle can also be quite prosperous, economically speaking but without the Condor and its capacity to feel, the quest for prosperity can result in damage to all the earth’s living beings, human and non-human.

In don Alverto Taxo’s view, neither power in itself is good or bad. He admits that the indigenous people of Ecuador need to study and learn more about the power of the Eagle. The Quechua people he says are quite happy and celebrate life, often giving thanks for the beauty and sheer goodness of life. He does not make claims that they never get sick. In fact, as healer he is well aware that his people can get out of balance, become depressed, anxious, as well as suffer from accidents and infections just like other peoples. He claims the conditions of life are hard economically and this can be frustrating. He is aware that Quechua people can suffer from a heart diseases (cardiac) related to dental caries, especially when teeth become infected (there is virtually no modern dental care in the High Andes). However, he claims the Quechua are a vibrant and spirited people and are in good health and marvelously resistant to sickness where they stay in balance and practice their indigenous ways of life, --and especially where they are not yet assimilating into the larger urbanized centers. Because the material conditions of life are difficult, and he feels his people now need access to the Internet and many of the educational, scientific and technological resources so plentiful in “the land of Eagles.”

When he turns a diagnostic eye toward the industrial North he says that there is great stress and widespread unhappiness in spite of all the wealth and technological conveniences. The people of the North have tremendously developed the powers of the mind, the thinker, but they need more development of the capacity to feel, because their hearts are not open and connected to the natural rhythms, the cycles and seasons. They do not know how to use the intelligence of the heart [24]. It is the heart which tells you what kind of life you most deeply want, and inspires you to live in a way that is natural to you. The mind (Eagle) cannot tell you this. The heart (Condor) is what gives you the calling, vision, or purpose for your life. Only following the leading of the heart can make you happy and help you know what is right for you. The mind’s job is to further clarify that, and help you plan, strategize, remove obstacles and make it happen. To be in balance the mind and heart, Eagle and Condor must be in right relationship, with the mind as the servant of the heart. In this way they can fly together so we can be in balance [24].

A feature of don Alverto’s cultural diagnostic of the “Land of Eagles” is that people become slaves to time pressure, and particularly have a conception of time that is artificial and not natural. It lacks the pulse, rhythm, and ripening of things in its own time quality. People are forced to live and move via imposed schedules that are not natural (i.e. they do not follow natural rhythms and cycles). He has found marriages suffering because work

schedules do not permit quality relationship/connection time. He finds it odd that some couples schedule sex and romance for a designated night of the week. In his culture he says, you make love when the spirit arises and both of you are feeling romantic. In Ecuador, he says, we eat when we are hungry, not because a clock strikes noon [24]. He claims that people of the North do not eat instinctually, when the body says its hungry. They do not pay attention in a fine discriminating way to what they are hungry for. In discussing the natural way to eat he mentions arranging the size of the meal to fit the energy expenditure levels of the day. In the morning eating a big meal makes sense to "power you up for the day." The midday meal should be off lesser size, and the evening meal should be quite small because he believes it will interfere with sleep and cause obesity and other health problems if you power your body with a large meal it cannot use.

Another kind of stress-causing pattern that he sees is the ceaseless wanting and self-doubt. "The mind", he insists, always wants to be kept busy, and when disconnected from the heart "drives you to want this and that, and it never is satisfied that it has enough of what it wants. It says you need more things to be happy, or more information. But its not true. You have everything you need to be happy if you open your heart in the moment and connect with whatever is before you, in the now. The mind is always telling you that you need more this or that before you can really live. But this is not true and the heart knows better, if it is listened to" [24].

Don Alverto does not only offer us a diagnosis of Western culture, he offers some therapeutic prescriptions as well. For the Kichwa peoples, as for indigenous peoples of the Americas generally, the Four Elements, Earth, Wind, Fire, and Water are celebrated as the simple and fundamental constituents of the world. To put yourself in balance, to create or maintain health, you must attune to these powerful elements of Nature. As a Iachak don Alverto advises us to begin spending time with each Element. He says you can spend time quieting the mind and just opening your heart and let yourself feel the wind blowing through your hair. You can watch the wind move in the tree tops, you can imagine it blowing through your hair and removing your stress. As it does this it helps calm and center you and put you back in balance. He encourages a simple practice of greeting each element, as if saying "Hello" to it with your heart. You can sit by a pond or river and let yourself feel the power of water to comfort and renew you. You can imagine that shower you take as cleansing away inside stress, letting go of cargo you no longer need. Sitting on the soil is very grounding, he says, and good for absorbing your stress. The "ceremony of eating slowly" while focusing attention on the taste of the food, and "feeling the love of the Earth Mother in the food" provides the most immediate connection to the Earth, and the awareness that "we are each Mother Earth walking" [24]. The element of Fire is also considered powerful because it relaxes, enchants, stirs the imagination, helps one center oneself and reflect naturally.

All these ways of connecting with the natural elements help to slow the mind, develop the capacity to feel, ease the stresses of living. They attune the person naturally, over time and practice, with the earth and landscape itself, its myriad life forms, its natural cycles and seasons. Living naturally is living healthfully in don Alverto's view. The tension and stress of living in the modern world, and the emotional and physical diseases associated with living in the Land of Eagles, can be greatly lessened if we can learn to live, breathe, eat, play, and create more connectedly to the heart and the natural environment [24, 25].

Hermeneutic Analysis

In order to translate these indigenous perspectives into our own modern cultural forms of understanding an interpretive analysis can be useful. The common thread running through this small qualitative sampling of four indigenous cultural diagnostic critiques of modern Western culture is the theme of mind (intellect) divorced from heart (core of aliveness) and the unfortunate effects this has in terms of personal stress and associated physical and psychological disorders, loss of truly supportive human community (isolation), damage to the environment, and so on. The indigenous conception of the "mind" views it as a psychological system that should be grounded in and synchronous with the psychological system associated with the more instinctual, intuitive, and holistic system of knowing and motivation of the heart (core of aliveness). In the indigenous view, the "mind" means more than the word "thinker" usually conveys in common modern usage. The "mind" being criticized is a psychological system that has its own kind of life and motivation when it is "disconnected" from the intuitive-instinctual-holistic psychology of the core. This mind, when cut off from its ground in the heart, is viewed as always wanting more and more. It is always wanting more knowledge, wanting more of whatever it focuses on, if it is money, then there is never enough, if it is sex, then it is never enough, if it is power or status, it is never enough.

This incessant wanting is believed to be the culprit resulting in many of the forms of sickness and disease that plague modern Western societies. The characteristics of this "mind" also include ongoing efforts to control and manipulate. Its capacity to reason and study in a rational manner is viewed by indigenous peoples as highly positive, but when the intellect is divorced from the core, it tends to control or dominate what does not come from within its own system. The feelings, the instincts, intuitions, tend to become repressed, dismissed, ignored, or viewed as irrelevant. In the indigenous view, the will to dominate becomes extended to nature, to other peoples, and is generally unhealthy for the human organism.

In the indigenous views presented here, the mind is not viewed as the cause of stress and resulting sickness. On the contrary it is typical for indigenous American peoples to admire the powers of the mind, particularly the intellect, and many of the good scientific and technological achievements of Western civilization that result from its high development. Don Alverto Taxo views the Internet, for example, as a real advantage, and many of the modern medical treatments are viewed as real triumphs of the mind [24]. What is considered the problem is the over-reliance on the mind when it is effectively cut off from its embodied and grounding core, the heart of the indigenous perspective.

It can be clarifying to compare the indigenous diagnostic idiom with analogous criticism coming within the modern idiom of Western society itself. The term "ego" can refer to ego-functions, that is rational and cognitive functions associated with reality-testing. These mental functions are analogous to the indigenous conception of mind and are an extremely important human capacity. On the indigenous view, "having a good head on the shoulders" is analogous to having good ego-functions. But "ego" carries another meaning, associated self-conception and ego-identity. This is the sense of "ego" can be amplified in a modern Western idiom where the indigenous critique is focused.

Psychologically speaking, the "ego" is a *concept of self* that is identified with early in life and reinforced by society and its' ideals and range of roles, functions, rewards and sanctions.

As an individual grows up within Western society, a mental concept is formed of "who I am" based on personal biographical and cultural conditioning. This concept of self is a kind of phantom, an abstraction of the complexity, and a reduction of the inexhaustible depth, and richness of a human life. We come to identify our *being* with this abstraction of the mind, at considerable cost to our bodily sensed comfort (the "feel" of *organismic rightness*) and depth of satisfaction in living. Since it is an ego-identification and not the real being of the person, this "egological self" always experiences itself as lacking and seeks to acquire what it lacks so that it can be satisfied, but it never feels satisfied because it always experiences itself as lacking. It does not turn to its own inward core to find what it seeks, but rather turns outward to external and social sources to acquire possessions which strengthen its ever-wanting sense of self. However, no possession seems to satisfy beyond a fleeting moment of acquisition. Hence the desire for more and more is set in motion. The indigenous viewpoint presented in this chapter can be considered more "being-oriented," and modern Western culture as more "having-oriented [26].

The ego, constantly searching for more and more things or qualities to identify with, seeks to promote itself and defend itself; seeks to conform and to avoid being judged by others. It enhances its sense of self through its identifications with a variety of external sources: possessions and money, the kind of work you do, the level of social status or recognition attained, the level of education, the degree of physical attractiveness, and various roles and functions (e.g. teacher, parent, entrepreneur, executive, etc.) and so on. As don Alverto Taxo says, "None of this is you!" It's all external goods and qualities. They may be of great personal and social value, but they may also be acquired at the expense of health and at cost to others. Ultimately they are transient and can be lost through misfortune or natural causes such as sickness, old age, and death. Such forms of self-affirmation are thus viewed as highly unstable and superficial. The indigenous prescription is not to base your value or fulfillment upon your possessions (*What* you *have*) but on your *being* (*Who* you authentically *are*). From the indigenous American perspective, it is only by living from the heart, with mind as its servant, that it becomes possible to find and experience this value and fulfillment.

This comparison of the indigenous idiom with a modern Western idiom should not mislead us into thinking that the Ego is the main focus of the diagnostic of the indigenous healers presented here. As such, the Western critique of the ego does not go deep enough. The ego is a product of the mind in its disconnection from the embodied heart (core of aliveness). In this disconnection from the core the person then identifies with a mental concept, the concept of the self, and this leads to a suppression of the body, and of its instinctual ad intuitive wisdom. People then begin to live ways that are out of balance, causing stresses and developing modifiable stress-based risk behaviors that give rise to illness.

Indigenous Lifestyle Factors

In the remainder of our discussion we shall shift away from the articulation of the indigenous paradigm cast in terms of the heart/mind and look at other pertinent dimensions of indigenous life, including patterns of diet and exercise as well as social dimensions not yet

included in our discussion. We will primarily focus on one specific subset of indigenous peoples—contemporary hunter-gatherers—as their way of life closely parallels that of our early ancestors during the 800,000 or more years of our evolution prior to the agricultural revolution 10,000 years ago (actually quite recent in evolutionary terms).

It has been said that to grasp the concept of 'low risk' and to apply it successfully in medical care and public health is to 'reach for the jugular' of the CVD-CAD epidemic [27]. The degenerative diseases of the industrialized world are rare or nonexistent among hunter-gatherers and other indigenous people who have not yet adopted Western diets and lifestyles [28].

> Comparative study suggests that the relative absence of modern "degenerative" diseases (heart disease, cancers, hypertension, diabetes, bowel disorders) reported among the San [of the Kalahari] is universal (or nearly so) among hunter-gatherers and subsistence farmers alike. Reports from a number of groups suggest that high serum cholesterol is extremely rare in such groups. Blood pressure is commonly low in such groups and does not increase with age, and widespread reports suggest that such intestinal disorders as appendicitis, diverticulosis, and bowel cancer are rare until groups are introduced to civilized diets. Diabetes mellitus is rarely observed--but becomes quite common among such populations introduced to civilized diets. Coronary heart disease and most cancers have been observed to be comparatively rare [28].

Accordingly, it may be useful to look at hunter-gatherer and indigenous lifeways for clues as to why this may be the case.

Western degenerative diseases have been shown to have a genetic component; our human bodies evolved over eons to 'expect' a specific set of conditions in order to thrive, just as is the case with other animals. Present hunter-gatherer peoples afford us a precious opportunity to look at these conditions in some detail. Their lifeways are not identical with those of our remote forebears, but the archeological record shows that they are very close.

In particular, these six points may be suggestive:

1. Evidence links a high dietary intake of protective phytochemicals [29] from various sources with a reduced incidence of coronary heart disease [30] and other Western degenerative diseases. This may partially explain why hunter-gatherer and indigenous diets are so uniformly healthful. Though these diets vary greatly in terms of what is eaten, including relative proportions and kinds of fat, protein, and carbohydrates [31], a common factor among them is a high level of phytochemicals [32] -as well as potassium and other micronutrients readily found in fruits and vegetables.

Most often phytochemicals are ingested by eating the plants themselves; however, in some instances of indigenous diet they are (or were) acquired indirectly, via animal products which are sources of them. This was traditionally seen in areas with short growing seasons and long winters. Examples of this are the red pigment astaxanthan acquired by indigenous circumpolar peoples from wild salmon (which get it from krill); the deep yellow and gold of traditional Swiss cheese made from the milk of cows and goats grazing in the high pastures of the Alps [33]; and the reindeer milk (mixed with greens and then stored through the winter) which the Saami of the circumpolar regions traditionally used. Circumpolar peoples also ate the stomach contents of the caribou:

> The lack of greens in the diet seems like an insurmountable problem to someone brought up in the south, but a surprising number of vitamins are present in parts of the animals that make up the traditional Inuit diet. Caribou liver, muktuk, and seal fat and liver provide vitamins A, B, C, and D. Polar bear liver has vitamin A at levels that are toxic to humans. Traditionally the stomach contents of a slaughtered caribou were eaten, we well as its flesh. In this way the reindeer moss, arctic moss, liver wort and red mushrooms consumed by caribou are "cooked" by its digestive juices. [34]

Thus, even in cultures where long winters precluded the eating of fresh fruits and vegetables for much of the year, there still was a dietary source of phytochemicals. Circumpolar peoples did eat plant phytochemicals in the brief summers: the Inuit gathered roots, greens, wild blueberries, crowberries, and salmonberries [35], and the Saami gathered wood sorrel, ancelica, cloudberries, lingonberries and bilberries [36].

Phytochemicals are often pigments [37], and this is not happenstance. A pigment is a substance that imparts color. Throughout the world, foods which we should eat are "pointed out" to us by nature (i.e. the substances are registered as 'colorful'). Our eyes draw us towards what is good for us. Examples of phytochemicals whose presence are signaled to us in this way are anthocyanins and betacyanins (red, blue, and purplish black); lycopene, and astaxanthan (red), beta-carotene and beta-cryptoxanthan (orange), lutein, zeaxanthan, and cucurmin (yellow).

It appears that the phytochemicals present in fruits and vegetables work synergistically rather than in isolation and it's best to eat them in whole food form where a variety are naturally present, rather than in the form of isolated extracts [38]. Of course they were *only* available in whole foods through most of history.

2. A refined sugar- and grain-based diet displaces phytonutrients; important classes of phytonutrients are missing in refined sugar and grain. Partially this is due to the refining process; but even whole grains lack important pigment phytochemicals. When grains displace fruits and vegetables in the diet, the protection these pigments afford is lost. Grains, and legumes, may also more directly cause problems due to their lectin content which can affect leptons [39]. Grains *indirectly* consumed (via grain-fed meat) are also problematic, as animals fed grain produce a different less-favorable ratio of fats [40], and their milk no longer contains those phytochemicals which would have been present had the animals been eating plants instead of grain.

By definition, the original hunter-gatherer diets contained little or no grain, since grain-based diets depend on agriculture. Some horticultural peoples have kept what could be considered an 'original' diet- for example the Kitava of Papua New Guinea. The diets of the Kitavans are grain-and sugar-free, and among them Western degenerative diseases are rare or non-existent, leptin levels are low, and insulin sensitivity is high [41]. (The Kitavan diet can be considered 'original' because it consists of substantially the same foods that would have been gathered from the wild in that geographic region prior to any cultivation.)

3. Some hunter-gatherer and indigenous peoples have low salt intakes—and most eat more potassium than sodium due to the natural abundance of potassium in fruits and vegetables—in contrast to Western diets in which the reverse is generally the case. A study of the Yanomamo, who add no salt to their food, shows that they maintain a low blood pressure

which doesn't increase with aging [42]. It's also been shown that adding salt to the diet of chimpanzees increased blood pressure for some [43].

However, limiting salt intake is not recommended for all people (in fact it's contra-indicated during endurance athletic events particularly in high-heat conditions, and for pregnant women), and there is not an invariable pattern of salt intake which can be pointed to across indigenous cultures, as an evolutionary justification for one position or another. For instance, the Inuit people lived much of the year on coastal ice (which is partially desalinated sea water), and much of their food consisted of soup made with meat in a broth from this brackish source of water. When they went inland to hunt, they traditionally added caribou blood (also a rich source of sodium) to their soup [44].

4. The portion of our genome determining basic anatomy and physiology has remained unchanged for about 40,000 years. Thus, the relation between energy intake and outgo, and the *kinds* of physical activities which are most optimal for us, is substantially the same as it was for our remote ancestors. Since our ancestors were hunter-gatherers up to about 10,000 years ago (when agriculture began) it can be instructive to study present-day hunter-gatherers to see the physical activity patterns for which we were designed [45].

We have lost the intimate working-body relation with our food—we no longer have to *expend* energy in order to *ingest* each calorie. In contrast, hunter-gatherers walk to procure food, while carrying the food they gather, children, etc. Men typically hunt 1 to 4 days a week, with rest days intervening between hunting days; and women gather every 2 or 3 days on average. On days when they are not hunting and gathering, people engage in lighter physical activities such as butchering, preparing food, making clothing, fetching water and firewood, and moving camp. Dancing is also a common and frequent activity [46].

Aside from walking which is a prominent feature of much hunter-gatherer exercise, it also appears that the human body was well-designed for endurance running in the heat of the day: though much of our structure equally supports walking, aspects of the structure of the buttocks and legs appear to be specifically designed for running, and the lack of body hair plus the ability to sweat copiously makes it possible for human beings to run down animals which are bigger and faster, but which have to stop and rest and cannot sweat to shed heat [47].

This kind of hunting has been practiced up to the present, for instance by the G/wi of the Kalahari who will take off in the heat of the day in temperatures ranging from 102 to 107 Fahrenheit and track one animal for 5 or 6 hours, over 10 to 20 miles, until they run that one animal down and kill it [48]. Among the G/wi this kind of hunting nets large amounts of meat—twice as much as with bow and arrow—and is more often successful than bow hunting. It's a highly successful strategy for which we are well adapted.

5. Hunter-gatherers are also still entrained in a daily *rhythm* of eating which keeps leptin levels high during the latter part of the sleep cycle, encouraging fat stores to be burned from that point until the fast is next broken. Leptin levels follow a diurnal rhythm and are highest between midnight and early morning hours and lowest around noon to midafternoon in all individuals—but the difference between nocturnal and afternoon levels has been shown to be significantly greater in lean individuals than in the obese [49].

The diurnal rhythm is very sensitive to disruptions in meal times:

> Phase shifts in plasma leptin levels are apparent within hours of changing the meal pattern, and are not correlated with cortisol, which is a robust marker of the circadian clock. The diurnal variation is also not altered by acute sleep deprivation, and thus is not likely to be regulated by growth hormone or other sleep-related hormones. This study provides direct evidence that diurnal variation in plasma leptin levels is entrained to meal timing [50].

The Agta of the Philippines eat 3 meals a day: one early morning, one early afternoon, and one early evening [51]. But most commonly, hunter gatherers tend to eat one big meal a day, in the late afternoon to early evening [46]. There are variations—for instance, Ache men will sometimes eat leftovers in the morning before they leave on the hunt, or if they are out on a hunt for several days will eat some of the fresh kill; and Ache women will sometimes stay in camp all day and snack through the day—but the central pattern is of one big meal in early evening. This meal pattern in which the last (or only) meal of the day is no later than early evening reinforces the natural leptin diurnal rhythm.

This single-large-meal pattern is also consistent with research which shows that less-frequent meals positively affect the plasticity of the nervous system and its vulnerability to neurodegenerative disorders: periodic fasting such as is typical of hunter-gatherers has been shown to be even more effective than limited daily feeding, in increasing the expression of HSP-70 and neurotrophic factors of brains of mice, and is also more effective than limited daily feeding in protecting hippocampal neurons against excitotoxic injury. On the days the periodically-fasting mice had access to food, they consumed twice as much mice fed ad libitum. These periodically-fasting mice did not lose weight. Even so, they had favorable changes equal or greater to changes seen with reduced-calorie mice, including decreased plasma insulin and glucose levels. These findings suggest that increasing the time interval between meals to eat more as hunter-gatherers do may be beneficial, even when the size of the meals are increased to a level that results in no overall decrease in caloric intake [52].

6. For hunter-gatherers, life is *autonomous*, has *immediacy*, and is *shared*, in a band which is an intimate social group. This social form is part of our evolutionary heritage:

> Although there may have been occasional visits with neighboring groups and likely seasonal rendezvous with other bands, Paleolithic life would generally have been lived in one's small band…Judging from social patterns among other apes and the archeological sites of related hominids, some version of a small human band extends several million years into our deepest past.
>
> When we consider how profoundly persistent our evolutionary adaptations to that scale of sociality are, we can then realize that the larger tribal groups that arose in the Holocene constitute a major qualitative shift. Indeed, there were many *threshold* effects associated with this increase from Pleistocene numbers and scale…
>
> Whatever the myriad dynamics and events of the past 10,000 years, I contend that the essential outlines of human culture were critically shaped by Pleistocene norms and I include human sociality in that, quite aware that our sociality is an amalgam of biology and culture [53].

It's been shown that close social connections have an effect on heart health:

> Men who are socially isolated have elevated levels of a blood marker for inflammation that's linked to cardiovascular disease, according data from the Framingham Heart Study presented today at the American Heart Association's 45th Annual Conference on Cardiovascular Disease Epidemiology and Prevention.
>
> "Our analyses suggest that it may be good for the heart to be connected," said Eric B. Loucks, Ph.D., an instructor in the department of society, human development and health at Harvard School of Public Health in Boston. "In general, it seems to be good for health to have close friends and family, to be connected with community groups or religious organizations and to have a close partner" [54].

Among the Ache, well over half of the food eaten by every man, woman, and child, was given to them by someone else. Those who are most skilled in hunting consistently share the most and receive the least, and the households with the most dependents receive the most food –that is, sharing is not an exchange, nor is it tit-for-tat reciprocity [31].

Those who give the most food are making a valuable contribution to their communities; their lives have *meaning* and *value* within their communities. Aside from the already-mentioned benefits of intimate social connection, life meaning has also been shown to be inversely related to male and female oncological, female cardiovascular, and total premature mortality rates [55].

Conversely, those who *receive* food have received *social support*.

The sharing experienced by hunter-gatherer peoples is profound. Not only food is shared: in addition, they share "tasks, dwelling places, company, stories, and memories. In a word, they share "each other" [56].

Social support has been found to have a threefold effect on stressor-strain relations: reducing the strains experienced, mitigating perceived stressors, and moderating the stressor-strain relationship [57].

Two other universally described aspects of hunter-gatherer life are also pertinent in job-related factors affecting cardiovascular health: *autonomy* [56], and *immediacy* [56].

Part of the inverse social gradient in cardiovascular disease has been attributed to low job control at work [58]. It has been shown that mean plasma fibrinogen is adversely affected in jobs where workers have less autonomy [59]; Time urgency and impatience (TUI) has been shown to have a long-term effect on hypertension [60].

The experience of immediacy is not one which is familiar to all Westerners. It has been described thus:

> When I allow the past and the future to dissolve into the immediacy of the present moment, then the "present" expands to become an enveloping field of presence. And this presence, vibrant and alive, spontaneously assumes the precise shape and contour of the enveloping sensory landscape [61].

Time urgency and impatience is future rather than present-oriented, in contrast to the experience of immediacy in which one dwells in the present. It drops out immediate sensory experience rather than enhancing it. A high-time-pressure, low control work situation is the

opposite of the autonomy and immediacy experienced by hunter-gatherers in the course of their daily lives.

These 6 points have been developed separately, but in fact, hunter-gatherer and indigenous diet, exercise, sociality, etc. are in inextricably bound together—not isolated, but integrated dimensions of life—and as an undivided whole may well be found to be synergistic, just as the phytochemicals mentioned earlier work most effectively together rather than in isolation.

Some Implications for Comprehensive Prevention Planning

Our ethnographic sampling of informants who offered cultural diagnosis on what they see as stress provoking and disease engendering factors within modern Western culture agree that the central problem is that we, the societal members, do not "check in with" or take our bearings in living from our own *central core*, what they call the "heart" in distinction to the cardiac pump.

They are clear that the mental powers associated with the intellect are magnificently developed in Western civilization and bring many benefits to humanity. They are also clear that there is an over-reliance on the mental activity that we associate with self-concept formation and under-reliance on taking direction in living from the experiential core, and its more holistic, instinctual and intuitive forms of knowing. Consequently they see members of our modern culture identifying with a socially constructed mental self-concept that is imposed on the rich intricacy of the human organism. This imposition causes stress, or distress to the organism as a whole, as the executive sense of self is taken from identification with a mental conception and not from the central core of the person. The strive-drive, the wanting of more and more that is never satisfied, all this leads to stress, unhealthy lifestyle choices (risk factors) and subsequently to human health problems and environmental harm.

From all this we submit that a key pathogenic variable in modern Western culture is a lack of emphasis, encouragement and support from an early age in developing the capacity to find, know, and honor our experiential core, and to use our intellect in solid *connection* with it, so that we can think with and from the "heart", forming our concepts and taking bearings in our life from this inward source of holistic, instinctual-intuitive knowing. This would be mind and body, intellect and heart in concert, such that in any situation we could check in with our core, with the IGS, to determine a right way forward for us with any problem or stress that challenges us. A converse implications is that if we do not make this kind of shift we will most likely remain stuck with imposing of concepts, goals, and actions that are not healthful to our organism. We most likely will continue in our stress-engendering ways, and compensate with gratifications that are destructive to the organism as a whole.

The kind of culture-wide shift needed will require research and efforts beyond that of any given health care or human service profession (medicine, psychology, social work, education, pastoral ministry), for to be culture-wide it must work its way into all levels of society. It will require efforts of all professional disciplines concerned with health care, and more generally need support from other disciplines such as philosophy, the arts, religion, and the media. This

may sound like a daunting task, and it is, but it is also doable. Social reform movements, such as the American Civil Rights movement, the Women's Liberation movement, have gained considerable ground over the past four decades.

We do not, however, need to start from scratch in comprehensive prevention planning of this culture-wide scope. There is a substantial body of research into how to develop skill in the kind of experiential knowing [bodily felt, instinctual-intuitive] by checking in with the core of person and organism through a "felt-sense." A felt-sense occurs or forms at the mind/body interface, an experiential zone in which the body influences the mind, and the mind influences the body [62]. The process of how to form and consult a bodily felt sense by dropping attention into the middle zone of the chest and attending inwardly there has been developed by Eugene T. Gendlin and fellow researchers at the University of Chicago [63]. Hendriks documents more than 80 research studies on experiencing level and focusing skill, how to teach it to a variety of populations from childhood to old age, and its beneficial effects psychologically, educationally, physically, and spiritually [64]. This research has shown that the capacity to focus on a felt-sense is essential to psychotherapeutic success regardless of theoretical orientation, and has many benefits in a variety of areas such as stress management, creative problem resolution, educational problem resolution, relationship problems, and coping with pain in cancer patients [62]. Focusing skills training, because it can be taught to virtually anyone, and can be taught to children at home and in the class room, offers one viable key prevention strategy in bringing "heart" and "head," body and mind into harmonious balance.

Conclusion

To open up research and inquiry into the role of culture in the formation of psychosocial risk behavior (for CAD / CVD), leverage is needed to examine our own culture and assumptive world from without and thereby render the unrecognized pathogenic influences as culture-dystonic (pathogenic and needing to be changed). Only when seen culture-dystonically can preventive strategies to change those pathogenic cultural influences become possible.

For individuals growing up within Western society, a mental concept is formed of "who I am" based on personal biographical and cultural conditioning. This concept of self is a kind of phantom, an abstraction of the complexity, inexhaustible depth, and richness of a human life. Identifying our being with this abstraction of the mind, exacts a considerable cost to our bodily sensed comfort (the "feel" of organismic rightness) and depth of satisfaction in living.

The tension and stress of living in the modern world, and the associated emotional and physical diseases, can be greatly lessened if we can learn to live, breath, eat, play, and create more naturally.

The indigenous prescription is not to base our value or fulfillment upon possessions (What we have) but on our being (Who we really are). Living from the heart--with the mind as the heart's servant--it becomes possible to find and experience the value and fulfillment of our being.

Besides living from the heart, there are other psychosocial dimensions to the ways indigenous peoples can offer a West now looking for more natural and healthful cultural patterns. Especially among indigenous hunter-gatherer peoples, nearly-universal patterns of sharing, autonomy, and immediacy--as well as common patterns of diet and exercise--are much closer to the conditions which obtained during the period in which we evolved.

It is not possible to isolate just one 'key' factor which accounts for the significant degrees of absence of degenerative disease associated with modern Western culture among those indigenous (and hunter-gatherer) people still living traditionally: many factors operate together synergistically. The factors we have chosen to focus on here, are those which have clear links to Western biomedical research findings.

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Chapter 12

Coping with Psychosocial Stress Reflects in Changes in the Neuro-Endocrine and Cardiovascular Profile of Africans

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Abstract

Psychosocial stress experienced by Africans during urbanization is associated with socio-cultural disruption and concomitant increases in risk factors for non-communicable diseases. Social and psychological resources are necessary to successfully cope with transitional changes or demands. An innate ability to resist or cope with psychosocial stress/urbanization may be seen in the negative effect of stress in the body, i.e. psychological distress, hypertension and the physiological dissociation/habituation of a specific coping style.

Introduction

The South African Demographic and Health Survey indicated that hypertension and Type 2 diabetes in the black African population group was, and still is to date a major source of concern, especially when urbanized [1]. Lifestyle is related to cardiovascular diseases [2] and men [3, 4] in general are believed to be at greater risk for cardio-metabolic and renal diseases than age matched, pre-menopausal women [5]. These results emphasize the need for

scrutinizing lifestyle changes [5] and its influence on health contributing to the health burden and decreased quality of life of black South Africans. Seedat [6] indicated that poverty as a ”second-wave epidemic” is sweeping through Sub-Saharan Africa and social, economic and cultural factors impair the control of hypertension, diabetes, obesity, tobacco use and other risk factors for cardiovascular disease.

According to the Medical Research Report [1] no single outcome study of hypertension treatment in Africa has been done and the changes in lifestyle in urbanized communities needs much more study to identify an intervention/outcome programme [6].

History and Background (Africans Refer to Black Africans Unless Otherwise Indicated)

From previous studies on Venda- and Tswana-speaking Africans it was found that Africans [7-9] exhibit exaggerated cardiovascular reactivity and peripheral vascular resistance responses at rest and when exposed to stressful situations. These results were accentuated in urbanized individuals and they are, therefore, seemingly more prone to develop cardiovascular diseases and/or hypertension [10-11].

Sympathetic nervous system hyperactivity or early stages of neurogenic hypertension could contribute to the exhibition of excessive cardiometabolic risk factors like left ventricular and arteriolar hypertrophy, elevated hematocrit and increased turnover of platelets [2]. The high hematocrit is due to alpha-adrenergic venoconstriction and the platelet overactivity is associated with increased adrenalin levels [12]. Tachycardia, which is the hallmark of the hypersympathetic state in hypertension, increases the risk of cardiovascular mortality/morbidity [13]. Although black Africans have low renin values (14) the higher vascular and plasma renin reactivity in African men indicate increased sympathetic nervous system activity resulting in peripheral vascular hyperreactivity [7]. The sympathetic hyperreactivity indicated by higher renin activity will enhance angiotensin II production, which in turn causes increased sodium reabsorption, renal vasoconstriction and resulting decreased pressure-natriuresis and eventually increased blood pressure [15]. With increasing blood pressure levels the hemodynamic pattern changes from a high cardiac output to a high vascular resistance pattern. At later stages with increasing age, left ventricular hypertrophy could develop, which in turn would result in hypertension [16, 17]. A recent review by Hinderliter, and co-workers [10] found that African Americans of both sexes indeed have greater left ventricular wall thickness than Caucasians and that their greater peripheral vascular resistance may perhaps be due to structural changes in the peripheral vasculature. However, we do not know if this holds true for black Africans.

Additionally, Huisman, et al. [9] confirmed the findings of Malan, and co-workers [18] on the experiencing of more sympathetic nervous system activity or stress of Africans during urbanization. Huisman, et al. [9] showed that urbanization (as a psychosocial stressor) could cause decreased cortisol and testosterone levels in African women with a corresponding increase in cardiovascular reactivity and prevalence of hypertension. Recently, hypocortisolism and hypotestosteronism have been shown to occur during chronic or prolonged stress [19] and hypogonadism has also been associated with type 2 diabetes [20].

In Africans, the increasing levels of acquired immune deficiency syndrome (AIDS) infection [21], which is associated with the activation of inflammatory pathways in the vascular wall, could increase the risk and complications of atherosclerosis and related cardiovascular events [22]. Sung, et al. [23] demonstrated a significant positive correlation between sympathetic hyperactivity, pro-inflammatory and type 2 diabetes markers [23]. Elevated levels of inflammatory markers appear to be affiliated with hypertension with greater associations occurring among women of all ethnicities and especially black ethnic groups [24]. Freestone, et al. [25] also suggested that inflammatory markers activate the HPA axis and, therefore, plays an important role in the association between the inflammatory state and probably stress. The hyperreactivity profile of urbanized black Africans with their high hypertension prevalence [1] could, therefore, be further broadened by a possible link to changes in their inflammatory status.

It seems apparent that the process of increased stress exposure when chronically challenged will be endured with the resulting cost of a high allostatic load [26]. This process could be detrimental to the vascular health of Africans. Prolonged, uncontrollable physical/psychological stress might influence their coping ability in a physiological and/or psychological way [26]. When subjects are exposed to more chronic psychosocial stress, which interact with biological, behavioral and psychological risk factors, an elevated secretion of catecholamines may be implicated [27-29].

Cassel proposed a hypothesis termed “host resistance”, which states that every person is subjected to stressors and that illness is not dependent on these stressors, but rather on the person’s innate ability to resist or cope with these stressors [30]. During urbanization, Africans tend to move away from their collectivistic nature towards a more individualistic culture [31] and may therefore in the process lose some of their coping resources. Although the association between psychosocial stress, coping styles and cardiovascular effects in Africans have been indicated [7], the association between coping styles, the stress profile and cardiovascular function in Africans is not known. The stress profile can be interpreted by respectively viewing the stress hormone levels of cortisol, testosterone and prolactin.

Therefore, the general aim of this chapter is to indicate how stress hormone levels and cardiovascular function of urbanized Africans, who employ a specific coping style, differ from their rural counterparts’.

Neuro-Endocrine Activity, Coping, Stress Hormones and Cardiovascular Function in Urbanized Africans

Neuro-Endocrine Activity

Herd [32] indicated that the environment and previous experiences influence the behavioral reactions towards a stressor. In this behavioral reaction towards a stressor, three biological systems are of importance: neural, neuro-endocrine and neuroendocrine-immune reactions [26]. Neuro-endocrine activity, the so-called fight-or-flight reaction with activation of the peripheral sympathetic nervous system and the concomitant release of norepinephrine

and epinephrine from the adrenal medulla, promote the necessary adaptation in the face of a stressor [33]. The allostatic stress model posits that the body is able to maintain stability through change [26]. Prolonged exposure to stress may, however, lead to wear and tear of these controlling systems and the systems that first protected, now damages [26]. The two physiological systems that are especially of importance are the sympathetic adrenal medullary (SAM) and the hypothalamic pituitary adrenocortical (HPA) system. Helhammer, et al. [34] revealed that chronic stimulation of the SAM may contribute to the development of cardiovascular disease, while chronic stimulation of the HPA-axis may be associated with the metabolic changes that are related to an increased risk of cardiovascular disease.

Dysregulation of the HPA axis with decreased or habituated HPA responses can be caused by the cumulative burden of chronic environmental stress challenges [35]. A heightened sensitivity of the HPA negative feedback inhibition may appear with a down-regulation of hypothalamic-corticotrophic-factor receptors and decreased levels of cortisol [33, 36]. This may contribute to the development of a variety of illnesses including hypertension, metabolic syndrome and distress [12, 37].

Gerra, and co-workers [33] further hypothesized that these two systems may be two different physiological coping systems activated by different thresholds and features of stress. The SAM is non-specific, activated by all types of stress, while the HPA-axis is more specific and activated by aggression and defence reactions [33]. Selye's general adaptation syndrome theory postulates that prolonged, uncontrollable physical and/or psychological distress may also ultimately result in a state of exhaustion [38]. The exhaustion preceding cardiac events is the consequence of prolonged psychological distress [39]. Distressing situations e.g., those characterized by threat, lack of control and anticipation of aversive events are associated with an HPA axis deregulation [36]. The sympathetic nervous system - HPA axis interaction has been the topic of many studies, but according to Schommer, et al. [40] it is necessary to study the possible implications of the individuals' habituation profile in chronic stressful situations [41].

Christensen and Jensen [42] indicated that dysfunctional coping styles seem to be the culprit concerning the harmful effects of psychosocial stress, such as that associated with urbanization. It was indicated that a specific response to stress and the coping style employed may be more harmful to health than a hyperactive HPA-axis and concomitant hyper secretion of sympathoadrenocortotical hormones [42]. This observation was substantiated by Malan, et al. [7] who revealed the association between specific coping styles and different patterns of cardiovascular reactivity in urbanized Africans. Their findings showed that urbanized men and women revealed increased peripheral vascular α-adrenergic responses and greater hypertension prevalence rates when compared to rural men and women. Furthermore, these effects on peripheral vascular responses were found to be more prominent in active coping (AC) subjects [7]. Urbanization, as a psychosocial stressor can therefore elicit a certain stress experiencing pattern through the activation of neuron-endocrine systems. This stress pattern may, however, be greatly influenced by the individual's inherent ability to cope with the situation.

Coping and Coping Styles

Although the coping construct is commonly used in various disciplines, a number of definitions and conceptualizations thereof can be found in literature. This is mainly due to differing theoretical perspectives on the nature of coping. Various coping models and associated scales have subsequently been developed. [43-45].

Lazarus and Folkman [43] conceptualised coping as a continuous process that could be divided into the following three phases:

- primary appraisal, which involves the process of determining whether a situation poses a threat to the self;
- secondary appraisal, which is the process of determining if there is anything that can be done about the stressful event as well as thinking of possible responses towards this perceived threat;
- and coping, the process of executing the chosen response [43]. A person's choice of coping response (during the secondary appraisal phase) can influence the outcome of the coping process, which might in turn alter the perception of the situation as not as threatening and therefore, not as stressful [43].

Zeidner and Zaklofske [46] see coping as an active and conscious process which interacts with factors like personality and previous experiences of stress management. Factors that influence a person's coping ability are personality [47], reality perspective, skills, locus of control and cognitive styles [48]. If the individual experiences that the demands are more than the resources he/she possesses, the demands will be threatening to the psychological, physical and sociological equilibrium of the individual.

A further complicating factor in the conceptualization of the coping process is the existence of cross-cultural differences in coping that are often related to differing perspectives on the self. The self forms the basis of what the individual thinks, feels and does [31]. This involves among other things the relative importance of the individual-self versus social-self [44]. Because the self is socially constructed, it shows a large degree of cross-cultural variance, and could, therefore, lead to culturally determined ways of coping. In collectivistic groups for instance, the self is defined as part of the inner group. Independency in collectivistic groups (in Africans) means that the individual does not want to be a burden to his/her inner group [49]. Independency in individualistic cultures (in Caucasians) indicates a need in the individual to do his/her own thing [50].

Due to the relative lack of research on the idenfitication and classification of coping strategies characteristic of specific cultural groupings in the African context, classification systems that were developed from a western perspective are often applied in the African context. Literature surveys by Erickson, et al. [51], Holahan, et al. [52] as well as Schwarzer and Schwarzer [53] indicate the frequent use of two basic approaches to the classification of coping strategies. The first approach emphasizes the focus of individuals' activities in response to a stressor in order to determine the basic function of coping strategies employed. A good example of this approach would be the classification of coping strategies into categories of problem- and emotion-focused coping. The second approach emphasizes the method of coping, and classifies the individual's response to a stressor in terms of the basic

process that was followed during the coping process. A good example of this approach to coping would be the classification of coping responses into categories of active and passive coping. These two different coping classification systems will subsequently be discussed.

Problem-Focused and Emotion-Focused Coping

Problem-focused coping is a direct approach in the management of stressors, during which the individual strives to solve the problem. In contrast, emotion-focused coping could be elicited by situations in which the person has little or no control over the situation and is aimed at reducing or managing the emotions or distress associated with a situation [44].

In stressful situations, both types of coping are usually employed. Problem-focused coping predominates when a person feels that something constructive can be done to change the situation. On the other hand, emotion-focused coping predominates when the person experiences the situation as being out of control and that it should simply be endured [44]. Rueda and Perez-Garcia [54] indicated that the continuous use of emotion-focused coping strategies can, in the long-term, effectively decrease both psychological and physiological well-being. However, different situations require different coping styles. Magaya, et al. [55] indicated that Zimbabwean adolescents employed emotion-focused coping more often than problem-focused coping, and found that this type of coping style was not seen as a maladaptive form of functioning, as it effectively reduced the stress experience on the short term [55, 56]. It is only when emotion-focused coping and downplaying of the importance of a problem undermines the motivation to adopt a more strategic response to manage the stressor that it becomes maladaptive [56].

Active and Passive Coping

Henry, et al. [57] proposed a model in which the stress reaction is divided into a defence or active coping (AC) response and a defeat or passive coping response. According to literature during active coping a feeling of control is elicited and the influence of a beta-adrenergic vasodilatory activity ($ß_1$ and $ß_2$) is more pronounced e.g. increases in catecholamines and increasing blood pressure via central cardiac mechanisms with increases in cardiac output and stroke volume [27, 56-58]. Active coping involves either behavioral or psychological responses aimed at changing the nature of the stressor. Activities like planning; restraint and suppression of competing activities form an important part of the active coping process [44]. Using AC as coping strategy, social support is sought in helping to solve the problem. All other competitive activities are suppressed until all problems are solved successfully with perfect timing and control in the execution of planned actions. This is the most adaptive and constructive effort/strategy where a person tries to change a situation/behaviour of others or evaluate his/her own attitude and needs and accordingly develops skills and strategies [29]. AC shows a strong semblance to the problem-focused approach that was discussed in die previous section.

On the other hand, defeat or passive coping (PC) responses are avoidant by nature and are thought to be a psychological risk factor or marker for more adverse responses [59]. In many hypertensives an anger suppressing style is found, which may be part of a psychological profile that includes a lack of appropriate assertiveness. They also have a tendency toward greater interpersonal self-consciousness, anxiety and submissiveness [60].

The individual experiences a serious doubt that he/she will reach desired goals. This is a negative cycle and leads to hopelessness and helplessness [44]. Such emotional reactions could produce a decrease in ß-adrenergic activity with an increase in HPA-axis activity and behavioral inhibition [60].

PC is a less adaptive strategy with short-term consequences or situations that cannot be solved and are out of the individual's control. Ethnic groups with limited resources as well as increased cardiovascular reactivity and more effortful coping to stress have greater chances of developing cardiovascular dysfunction and/or hypertension [61]. In older individuals the use of more complex psychological processes and more coping strategies, especially passive coping strategies, are observed [62].

Here the influence of an alpha-adrenergic vasoconstrictory activity is more pronounced with smaller changes in catecholamine secretion. Blood pressure is elevated via vascular or peripheral mechanisms with increases in diastolic blood pressure and total peripheral resistance [28]. This passive form of coping, as termed by Lazarus and Folkman [43], is in certain ways closely associated with emotion-focused coping [44] that was discussed in the previous section.

The Stress Response

Selye's theory of the General Adaptation Syndrome divides the stress response into three separate stages [38]. The first stage is the 'alarm reaction', the classic fight-or-flight reaction in which the sympathetic nervous system (SNS) is immediately activated *(e.g. increases in catecholamines if exposed to a psychosocial stressor such as urbanization).* Thereafter, the 'stage of resistance' takes place, during which the HPA-axis is chronically activated (*e.g. increases in blood pressure and cortiso*l in an effort to cope with *lifestyle demands, less social support, technology).* Finally, the 'stage of exhaustion' takes place during which serious damage to organs and bodily systems occurs (*e.g. physiological dissociation of a coping style: vascular hyperreactivity, hypertension, psychological distress, and altered stress hormones).* The time-span between each of these stages may differ from individual to individual, dependent on the severity and duration of a specific situation, the person's own subjective appraisal of the situation, as well as individual biological differences [63].

a) The Alarm Reaction: Stimulation of the SNS during the alarm reaction leads to the release of epinephrine (E) and norepinephrine (NE) from the adrenal medulla. E has a stimulatory effect on the β-receptors and thereby increases heart rate, stroke volume and contractility [64]. Furthermore, E and the associated stimulation of the β-adrenergic receptors are associated with an active or 'defence' coping style [57, 63, 65].

A study by Ma and Morilak [66] indicated that the medial amygdala (MeA) plays a central role in the stress response, through the release of NE. The release of NE from the adrenal medulla leads to a cascade of physiological events. Firstly, NE activates α1-receptors which facilitate the stimulation of the HPA-axis with the concomitant release of corticotrophin releasing hormone (CRH) [66]. Secondly, Opie [64] elucidated the two-fold action of NE on the cardiovascular system. When NE binds to β-adrenergic receptors, it causes an increase in heart rate and contractility, with the binding of NE to α-adrenergic

receptors leading to an increase in peripheral vascular resistance [64]. Studies have further shown that the adoption of a more passive or 'defeat' coping style in handling a situation is associated with NE outflow [63].

b) The Stage of Resistance: The stress response is mediated by two components of the hypothalamus and the brainstem: the CRH-receptors and the locus coeruleus-norepinephrine/ sympathetic system [67]. The stage of resistance could imply increased activity of the CRH-receptors and the locus coeruleus-norepinephrine/sympathetic system with concomitant abnormal levels of cortisol and the accompanied effects on bodily systems [67]. Chronic stress induced by higher demands from the environment can, however, decrease the responsiveness of the HPA-axis and desensitize it, thereby leading to initial high levels of cortisol which stabilizes thereafter [41, 68].

c) Stage of Exhaustion: The stage of exhaustion phase preceding cardiac events could involve the consequences of prolonged psychological distress [39]. Psychological distress is characterized by a lack of energy, increased irritability and demoralization [69]. Subjects with a tendency to experience distress tend to reflect a chronic psychological condition and subjects who display the largest increase will then also be at increased risk for hypertension [37].

In severe and chronic stressful situations the HPA-axis might also even become hyporesponsive, which in turn can lead to hypocortisolism [70]. Huisman, et al. [9] emphasized this phenomenon in urbanized Africans where cortisol levels were found to be lower in the face of continuous stressful situations. This response could imitate the phase of exhaustion [63] and is supported by the findings of Malan, et al. [7]. Malan, et al. [7] found a dissociation/habituation of AC urbanized subjects' physiological responses in comparison to their rural counterparts where their responses resembled the PC urbanized subjects' physiological responses indicating a dissociation/habituation of certain physiological systems. It implies the following: AC rural Africans responded to a handgrip test with a more typical central cardiac ß-adrenergic reaction than their urbanized counterparts. All PC rural groups, AC and PC urbanized groups though showed a peripheral vascular α-adrenergic response with increases in total peripheral resistance, diastolic blood pressure and decreases in arterial compliance. This peripheral vascular effect was emphasized in the AC urbanized men and women and accentuates the observation that during urbanization, an atypical physiological AC cardiovascular reaction pattern occurs, which are contradictory to literature [57]. It appears that the cardiovascular responses of the urbanized AC men and women are dissociated from the "normal" typical AC physiological responses (ß-adrenergic) and are exhibited as typical PC physiological (α-adrenergic) responses. Heightened vascular reactivity responses have been associated with the development of hypertension [10] and, therefore, the urbanized AC groups with enhanced vascular reactivity are at larger risk. The reader must still be reminded that this happened in urbanized active coping Africans employing a behavioral active coping style [7].

During urbanization, Africans are moving away from their collectivistic nature towards a more individualistic culture [31] and may in the process sacrifice some important coping resources. Urbanized subjects encounter unchangeable stressors (e.g. urbanization) with high intensity and duration and this could be associated with habituation/adaptation of certain physiological systems. This process of changes could occur during uncontrollable

threats/situations because the body could not cope successfully with or adapt to the challenge [71]. Rapid sociocultural changes occurring during modernization or urbanization with resultant lower social support [30] lead to loss of cohesive group activities and achievements that promote a sense of stability and togetherness.

However, the stress response and the applictaion of different coping strategies in certain cultural settings is clearly a complex system which is, even now, not fully understood.

Stress Hormones

As discussed above, the HPA-axis is the controlling centre for endocrine activity in stressful situations [68, 72, 73]. The stress hormones under discussion are cortisol, testosterone and prolactin. Increases in cortisol levels are indicative of stress as cortisol levels could increase with the expectation of an oncoming stressful situation [74, 75]. Cortisol levels are furthermore also good indicators of hypo- or hyperactivity of the HPA-axis and could thereby also indicate the nature of the stressor exposed to [41, 76]. Testosterone levels on the other hand are a strong indication of an expectation of success [75] and can, therefore, provide valuable information regarding the expectancy and mindset of the individual within a specific situation. Prolactin is indicated as a stress hormone, as prolactin levels could be associated with a feeling of control [75] and this, in turn, can also be indicative of the mindset of the individual.

These stress hormones can, therefore, clearly indicate the activity and responses of the HPA-axis within the stress experience as well as the psychological responses involved. Each of these hormones will subsequently be discussed in detail to investigate each hormone's characteristics and function.

Cortisol

Cortisol is a glucocorticoid hormone secreted by the adrenal cortex, whose secretion is closely regulated by adrenocorticotrophic hormone (ACTH). Greenspan and Strewler [76] indicated that the circadian rhythm of ACTH secretion, responsiveness of the HPA-axis to stress and the feedback inhibition of cortisol through ACTH secretion, are all under neuroendocrine control. A study revealed that while the HPA-axis is not abnormally active during rest, it does, however, become hyperactive and it stimulates the release of cortisol with stimulation [77].

Cortisol enhances vascular reactivity in response to stimuli such as norepinephrine (NE) [78] and, therefore, has a permissive effect on the secretion of NE from the adrenal medulla. Ma and Morilak [66] further indicated the effect that NE has on cortisol secretion through stimulating CRH secretion, as discussed above. The effect that elevated cortisol levels have on the cardiovascular system can thereby be closely linked with the effects of NE on the cardiovascular system. Whitworth, and co-workers [79] substantiated this statement by elucidating the effects of cortisol on the cardiovascular system especially. They found that elevated levels of cortisol may be associated with hypertension through several mechanisms, including sodium retention, haemodynamic changes, hyperinsulemia, vascular responsiveness and increased sympathetic nervous system (SNS) activity.

Elevated cortisol levels can, therefore, be seen as a stress hormone marker associated with various damaging effects on the cardiovascular system. Malan, et al. [18] elucidated the

effect of cortisol further by attributing the adverse effects that stress, such as is caused by urbanization, has on health, to the increase in glucocorticoid hormones in chronic and acute stress situations. Huisman and co-workers [9] could, however, not substantiate this association in another subgroup of Africans, as cortisol levels were not associated with increases in blood pressure of vascular responsiveness. A possible explanation for this is given by Rosmond [67] who found that the chronic release of cortisol due to stress may have deleterious effects on health, through a dysregulated HPA-axis.

Abdominal obesity and metabolic syndrome patients showed sensitizations of the HPA axis [80]. Cortisol activates lipoprotein lipase, the gatekeeper of lipid accumulation in adipocytes [67]. Furthermore, cortisol in the presence of insulin inhibits the lipid mobilizing system. These events are mediated by the glucocorticoid receptors and the density of these receptors is higher in intra-abdominal areas and visceral rather than other fat depots. The activity of cortisol leading to an accumulation of fat will then be accentuated in this adipose tissue [77]. Available literature on the mechanisms of cortisol and especially HPA-axis activity in the face of a stressful situation, such as urbanization, is still contradictory.

An excess of body weight or increased abdominal fat has a consistent correlation with increased blood pressure. The risk for hypertension increases and is related to HPA axis dysregulation and insulin resistance [77, 81]. The risk of developing heart disease increases in women aged 45 – 54 years from 26% in the non-obese to 37% in the obese [82]. The association between blood pressure and body weight is at least as strong as that between blood pressure and age and is especially prominent in certain ethnic women [81], including African women [14]. Obesity is associated with increased intravascular volume and cardiac output, accompanied by inappropriately normal total peripheral resistance. Left ventricular hypertrophy is a consequence of a sustained pressure overload and is often associated with diastolic dysfunction [64] in African Americans [10].

Elfhag and Rossner [83] reviewed the literature on factors associated with weight-loss maintenance and weight regain. Poor coping and passive reactions to problems are seen as negative factors that may pose a risk for weight regain after dieting. Obesity is a complex matrix but abnormal eating behavior plus profiling of psychological correlates are suggested to improve the outcome of weight loss programmes in the prevention of lifestyle diseases [84].

Testosterone

Testosterone is part of the 19-carbon class of steroids, known as androgens. In men, it is secreted by the Leydig cells within the testes in response to stimulation by circulating luteinizing hormone (LH) [37]. The secretion of testosterone starts with the activation of the hypothalamus, which leads to the release of gonadotrophin-releasing hormone (GnRH). GnRH then circulates to the anterior pituitary where it stimulates the secretion of LH. LH is absorbed by the Leydig cells where it eventually leads to the secretion of androgens, and mainly testosterone [37]. In women, small amounts of androgens are secreted by the ovaries while larger amounts of androgens are secreted by the adrenal cortex under HPA-axis control [78]. The hypothalamus is, therefore, directly involved in the secretion of testosterone. Elman [85] found a negative correlation between testosterone and epinephrine levels with activation of the adrenomedullary hormonal system, leading to decreases in testosterone levels. Henry

[75]) substantiated this finding by indicating that increased testosterone levels can be associated with a feeling of control over the situation. Therefore, in stressful situations testosterone levels may decrease [86] yet with a feeling of control it will increase again.

The role testosterone might play in the development of hypertension was elucidated by Reckelhoff [87] who indicated that testosterone is known to increase blood pressure values in both men and women. Huisman and co-workers [9] found contradictory evidence in African women, where they indicated that testosterone correlated with compliance with low levels of testosterone, which is associated with increased vascular responsiveness.

From the above it follows that the effect testosterone has on cardiovascular and stress responses in men and women are still contradictory and complex concerning Africans.

Prolactin

Prolactin is a 198-amino-acid polypeptide that is secreted by the anterior pituitary [76]. One of its functions in women is to inhibit gonadotropin secretion and it has been shown that hyperprolactinemia leads to hypogonadism [76]. This finding was further substantiated by a study which revealed that high prolactin levels might indeed suppress testosterone levels in urbanized African men [9]. This interaction might, in turn, be associated with increases in vascular responsiveness in Africans [9].

The available research of prolactin and psychological responses is currently scarce and contradictory. An important function of prolactin within the stress response is its actions as a cortisol antagonist, which has a modulatory effect on the anti-inflammatory action of cortisol [88] and therefore, these actions indicate the severity of the stress experience.

Additionally, Henry [75] indicated that prolactin levels will increase as the perception of control over a situation decreases [86]. Prolactin secretion might be stimulated by neurotransmitters such as dopamine, serotonin and NE. Prolactin levels may therefore be indicative of the activity of the central dopaminergic system [89]. It can, therefore, be deduced that the HPA-axis also plays a role in the secretion of prolactin in stressful situations. Distal and his team [90], however, found that prolactin levels will increase initially, but not continually, in the face of a prolonged stressful situation.

The interpretation of prolactin levels is complex, but of importance as it may be indicative of a feeling of control or depression in the long run. Its effect on testosterone is also of importance to better understand the concomitant cardiovascular effects these hormones may have.

Stress Hormone Ratios

In Africans, Malan, and co-workers [18] found the relationship between endocrine activity and the emotional experience of stress to be very complex. Henry, et al. [57] indicated the association between a larger cortisol:testosterone ratio and a depressed state of mind. Malan, et al. [18] found this to be true in rural Africans, as they were subjectively experiencing the most stress in the experimental setup. The urbanized Africans showed a smaller resting cortisol:testosterone ratio, which in turn could be indicative of a lesser stress experience [18].

A larger cortisol:prolactin ratio (C:P) is suggestive of control over the situation, as Henry, et al. [57] indicated that a smaller C:P indicate a feeling of loss of control. In contrast

to this, a larger C:P might also indicate habituation of the HPA-axis with the concomitant decrease in cortisol secretion, as experienced during prolonged exposure to a stressful situation [41]. A further explanation for this phenomenon is given by Greenspan and Strewler [37] who indicated that cortisol is a prolactin antangonist and thereby effectively decreases prolactin levels. In the THUSA study (Transition and Health during Urbanization of South Africans) urbanized individuals revealed increased prolactin values with the urbanized men showing lower testosterone values compared to their rural counterparts [86]. Additionally, the urbanized men revealed significant differences regarding the stress hormone ratios with smaller C:P and larger C:T than rural men. When adding coping styles, it was clearer that the urbanized AC men revealed the poorer cardiovascular and endocrine pattern, with higher blood pressure values as well as higher prolactin and lower testosterone values coupled to a larger C:P ratio. It, therefore, seems that it is indeed the AC urbanized men revealing a greater stress experience and greater loss of control [86].

The relationship between the prolactin:testosterone ratio (P:T) and the stress experienced is currently not known. From the available literature, it is, however, possible to deduce that a greater P:T may indicate a feeling of loss of control and depression as high levels of prolactin together with low levels of testosterone are associated with a depressed state of mind [75]. This deduction is in accordance with results from Malan, and co-workers' [18, 86] research, which indicated that high prolactin and low testosterone levels are indicative of a loss of control and the experience of more stress in Africans.

Cardiovascular Function

Blood pressure = Cardiac output (CO) x Total peripheral resistance (TPR) [64]. From the equation the importance of TPR in the control of blood pressure is quite apparent. The following three mechanisms are responsible for regulating TPR within the cardiovascular system: Autonomic control (vasoconstriction vs. vasodilatation), vasoconstrictive hormones and endothelial control [64]. Neurotransmitters such as NE are known to be vasoconstrictive due to local α-adrenergic stimulation, with adenosine and nitric oxide (NO) having a vasodilatory action on the arterioles (Opie, 2004). When TPR increases, diastolic blood pressure (DBP) is more susceptible to increases than systolic blood pressure (SBP) [64] as TPR is a good indication of the resistance against which the heart must pump [74].

Cardiac output (CO), on the other hand, is a good indicator of the working of the heart itself [64, 74]. It is defined as the amount of blood pumped into the aorta by the heart each minute and it is mainly regulated by two factors, namely TPR and heart rate (HR) [74].

Compliance can be defined as the change in volume of the artery per unit pressure [74] and it can, therefore, be described as the ability of the artery to maintain volume flow despite changes in pressure. The windkessel effect (Cw), as described by Middlemost [91], is the ability of the arteries to store part of the stroke volume (SV) during systole and drain it during diastole and thereby maintaining volume flow and ensuring smooth blood flow. Compliance and TPR are seen as the two main determinants of afterload on the heart [91]. Furthermore, Cw can be seen as a risk factor for cardiovascular events, as Cw is decreased in the early phases of hypertension [91].

The cardiovascular system is, therefore, a closely interlinked system with small changes in one area leading to big effects in another, as can be seen in the interaction between TPR,

CO, HR and Cw. This system is also very sensitive for other influences, as increased SNS activity has been shown to lead to increased vascular muscle tone, as can be reflected in an increased TPR [74] and concomitant decreased compliance and is thereby a good indicator of future cardiovascular dysfunction [92].

Cardiovascular Risk Factors

The exact incidence of hypertension is not known in Africans, but the African Union has called hypertension one of the continent's greatest health challenges after AIDS [93]. Hypertension is likely to be one of the most common causes of heart failure in Africa [21]. Several risk factors that may have adverse effects on the cardiovascular system were identified within the North-Western region African group in South Africa. Risk factors in the development of hypertension cannot be ignored and it is, therefore, of importance to understand the effects each of these factors better.

Gender as a Risk Factor in the Development of Cardiovascular Dysfunction

The WHO recognises gender as one of the non-changeable risk factors in the development of cardiovascular disease [94]. It is now well known that men are more at risk concerning the development of cardiovascular dysfunction than their female counterparts. Opie and Seedat [14] found that hypertension prevalence rates were higher in African men than those found in women [7]. Another study substantiated this finding by indicating that men have a slower return to a normotensive state after a stressful event than women, which can be attributed to the vasodilatory effect of estrogen [63]. This is probably due to the negative influence androgens may have on the cardiovascular system, coupled to the protective function of estrogens against cardiovascular disease [95]. Reckelhoff [87] supported this finding showing through her study that the higher prevalence of hypertension found in men, could be attributed to the role of testosterone and the stimulatory effect it may have on the renin-angiotensin system (RAS).

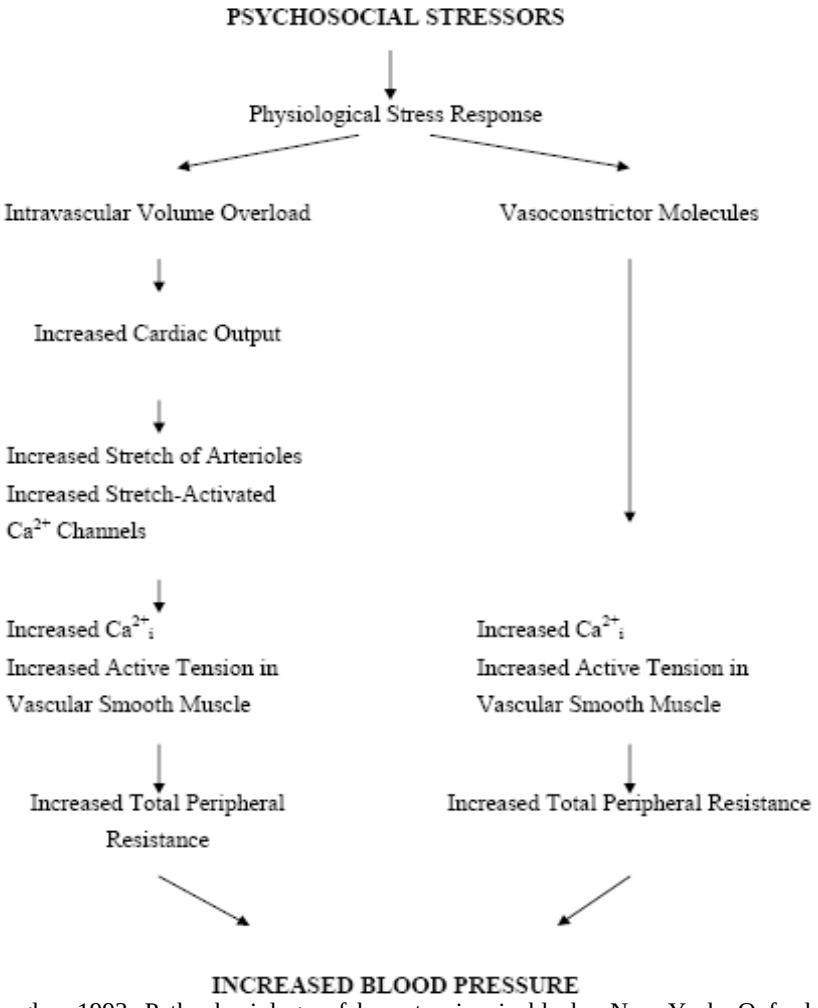
Race as a Risk Factor in the Development of Cardiovascular Dysfunction

Fray and Douglas [96] indicated that 25% of the reported 60 million hypertensive patients in North America today are African-American. They further stated that cardiovascular disease found in African-Americans are more severe, diagnosed at an earlier age and more fatal at a younger age, when compared to their Caucasian counterparts [96]. A possible explanation for this phenomenon is that African-Americans show a greater total peripheral resistance (TPR), probably due to hypertrophy of the vasculature or an increased reactivity. Additionally, it has been indicated that African-Americans [60, 97] and Africans [8] show greater sympathetic and cardiovascular reactivity [65] towards a stressor with concomitant increases in vascular resistance and higher prevalence rates of hypertension.

Mufunda and Sparks [98] attempted to understand this greater prevalence of cardiovascular disease better by investigating salt sensitivity in Africans. They, however, concluded that while Africans showed an increased salt sensitivity, this increase is not sufficient to be the cause of hypertension on its own. Supporting this profile, Africans with a greater inherent salt sensitivity and low renin-angiotensin hypertension [64] were found to

show higher plasma renin activity [99] during acute stress, which may contribute to the higher hypertension prevalence rates found amongst urbanized Africans [18].

The need has, however, arisen to view race not as a risk factor, but rather as a risk marker in the development of cardiovascular disease [39, 95]. Appel and co-workers [39] indicated that other factors such as body mass index (BMI) and educational levels are more reliable predictors of cardiovascular risk. Other studies supported this by showing that the high prevalence of cardiovascular disease found among African-Americans is mediated by other risk factors and not purely race [70, 100]. It is, therefore, necessary to proceed with caution when viewing race as a risk factor, since it may be necessary to refer to the contextual model as conceptualised by Anderson and McNeilly [60] which states that race should not be viewed as a proxy for genetic differences, but rather as a proxy for the effect of exposure to chronic social and socio-cultural factors.



Fray and Douglas, 1993. Pathophysiology of hypertension in blacks. New York: Oxford University Press.

Figure 2.1. Pathogenesis of sustained hypertension in blacks.

Urbanization as a Risk Factor in the Development of Cardiovascular Dysfunction

Opie and Seedat [14] indicated that the high prevalence of urbanization among Africans, accounts in part for the high occurrence of hypertension, especially in African men. Urbanization is further associated with an increase in both systolic and diastolic blood pressure in Africans [102]. Schutte, and co-workers [102, 103] concluded that the urbanization of African men is associated with an increase in blood pressure through a peripheral mechanism. Another study elaborated that all urbanized individuals are more at risk for the development of hypertension through the effects on the vascular system [103]. Malan, et al. [7] supported these findings by indicating that urbanized Africans showed higher hypertension prevalence rates and vascular responsiveness compared to rural groups. These results were emphasized in Africans with a behavioral active coping style [7]. Additionally, Knardahl [104] indicated that environmental and predisposition factors are of importance in the development of cardiovascular disease. This statement is supported by the work of Mufunda and Sparks [99] who revealed that although Africans show an increase in salt sensitivity, it is rather psychosocial stress caused by urbanization coupled with Westernised living habits such as increased alcohol consumption, more obesity, increased consumption of carbohydrates and altered dietary electrolytes, that play a role in the development of hypertension in urbanized Africans.

Figure 2.1 provides a graphic representation of the pathogenesis of hypertension in Africans. Fray and Douglas [96] additionally indicated that neural influences might be the profound influence in the physiological stress response leading to vascular reactivity, increased CO and TPR through an α-adrenergic response. This model enforces the term “psychosocial stressor induced-hypertension” as termed by Fray and Douglas [96] and it could be a more accurate description in the development of hypertension in Africans, than essential hypertension.

Interaction between Stress Hormones and Cardiovascular Function

A study by Nykli´cˇek [105] has indicated that some hypertensive subjects not only have a hyperactive cardiovascular system, but also an overactive HPA-axis and immune reactivity towards stress. Furthermore, a study conducted on cynomolgus monkeys by Rosmond [67] showed that the continuous activation of the HPA-axis can lead to a series of physiological events that may result in myocardial ischemia, ventricular fibrillation, plaque rupture and coronary thrombosis. The effect of cortisol has been shown to increase heart rate and blood pressure causing constriction of the coronaries and accumulating lipids in the intima, all of which can be the precursor of the above cardiovascular dysfunction [67]. Cortisol seems to have an indirect, rather than a direct effect on the cardiovascular system through the effects it may have on fat distribution and insulin resistance [67, 77]. Additionally, cortisol may further exercise its effect on cardiovascular function through the permissive effect it has on NE secretion [78] as was discussed earlier.

Research on the specific effect of testosterone on the cardiovascular system is currently contradictory. Some studies found the testosterone levels of Africans to be negatively associated with hypertension [9] while Reckelhoff (87) indicated a positive association with the development of hypertension. In his attempt to elucidate the effect of testosterone on cardiovascular function, Khalil [106] has shown that testosterone and other sex hormones stimulate endothelial cell growth and inhibit smooth muscle cell proliferation. Relaxation of the endothelium also occurs with stimulation of the sex hormone receptors [106], thereby leading to vaso-relaxation. On the other hand, increases in androgens, such as testosterone, is known to increase blood pressure through the hypothesised mechanism of sodium reabsorption and its effect on the renin-angiotensin system [87]. Additionally, renin activity [18] and salt sensitivity are both seen as risk markers for the development of hypertension in Africans [64, 97]. Huisman, et al. [9] indicated that lower testosterone and elevated prolactin levels are associated with increased diastolic blood pressure (DBP) and total peripheral resistance (TPR) reactivity in urbanized African women. This might also be an explanation of the higher hypertension prevalence found in this specific subject group compared to the rural African women [9].

From literature, cortisol is known to increase the risk of cardiovascular incidents. However, information regarding the specific effect testosterone has on the cardiovascular system, is currently contradictory, and the available research on the effect of prolactin is insufficient.

Interaction between Coping Styles and Cardiovascular Function

The contextual model as discussed above, considers the role of psychosocial factors in the development of hypertension in African-Americans. Dressler [30] showed that the risk of hypertension in African-Americans may be caused by a high status lifestyle, low class rank and little perceived social support.

The specific interaction between coping styles and cardiovascular function is however, still complex and contradictory. Numerous studies have indeed indicated that African-Americans, who actively cope with life demands through increased effort, determination and with the perception of little chance of success ("John Henryism"), run a higher risk for the development of cardiovascular disease [96] and hypertension prevalence rates [107]. Fray and Douglas [96] enforced this finding by revealing that the final manifestation of active coping (AC) is increased cytosolic calcium with its concomitant cardiovascular effects. Finally, it was indicated that active coping together with its associated SNS induced vascular hyperreactivity and hypertension are associated with salt retention in African-Americans. This deranged salt metabolism may be due to altered sodium transport in the kidneys and may be the pathogenic manifestations of chronic exposure to psychosocial stressors [96].

The increased cardiovascular risk associated with active coping styles was supported by Malan, and co-workers' [7] study, which indicated that AC urbanized subjects showed higher blood pressure values, especially regarding vascular values, when compared to AC rural subjects. These changes were more apparent in active coping African men.

Contrary to these findings, Henry, et al. [57] proposed in his model that AC is characterised by an increase in β-adrenergic activity and cardiovascular reactivity, with an increase in cardiac output (CO) and a decrease in total peripheral resistance (TPR). On the other hand, Henry, et al. [57] found that passive coping (PC) is characterised by an increase in α-adrenergic activity and cardiovascular reactivity with a decrease in CO and an increase in TPR. Additionally, the vascular hyperactivity model states that "beta-activity" causes increases in heart rate, stroke volume and CO, with "alpha-activity" causing increased TPR [96].

It, therefore, appears that the available research on the association between coping styles and cardiovascular function is still unclear, especially with regard to Africans.

Interaction between Coping Styles and Stress Hormones

Perceived control and the adoption of an active style of coping lead to decreased physiological reactivity and concomitant decreased cardiovascular and endocrine reactivity [56]. According to Matheson and Cole [56], this is true especially for cortisol, due to a decrease in glucocorticoid and sympathetic nervous system activity.

Other studies have indicated that the perception of control over a situation is the cause of different endocrine activation patterns [75, 108]. Henry's (1992) animal model has revealed that with an expectation of success and the concurrent feeling of control, testosterone levels rise. As the animal gradually loses control, the coping strategies employed become more passive and the prolactin levels rise. During stressful situations, the initial cortisol levels are high, but with prolonged exposure to stress, the cortisol levels return to normal [75]. According to Huisman, and co-workers [9] urbanized African females indicated an endocrine pattern of lower cortisol levels coupled with low testosterone and high prolactin levels, which might indicate a perception of unavoidable and ongoing stress and the use of passive coping strategies. According to Huisman, and co-workers [9] this may lead to a desensitizing of the HPA-axis with lower cortisol levels. In a study regarding the influence of acculturation on endocrine reactivity in Africans, Malan, et al. [18] showed that the endocrine reactivity of rural Africans differed significantly from urban Africans and Caucasians, and that these patterns were altered during the urbanization process. Additionally, urbanized African men showed the highest cortisol levels, low testosterone and high prolactin levels when compared to rural groups, which was indicative of the experience of stress [18].

Henry, et al. [57] also indicated that a greater cortisol to testosterone ratio (C:T) is indicative of a tendency to a depressed state of mind, while a low cortisol to prolactin ratio (C:P) is more suggestive of the perception of the situation not being as stressful.

In our own research we found that urbanized AC African men when compared to their rural counterparts indicated higher hypertension prevalence rates coupled to higher prolactin and lower testosterone values as well as a larger C:P ratio. It, therefore, seems that AC urbanized men with their larger vascular activity [7] experience more stress, depression and a greater loss of control during urbanization [86]. The findings of Hamer, et al. [109] could

support our data namely that heightened central adrenergic activation is associated with depressive and/or psychological distress symptoms.

From existing literature it therefore seems that there is a clear interaction between stress experience and the secretion of stress hormones. However, the nature of this interaction, as well as the possible role that specific coping styles might play in mediating the relationship between stress and endocrine activity in Africans, still warrants further research attention.

Conclusion

Numerous studies have been conducted to elucidate the specific cardiovascular effects that urbanization, as a psychosocial stressor, has on Africans [6-8, 14, 18, 21]. Psychosocial stress, such as urbanization, is also known to elicit an endocrine pattern, which is greatly altered by the perception of control over the situation or the specific coping style employed [56-57, 108]. However, the effect that these coping styles could have on the stress hormone levels and concomitant cardiovascular effects are still unclear.

The main focus of this chapter was to elucidate the association between coping styles, stress hormones and cardiovascular function in Africans. Although the findings cannot be generalized to the whole African population, it could serve as a foundation for future studies.

Urbanization in Africans could be associated with increased psychosocial stress, vascular blood pressure values, hypertension prevalence rates and altered endocrine patters (i.e. increased prolactin and decreased testosterone values, coupled with smaller C:P and larger C:T ratios). All these associations were evident in AC Africans and the cardiovascular risk was emphasized especially in the men where an endocrine pattern of a larger C: P ratio was evident, which could be indicative of an experience of loss of control over the situation.

Certain coping styles could, therefore, be associated with a poorer cardiovascular and stress experiencing pattern in urbanized Africans. A propensity to perceive daily events as stressful might result in an increase in perceived stress symptoms and psychological distress [110], which may be associated with heightened cardiovascular activation [110] and was more evident in urbanized Africans compared to their rural counterparts. Though the urbanized AC African women reported a perception of good health they had a poorer cardiovascular profile, which was difficult to explain [86]. Perception of health data did not lead to an obvious explanation but it may appear that behaviorally they are apparently challenging the stress but physiologically are experiencing it as uncontrollable.

The dissociation of AC subjects' physiological responses during urbanization and their resemblance to the PC urbanized subjects' responses could indicate a habituation of certain physiological systems. A physiological PC style and PC (behavioral and physiological) responses were associated with these changes. A PC style in the traditional, collectivistic African context might not be as negative or dysfunctional as within the Westernized individualistic culture. This may, therefore, be an over-simplification of a very complex phenomenon, since in certain situations a PC approach might be more constructive than an AC approach.

Presentation of this profile occurs in a traditionally African collectivistic culture context with less support from traditional extended families and communities. The urbanized subjects

encounter unchangeable stressors (e.g. urbanization) with high intensity and duration and this could be associated with habituation/adaptation of certain physiological systems. This process of changes could occur during uncontrollable threats/situations because the body could not cope successfully with or adapt to the challenge [71]. Rapid sociocultural changes occurring during modernization or urbanization with resultant lower social support lead to loss of cohesive group activities and achievements that promote a sense of stability and togetherness. The results accentuate the influence of the environment regarding coping with psychosocial stress/urbanization.

It is recommended that studies be planned on direct markers of sympathetic activity in Africans. Their coping styles and cardiovascular responses when exposed to mental stressors which elicit typical α- and ß-adrenergic responses must be evaluated. There is also a great need for the development of coping measures from an African-centred perspective in order to establish an emic pattern of coping within the African population.

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Chapter 13

Sudden Death: Neurocardiologic Mystery

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Abstract

Central nervous system (CNS)/cardiac interactions in cardiac and epileptic patients are examined for sudden death risk factors, including arrhythmias, respiratory (hypoxia) and psychological (stress) factors. Possible overlapping risks of sudden unexpected death for epilepsy (SUDEP) and cardiac disease are examined. Interactions between the CNS, peripheral autonomic nervous and cardiopulmonary systems are explored. Potential interactions of subtle genetic arrhythmogenic risk factors predisposing to seizure related arrhythmias are discussed. We speculate about preventive measures to minimize the risk of SUDEP and sudden cardiac death. While cardiac and psychiatric patients, and certain ethnic groups, are at risk for stress related unexpected sudden death, stress as a risk factor for SUDEP is unexplored. The impact of emotional states on autonomic control of cardiac rhythm is an important factor in cardiac dysrhythmias. The association of epilepsy with neurogenic arrhythmias, microscopic perivascular and interstitial fibrosis, and with depression and anxiety indicates that emotional stress may be a potential risk factor for SUDEP. The role of emotion in increasing the risk of seizure occurrence indicates a need to study stress management intervention in helping to prevent seizures. Clarification of risk factors and the mechanisms will help to prevent SUDEP in patients unable to achieve seizure control. Patients with epilepsy should be encouraged to use life style modifying interventions that have preventive medical benefits even if there is as yet no consensus that these help prevent sudden death. Other animal and clinical studies are needed to address the roles of Omega-3 fatty acids, cold temperatures, exercise, and heart rate in cardiac arrhythmias and/or SUDEP.

Keywords: *Sudden death; Sudden unexpected death in epilepsy; Epilepsy; Cardiac risk factors for sudden death; Stress; Interventions*

Model, Symptoms and/Or Associated Changes with Sudden Death

While many published epidemiological studies speculate about mechanisms of death in SUDEP, few basic research studies have addressed this issue. Epilepsy associated cardiac arrhythmias associated with centrally mediated respiratory depression are considered to be important risk and/or mechanistic factors. In animal models of fatal cardiac arrhythmias using ouabain-induced toxicity [1-8], nonuniform cardiac postganglionic sympathetic neural discharge, characterized by increases, decreases, or no change in discharge activity, was associated with induction of arrhythmia (Table 1). Beta-blockers, quinidine, and procainamide modified the neural nonuniform discharge and arrythmia. Other drugs did not exert any beneficial effect. [6,7,8,9] Nonuniform neural discharge associated with arrhythmias occurred in a non-pharmacological coronary occlusion model of arrhythmia and sudden death. [4,8,10] Hypoxia leading to myocardial ischemia, myocardial infarction, or ventricular fibrillation is a major mechanism of sudden death in cardiovascular diseases in combination with associated adrenergic surges. This mechanism could contribute to sudden death in epilepsy. This sequence of events could also be associated with acute hypothalamic stimulation with consequent increased blood pressure, which reflexively evokes parasympathetic discharge and subsequently triggered cardiac arrhythmias. [11]

Using a feline model to examine possible mechanisms of SUDEP, the relationships among epilepsy, autonomic neural, and the cardiopulmonary system were explored. Similar to observations in the coronary artery occlusion model mentioned above, Lathers and Schraeder [12-16] found nonuniform cardiac neural autonomic dysfunction and cardiac arrhythmias associated with cortical seizure discharges. The hypothesis of a nonuniform cardiac sympathetic neural nonuniform discharge association with arrhythmias was based on the studies of Han and Moe. [17] Cardiac sympathetic neural disturbance increased temporal dispersion of recovery of ventricular excitability, leading to electrical instability predisposing the ventricular myocardium to arrhythmia.

Similar to ictal discharges induced by pentylenetetrazol (PTZ), interictal cortical discharges also were associated with altered autonomic nonuniform postganglionic cardiac and sympathetic and parasympathetic postganglionic cardiac neural discharge, and cardiac conduction and rhythm changes. [12-16] Phenobarbital pretreatment [18,19] delayed onset of interictal and ictal activity but did not prevent the associated autonomic neural changes once epileptogenic discharges were established A model of focal epilepsy utilizing injection of penicillin into the hippocampus of the cat [20,21] found similar results. Other experiments [22-24] reported the effect of phenobarbital on the lock step phenomenon (LSP). LSP was defined as synchronization of interictal cortical discharges with postganglionic cardiac sympathetic and parasympathetic neural discharges. LSP was also associated with changes in blood pressure and cardiac conduction and rhythm. [23,24] In hemispherectomized rats, epileptogenic activity induced by penicillin applied to the hypothalamus, interictal and ictal

activity induced cardiac arrhythmias [25] and confirmed the arrhythmogenic capability of epileptiform discharges in the feline model. [12-16,18-24,26]

Table 1. Pathophysiological Mechanisms

Model, Symptoms and/or Changes	Mechanisms of Sudden Death
Nonuniform autonomic cardiac postganglionic neural discharge associated with coronary occlusion of left anterior descending coronary artery and/or ouabain toxicity in cats	Nonuniform (increases, decreases, and/or no change) autonomic neural postganglionic cardiac sympathetic discharge traveling through the stellate ganglia, causes cardiac arrhythmias, ventricular fibrillation and/or SUD in manner described by Han & Moe i.e., nonuniform recovery of excitability in ventricular muscle. [1-10,17]
Arrhythmia monitoring of pacemaker patients	Revealed tachycardias, most likely ventricular tachycardia, to be related to SUD, giving insight of terminal event mechanisms. [162,288]
Nonuniform autonomic cardiac postganglionic neural discharge associated with pentylenetetrazol-induced interictal epileptogenic activity in cats	Nonuniform autonomic neural discharge, autonomic neural imbalance of postganglionic cardiac sympathetic and vagal discharge causes cardiac arrhythmias, ventricular fibrillation and/or asystole and/or SUDEP. [15,16]
	Lock step phenomenon considered to be one potential mechanism for SUDEP. [12-16,18-24,26,52-55]
Lock step phenomenon (LSP). Cardiac postganglionic sympathetic and vagal discharges were synchronized one for one with both ictal and interictal discharges and premature ventricular contractions, ST/T changes, and conduction blocks and precipitous changes in blood pressure occurring concurrent with interictal spikes.	Spatial and temporal summation of neuronal discharges in a subcortical center producing a stimulus strong enough to overcome the cortical and ganglionic threshold [58] Increased synaptic recruitment, resulting in amplification of subcortical stimuli along their path so when reaching the cortex and sympathetic ganglion, they are capable of causing these neurons to discharge: and increased irritability of all neurons so that subcortical impulses could stimulate cortical and ganglionic neurons [58].
	A periodic rhythm imposed upon the brain, where normally rich complexity exists, implies a susceptibility to failure that may result in death. [65]
Chaos Science: simple systems, such as periodic ones, are easily perturbed and less able to return to the preperturbed state.	Occurrence of a very regular oscillator in the brain is theoretically dangerous, regardless of mechanism. Fractal processes are ubiquitous in biological systems, include brain electrical depolarizations, and are systems that convey different information. Complexity of a fractal process may at times depreciate into a simple periodic process represetnin decay of the system and dramatic change. [62,66]
Mode locking. Epileptic focus and medullary cardiac center may be locked one to one during state of LSP. [65]	Causes of death include failure of brain and heart. If brain sends a message to the heart triggering a fatal arrhythmia, or if the heart enters an arrhythmia via its own initiative, sudden death will occur. Perturbations of cardiac electrical depolarization may have several mechanism, any or several of which may be operations. [54]

Table 1. Pathophysiological Mechanisms (Continued)

Model, Symptoms and/or Changes	Mechanisms of Sudden Death
Power Spectral Analysis [100]	Time-frequency domain analyses of heart rate variability in patients with epilepsy and time-frequency mapping of R-R intervals during partial seizure may provide procedure to assess autonomic activity related to risk factors for SUDEP. [101-103]
Sympathetic innervation is critical for effective cardiac function. Developmental and regulatory mechanisms determining density and pattern of cardiac sympathetic innervation unclear, as is role of innervation in arrhythmogenesis. Sema3a establishes cardiac sympathetic innervation patterning. Sema3a is abundantly expressed in the trabecular layer in early-stage embryos but is restricted to Purkinje fibers after birth, forming an epicardial-to-endocardial transmural sympathetic innervation pattern. Sema3a(-/-) mice lacked a cardiac sympathetic innervation gradient and exhibited stellate ganglia malformation, leading to marked sinus bradycardia due to sympathetic dysfunction.	Cardiac-specific overexpression of Sema3a in transgenic mice (SemaTG) associated with reduced sympathetic innervation and attenuation of epicardial-to-endocardial innervation gradient. SemaTG mice demonstrated sudden death and susceptibility to ventricular tachycardia, due to catecholamine supersensitivity and prolongation of the action potential duration. It can be concluded that appropriate cardiac Sema3a expression is needed for sympathetic innervation patterning and is critical for heart rate control. [39]
Sympathetic dysfunction: altered postganglionic cardiac sympathetic innervation in patients with chronic temporal lobe epilepsy	Altered postganglionic cardiac sympathetic innervation may increase risk of cardiac abnormalities and/or SUDEP. [24]
Amygdaloid kindled seizure effect on cardiovascular system examined in rats. An abrupt 50% increase in mean arterial pressure (BP) lasting 20-30 s after initiation of seizure occurred with a profound bradycardia characterized by a rate about half recorded before stimulation. Changes in heart rate and BP observed during amygdaloid kindled seizures similar to those observed during secondary spontaneous seizures. Effects apparently are independent of kindling stimulus because stimulus-induced cardiovascular changes were not present at beginning of kindling.	Results suggest kindling seizure model is useful to study underlying mechanisms of seizure-induced cardiac arrhythmias and possibly the clinical phenomenon of SUDEP. [34,42]
Use of electrical stimulation as a therapy for epilepsy is currently being studied in experimental animals and in patients with epilepsy. This study examined the effect of preemptive, low-frequency, 1-Hz sine wave stimulation (LFS) on incidence of amygdala-kindled seizures in rats.	Dramatic decrease in incidence of stage 5 seizures in fully kindled animals after preemptive LFS suggests LFS may be an effective therapy for prevention of seizures in patients with epilepsy. [43]

Table 1. Pathophysiological Mechanisms (Continued)

Model, Symptoms and/or Changes	Mechanisms of Sudden Death
Amygdaloid kindled seizures in unanesthetized rats induced abrupt elevation of blood pressure accompanied by a significant decrease in heart rate.	Muscarinic receptor blockade with atropine (1 mg/kg, i.v. abolished seizure-induced bradycardia. Seizure-induced hypertension was unaffected by beta-adrenergic blockade with timolol (1 mg/kg, i.v.), but reduced by phentolamine (5 mg/kg, s.c., an alpha-adrenergic receptor antagonist. Chemical sympathectomy was induced with 6-hydroxydopamine (100 mg/kg, i.v.), an agent that does not cross the blood-brain barrier, eliminated the pressor response but did not completely block seizure-induced bradycardia. Effectiveness of 6-hydroxydopamine was tested with tyramine (0.5 mg/kg, i.v.) an agent that releases endogenous catecholamines. Results indicate amygdaloid kindled seizures activate both branches of the autonomic nervous system. Bradycardia was mediated by the parasympathetic system; the pressor response was caused by an increase in peripheral resistance due to alpha-adrenergic receptor activation. Findings show kindling is a useful seizure model for future studies on effect of seizures on cardiovascular function and possible mechanisms of seizure-related sudden unexplained death. [41]

Resolution of whether enkephalins elicit epileptogenic activity and autonomic dysfunction via inhibition of GABA release could eventually allow design of pharmacological agents to prevent epileptogenic activity and autonomic dysfunction and lower the risk of SUDEP. [26-32] Data support a role for prostaglandin E 2 and enkephalins in autonomic dysfunction characterized by nonuniform discharge [27-32], suggesting presynaptic gamma aminobutyric acid (GABA) release by prostaglandin E2 could elicit arrhythmias. [27] A prolonged increase in methionine (met)-enkephalin content in rat septum, hypothalamus, amygdala, and hippocampus occurred after pentylenetetrazol-induced convulsions. [33] Increased met-enkephalins were associated with a greater percent inhibition of potassium-stimulated GABA release. [34] Central leucine-enkephalin may induce epileptogenic activity [35]; (d-alanine2) met-enkephalin produced a centrally mediated vasopressor response and attenuated the baroreceptor reflex in conscious cats. [36] and may have contributed to autonomic imbalance and arrhythmias. Numerous studies implicate prostaglandins as potential modulators in seizure activity. [37] Rofecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor potentiates anticonvulsant activity of tiagabine vs. pentylenetetrazol-induced convulsions in mice. Rofecoxib or similar drugs may have a place as adjuvant therapy in reducing the risk of adverse cardiac events if used with antiepileptic drugs, although adverse consequences have been noted with these drugs in patients with coronary artery disease.

Sympathetic dysfunction evidenced by altered postganglionic cardiac sympathetic innervation in patients with chronic temporal lobe epilepsy has been found and suggests altered postganglionic cardiac sympathetic innervation may increase the risk of cardiac abnormalities and/or SUDEP. [38] These data obtained in humans confirm the animal studies

conducted by Lathers in which postganglionic cardiac sympathetic neural discharge was monitored before and as arrhythmias developed. (Table 1). SemaTG mice manifested sudden death and susceptibility to ventricular tachycardia due to catecholamine supersensitivity and prolongation of the action potential duration, suggesting appropriate cardiac Sema3a expression is needed for sympathetic innervation patterning and is involved in heart rate control. [39] Cardiac-specific overexpression of Sema3a in transgenic mice (SemaTG) was associated with reduced sympathetic innervation and attenuation of epicardial-to-endocardial innervation gradient.

Since the amygdala has complex interconnections with multiple cortical and brainstem regions (Table 1) and is involved in production of autonomic temporal lobe epilepsy phenomenology, its role in seizure induced cardiac arrhythmias must be considered. Amygdala kindled seizures in rats are associated with an abrupt 50% increase in mean arterial blood pressure and a profound bradycardia characterized by a rate about half that occurring before stimulation. Amygdaloid kindled seizures activate both branches of the autonomic nervous system, with bradycardia mediated by the parasympathetic system and the pressor response from increased peripheral resistance due to alpha-adrenergic receptor activation, suggesting kindling is a useful seizure model for future studies on cardiovascular function and mechanisms of SUDEP. [40-42] Neurons within the amygdala will, when stimulated [43], result in the combination of bradycardia and apnea, or in tachycardia and hyperpnea. These observations raise the possibility of the amygdala having a role in ictally-related apnea, bradycardia, and tachyarrhythmias. One may speculate that there could be an adverse effect in persons with epilepsy and some genetically determined subclinical cardiac predisposition for fatal arrhythmia. Incremental pentylenetetrazol doses in the animal model for SUDEP [12-16] triggered decreased sympathetic cardiovascular modulation and baroreflex sensitivity after temporal lobe epilepsy surgery [44], suggesting temporal lobe epilepsy surgery reduces the risk of sympathetically mediated tachyarrhythmias and excessive bradycardia counter-regulation. Both factors may be involved in SUDEP pathophysiology. Successful temporal lobe surgery for epilepsy may contribute to a reduction in the risk of SUDEP.

In a status epilepticus model that was developed in unanesthetized, chronically instrumented sheep, sudden death and pulmonary edema occurred (Table 2) in association with a difference in peak left atrial and pulmonary artery pressures and extravascular lung water. However, since the increased pulmonary extravascular water was not thought to be significant enough to contribute to the animals' deaths, centrally mediated hypoventilation was considered to be the mechanism of death. The studies support use of this model of epileptic sudden death to study the role of central hypoventilation in SUDEP. [45-47]

In a different animal model, DBA/2 mice have been proposed to study SUDEP because respiratory arrest is observed after audiogenic seizures. Since respiratory mechanisms are modulated, in part, by serotonin, the effect of serotoninergic agents on respiratory arrest has been studied. [48,49] Fluoxetine, a selective serotonin reuptake inhibitor, significantly reduced the incidence of respiratory arrest and indicate fluoxetine should be evaluated for SUDEP prevention.

It is likely that no one mechanism of SUDEP will explain the contributory risk factors involved in all patients with epilepsy who die suddenly and unexpectedly. Multiple animal models of SUDEP, exploring different potential mechanisms and, especially, their

interaction, are needed to help delineate mechanisms of SUDEP in humans. No one animal model addresses all of the potential contributory risk factors.

Table 2. Respiratory Factors and Hypoxia

Model, Symptoms and/or Change	Mechanisms of Sudden Death
Pulmonary edema model of status epilepticus in unanesthetized, chronically instrumented sheep in which sudden death and pulmonary edema occur.	Catecholamine levels, seizure type and duration did not differ between animals dying suddenly or those surviving. Benign arrhythmias were generated in all animals; in no case did an arrhythmia account for death of an animal. Striking hypoventilation demonstrated in sudden death group but not in surviving animals. Differences in peak left atrial and pulmonary artery pressures, and in extravascular lung water; pulmonary edema did not account for demise of sudden death animals. Thus, this model of epileptic sudden death supports a role of central hypoventilation in etiology of sudden unexpected death and shows association, albeit not fatal, with pulmonary edema. The importance of arrhythmia in its pathogenesis is not confirmed. [46]
Audiogenic seizures: respiratory arrest	Respiratory arrest mechanisms, modulated in part by serotonin, may cause SUDEP. [48-49]
Central alveolar hypoventilation syndrome (Ondine's curse)	Central alveolar hypoventilation syndrome causes SUD. [165]
Risk factors include uncontrolled convulsive seizures, respiratory and cardiac factors relating to treatment and supervision.	Both respiratory and cardiac mechanisms important. Apparent protective effect of lay supervision supports a role for respiratory factors, in part amenable to intervention by simple measures. Malignant tachyarrhythmias are rare during seizures, sinus bradycardia/arrest, although infrequent, occurs. Both types of cardiac arrhythmias can have a genetic basis as a contributory factor. Authors explore potential of coexisting liability to cardiac arrhythmias as a contributory factor, but acknowledge bridging evidence between cardiac inherited gene determinants and SUDEP is lacking. [166-169]
Epilepsy Related Hypoxia	Central apnea with seizure.[168] Neurogenic pulmonary edema and adult distress syndrome [166]
Ictal apnea	[170,171]
Obstructive sleep apnea (OSA)-induced cardiovascular complications.	Implicated in pathogenesis of various cardiovascular diseases, including systemic hypertension, coronary artery disease, congestive heart failure, pulmonary hypertension, stroke, and cardiac arrhythmias. Mechanisms by which OSA affects cardiovascular system may involve mechanical effects on intrathoracic pressure, increased sympathetic activation, intermittent hypoxia, and endothelial dysfunction. [172-173]
Likely processes of the Sudden Infant Death Syndrome (SIDS) identified (apnea, failed arousal, failed autoresuscitation, etc. The way in which epidemiological risk factors, genetics, neurotransmitter receptor defects and neonatal cardiorespiratory reflex responses interact to lead to sudden death during sleep is unclear.	Hypothesize neurophysiological basis of SIDS resides in a persistence of fetal reflex responses neonatal period, amplification of inhibitory cardiorespiratory reflex responses and reduced excitatory cardiorespiratory reflex responses. Explores ways in which multiple subtle abnormalities interact to lead to sudden death and emphasizes difficulty of ante-mortem identification of infants at risk for SIDS. Respir Physiol Neurobiol. 2007. Mechanisms of Pathogenesis in the Sudden Infant Death Syndrome. [127]

Mechanisms for Risk of SUDEP

The occurrence of sudden death probably depends on the status of interactions between acutely occurring events and/or the stage of disease present just prior to the time of death. Most likely any underlying undefined genetic predisposition to arrhythmias, and thus a contributory mechanism of sudden death, varies from patient to patient. A number of factors must be considered when ranking the most important and likely mechanism(s) of SUDEP. Autonomic dysfunction associated with epileptogenic activity, initiating cardiac arrhythmias, is postulated to cause be a mechanism of SUDEP. [50,51] Lock Step Phenomenon (LSP) related patterns of precipitous instability in blood pressure are indicators of changes in autonomic function (Table 1). [22,23,52-55] Understanding the role of epileptiform discharge related autonomic changes, as indicated by precipitous changes in blood pressure (PCBP) associated with LSP, may contribute to development of strategies for SUDEP prevention. LSP postganglionic cardiac sympathetic discharge time locked to cortical epileptiform activity may initiate arrhythogenic potentials. [22-24] Cardiac postganglionic sympathetic and vagal discharges were synchronized with ictal and interictal discharges and premature ventricular contractions, ST/T changes, and conduction blocks and occurred concurrent with interictal spikes. The relationship between LSP and PCBP (greater than 23 mm Hg in 10 sec) was determined. [23] Four categories of LSP were defined: LSP absent; stable LSP with 2.8 sec interval; stable LSP without 2.8 sec interval; and unstable LSP with increasing or decreasing rates of discharge. A one-way repeated measures ANOVA and the Newman-Keuls post-hoc test showed that a higher mean proportion of time spent in PCBP was associated with the unstable LSP pattern ($P < 0.05$) [22,23,52-55], indicating that autonomic abnormalities characterized by precipitous blood pressure changes, are associated with unstable LSP patterns.

At least three mechanisms can be postulated through which LSP may cause arrhythmia and SUDEP (Table 1). [53] The first is excessive sympathetic stimulation of a heart that is electrically unstable due to prior damage with microscopic pathological changes in the myocardium consistent with repeated high levels of catecholamines. [56] Microscopic damage to the heart may provide a locus where fatal arrhythmias begin when the heart is again stimulated by LSP related sympathetic discharge. The second possible mechanism involves nonuniform discharge of the postganglionic sympathetic nerve branches innervating the heart, similar to that associated with arrhythmias using the ouabain toxicity model [1-8] and also found to occur in cats with PTZ-induced seizures. [12-16] Nonuniform cardiac neural discharge was associated with epileptogenic activity related changes in autonomic parameters of mean arterial blood pressure and cardiac rhythm and may contribute to SUDEP. The possible third mechanism may be that precipitous blood pressure changes per se could be a factor in arrhythmia development in persons with epilepsy. Allen [57] found premature systolic arrhythmias followed by an increase in blood pressure induced by stimulation of the superior colliculus in rabbits. Arrhythmias were not observed when blood pressure was maintained at a constant level during stimulation, suggesting increased risk for arrhythmias could be attributed to unstable blood pressure changes. Evans and Gillis [11] elicited blood pressure increases by stimulation of the hypothalamus and concluded arrhythmias occurring after but not during such stimulation resulted from a sudden surge of

parasympathetic activity reflexly evoked by the rise in blood pressure. A case report of a 23-year old male with sinus arrest lasting up to nine seconds, as well as bradycardia of 40- to 5-bpm, occurring during clinically observed seizures [51], suggest the parasympathetic nervous system may be involved in production of arrhythmias in some persons with epilepsy. Although blood pressure remained stable during the seizures in this patient, the autonomic manifestations suggest a role for parasympathetic involvement. While these three mechanisms leading to arrhythmia and SUDEP are not mutually exclusive, it is likely that no single mechanism can explain all cases of SUDEP. Perhaps some cases of SUDEP are caused by ventricular fibrillation related to a lower ventricular fibrillation threshold associated with increased cardiac sympathetic discharge. Other SUDEP cases may result from sinus arrest related to reflex parasympathetic discharge evoked by precipitous blood pressure changes, especially if there is cardiac damage produced by prior sympathetic stimulation. The association of cardiovascular autonomic events with LSP indicates further investigation is warranted.

Dodd-o and Lathers [55] examined the lock step phenomenon in phenobarbital pretreated cats (Table 1). Epileptogenic activity induced by PTZ is an experimental model of primary generalized epilepsy that allowed LSP to be expressed. Incremental doses of PTZ allowed first interictal and then ictal activity to develop. Three proposed methods of action for PTZ that would allow the LSP to be expressed are presented in Table 1. [22,23] In each case, PTZ effectively creates a hyperirritable state of epileptogenic electrical activity present in the central and autonomic nervous systems. [58] While Phenobarbital tended to minimize this irritability, its effect was eventually overcome by increased epileptogenic activity elicited by increasing amounts of itcal activity and diminished interitcal activity. The closely related central and autonomic rhythmic activity appears to be important to maintain homeostasis. When a stable LSP was lost, both precipitous mean arterial blood pressure changes and ECG changes occurred more frequently. Data suggest the concept of LSP related rhythmic neuronal activity associated with normal central and autonomic nervous system may, either by its mere presence or by the rhythm at which it occurs, play a role in the origin of autonomic dysfunction and contribute to the occurrence of SUDEP. [55] When a temporal relationship between discharge patterns of the central and autonomic nervous system occurs [59] loss of rhythmic stability can alter neurotransmitter release [60,61] and initiate autonomic dysfunction. [1-8,12-16]

The occurrence of LSP in association with active epileptogenic cortical activity may help to explain at least one possible mechanism of SUDEP and, upon autopsy have static cortical lesions, which underlie seizure foci during life (Table 1). [56] O'Rouke and Lathers [54] described the anatomical location of three oscillatory drivers of concern in LSP and cardiac arrhythmias that include the: 1) cortex focus, 2) cardiac centers in the medulla, and 3) SA node, i.e., the pacemaker influenced by discharge of parasympathetic and sympathetic autonomic nerves innervating it. LSP appears to occur when the oscillatory driver of the interictal cortical focus becomes linked to the oscillatory driver of the autonomic cardiac nerves. Actual cause of death could be hypothesized to be dependent on function of cardiac autonomic neural discharge, which would then be driven at the rate of the epileptogenic focus. Since autonomic nerves innervate the heart, the finely tuned electrical depolarization system of the heart could be disturbed. Autonomic dysfunction may directly precede cardiac

arrhythmias and may be viewed in terms of the science of chaos, a concept in physics that is applicable in modeling observed natural phenomena. Chaos identifies pattern and regularity in seemingly disorganized events. [62] The science of chaos predicts activity of nonlinear, noncyclical functions, such as intervals between depolarizations in an EEG showing LSP or a lot of increased ventricular depolarizations in atrial fibrillation monitored by ECG. Principles of chaos substantiate association of LSP and SUDEP. LSP occurs as a dicotomy, i.e., it is either on or off. [54] Discharge patterns characteristic of LSP, once present, were not altered appreciably by increasing PTZ until the lethal dose. Interspike interval (ISI) histograms found discharges recorded in the EcoG were correlated with simultaneous discharges occurring in two postganglionic sympathetic nerves monitored in the same cat. Intervals in the ISI histograms were distinct from one another by a one-way ANOVA with $p<0.01$. Cardiac accelerator nerve recordings assess partial output from the cardiac center in the medulla. The operative mechanism in LSP may be that the epiletogenic cortex fires constantly, but at varying frequency, during both ictal and interical periods. During the ictal period, intensity of the depolarization originating at the focus is strong enough to spread to areas of the brain, which elicit clinically noticeable phenomena. The spread is so extensive in a generalized seizure that the reticular activating system is involved and the patient looses consciousness. During the ictal period depolarizations overwhelm nearby cells and seizure discharges spread. In the interictal period cells may continue to depolarize. If these cells fire with an electrical potential strong enough, and at the proper frequency to overtake another group of cells, the rate of depolarization of the latter group of cells will be driven to seizure activity. This sequence of events will serve as pacemaker for the second group of cells, the nucleus of sympathetic nerves located in medullary cardiac centers. These nerves innervate the heart and exhibit both chronotropic and inotropic effects; excessive stimulation will cause cardiac arrhythmias. [63] Medullary centers have ability to influence activity of the SA node but not to directly drive it [64]. In the normal state the rate of firing of the SA node, and thus the heart rate, and the depolarization of the nerves reaching the heart will not be correlated one to one since the heart has its own automatic pacemaker. However, development of interictal and ictal discharge and occurrence of LSP and cardiac arrhythmias may occur in an unpredictable dysfunctional manner and contribute to the risk of sudden death.

Application of the science of chaos involves the principle that simple systems, such as periodic ones, are easily perturbed and less able to return to the preperturbed state (Table 1). Thus, a periodic rhythm in the brain, where there is normally rich rhythmic complexity, implies a susceptibility to failure that may result in death. The epileptic focus and the medullary cardiac centers may be locked one to one during the state of LSP in what physicist call mode locking. [65] Occurrence of a very regular oscillator in the brain is theoretically dangerous, as exemplified by synchronous seizure discharges, regardless of its mechanism of known effect. Fractal processes, ubiquitous in biological systems including the brain, are systems that convey different information. [66] Electrical depolarizations of the brain are examples of a fractal process. The complexity of a fractal process may at times depreciate into a simple periodic process representing decay of the system and a dramatic change. Causes of death include failure of one of the two major electrical systems in the body, i.e., the brain and heart. If the brain fails to send out an impulse from the respiratory centers, then respiratory failure will be the immediate cause of death. If the brain sends a message to the

heart triggering a fatal arrhythmia, or if the heart enters an arrhythmia via its own initiative, once again sudden death will occur. Associated factors may play a role in disturbance of the normal healthy state, such as a fixed lesion in the heart, which alone would not explain death and/or autonomic dysfunction. [53,67] Central respiratory failure and arrhythmia are the only obvious etiologies that would leave no signs at autopsy. [50] Perturbation of cardiac electrical depolarization may have several mechanisms, any or several of which may be operational.

The specific mechanism of death in epileptic persons may be more complicated, i.e., periodic system changes allowing for ease of perturbation, than just changes in the sympathetic discharge rate. Area damage to the cardiac electrical stimulation system such as the His-Purkinje system, may be caused by continual stimulation of beta-receptors by sympathetic nerves innervating these receptors. Stimulation might produce a fixed microscopic lesion, which alone would be harmless but still sufficient to cause this portion of the myocardium to be less flexible in its response to other insults, such as excessive sympathetic discharge or an acute increase in blood catecholamine levels. A second possibility is focused on arrangement of ventricular receptors. Ventricular beta-receptors are arranged in a pattern with highest density in the apex and a gradually decreasing density near the base. [68-70] Down regulation of beta receptors from continual sympathetic discharge might disturb this graduation, setting up an arrhythmic situation. A pattern of increased sympathetic depolarization could be the fatal step in a two-stage process. [70-73] A third possibility is that of a normally forbidden sequence of sympathetic depolarizations, i.e., a pattern of depolarizations from sympathetic nerves, which interrupt the regular electrical depolarization. Winfree [62] characterized this in terms of chaos modeling of the heart. Cardiac mathematical models developed by Salata and Jalif [74] may facilitate understanding.

Stauffer et al [53] describe pathways involved in the brain that may be the basis for LSP. Epileptogenic activity originating in the cortex may be transmitted to the hypothalamus and brain stem to alter autonomic neural control of blood pressure and cardiac rate and rhythm. The anterior and medial hypothalamus regulate parasympathetic function while the posterior and lateral hypothalamus regulates sympathetic function. Direct projections exist from the hypothalamus to preganglionic sympathetic neurons of the intermediolateral cell column and to parasympathetic nuclei of the brain stem. [75] The mammillotegmental tract connects the hypothalamus with the reticular formation. The latter contains multisynaptic descending pathways linking the hypothalamus with autonomic areas in the brain stem and spinal cord. The medullary reticular formation contains cardiovascular areas capable of producing changes in heart rate and blood pressure. These areas produce their effects through reticulospinal connections to the intermediolateral cell column and connections to preganglionic parasympathetic neurons. [76] The intermediolateral cell column also receives input from the following regions of the medulla: A1 (norepinephrine-containing) neurons; C1 area (epinephrine-containing neurons); raphe; and nucleus tractus solitarius. The nucleus tractus solitarius receives afferent projections from arterial baroreceptors. In addition to its medullary input, the intermediolateral cell column receives projections from the A5 area, a group of norepinephrine-containing neurons located in the pons. [77] The hypothalamus is also connected to the brain stem by the medial forebrain bundle, which projects to midbrain reticular formation and provides another pathway for descending control over the autonomic

nervous system. The medial forebrain bundle connects the hypothalamus with structures in the forebrain, including the septal area, anterior olfactory nucleus, and pyriform cortex. The medial forebrain bundle also contains fibers from the fornix and the orbitofrontal cortex, with the latter structure projecting to the thalamus and amygdal [78], connected to the hypothalamus by the stria terminalis and ventral amygdalofugal pathway. It is postulated that information from the cortex travels via cingulate gyrus to the hippocampus, which projects to the hypothalamus via the fornix. Papez [79] The mamillothalamic tract connects mammillary bodies to the anterior thalamic nuclei. The circuit is completed by a pathway connecting the thalamus and cingulate gyrus. Electrical stimulation of the hypothalamus or other structures in the Papez circuit results in autonomic responses, as does stimulation of other cortical areas. Experiments are needed to identify which of the above three mechanisms or combination thereof is active in the patient with epilepsy who dies of SUDEP.

Neocortico-hypothalamic connections likely exist in man so that probably the dorsomedial nucleus of the thalamus, which connects with the prefrontal cortex, may project to the hypothalamus. [80-82] Neural pathways exist through which epileptogenic activity originating in the cortex could reach the hypothalamus and brain stem, resulting in discharge from the autonomic nervous system and eliciting phenomena such as blood pressure changes and cardiac arrhythmia. Electrical stimulation of the cerebral cortex in man and animals results in autonomic responses such as changes in blood pressure [83, 84], heart rate, and pupil dilatation. [83] Blood pressure changes can be evoked via stimulation of various cortical regions, including tips of the temporal lobes [83], motor cortex, premotor cortex, parietal cortex, and cingulate gyrus. [84] Autonomic changes, including alterations in blood pressure, are associated with epileptogenic activity. Experiments involving electrical stimulation of the cortex demonstrated similar directional blood pressure changes. Wall and David **[**80] and Delgado [85] found both increases and decreases in blood pressure upon cortical stimulation. Three cortical areas in monkeys exist where blood pressure changes of greater than 10-20 mm Hg were produced with electrical stimulation. [80] The first area is the sensori-motor cortex; the descending pathway from this area is independent of the hypothalamus and closely related to the pyramidal tract. The second area is the orbitofrontal cortex, a pathway that begins in this area and passes through the hypothalamus. The third area is the anterior temporal lobe; the pathway from this area of the cortex is partially dependent on the hypothalamus and partially direct to the tegmentum and pons. Kaada et. al. [86] elicited both increases and decreases in blood pressure with electrical stimulation of the cortex, and biphasic responses in which an increase in blood pressure was followed by a secondary decrease or a decrease in blood pressure followed by a secondary increase. The presence of defined pressor and depressor points in the cortex located in close proximity to each other [84] may explain several things in the experiments of Lathers, Stauffer et al: inconsistency of the direction of precipitous blood pressure changes; relationship of blood pressure changes to unstable LSP; and why the direction of blood pressure changes was not related to that observed in unstable LSP (i.e., increasing rate or decreasing rate). If predominantly pressor areas are stimulated by epileptogenic activity and if the frequency of the epileptogenic activity increases, the blood pressure my increase. If the epileptogenic activity decreases, the blood pressure may decrease. However, if predominantly depressor areas are stimulated by epileptogenic activity, blood pressure may decrease with increasing

epileptogenic activity and increase with decreasing epileptogenic activity. Another important paradox to be addressed is how the mean arterial blood pressure can decrease in spite of an increased rate of postganglionic cardiac sympathetic discharge.

Over 60% SUDEP cases were found to have static nonprogressive structural brain lesions, including old contusions of frontal and temporal lobes, brain tumors, cortical malformations, evidence of craniotomy, focal atrophy or hemiatrophy. [56,87] However, persons with epilepsy without such lesions may also die suddenly. The thalamus and the midbrain reticular formation are involved in generalized epilepsy, perhaps as a site of origin for seizure activity. [88] The thalamus, being part of the Papez circuit and having connections to the cortex, is capable of transmitting epileptogenic activity to the hypothalamus, producing autonomic manifestations. The reticular formation contains multisynaptic pathways connecting the hypothalamus with autonomic areas in the brain stem and spinal cord. Seizure activity involving the reticular formation could be transmitted to autonomic areas of the brain stem and spinal cord by these pathways. [1-8] If 2 or 3 branches of postganglionic cardiac sympathetic nerves exhibit a nonuniform discharges pattern, then the possibility exists that discharge from sympathetic nerves that innervate the blood vessels and control blood pressure may not be uniform, in which case, blood pressure could decrease inspite of the fact that discharge in some cardiac sympathetic branches was increased.

Changes in the rate of autonomic discharge from postganglionic cardiac sympathetic branches may contribute to cardiac dysrhythmias (Table 1). [1-8] The association between epileptogenic activity and autonomic dysfunction evidenced in both animals [12-16,95-97] and humans [50,67] may be a manifestation of disruption of a normal pattern of a temporally related intrinsic cortical and autonomic discharges. Diverse models show intrinsic activity at various levels in the nervous system. Cortical rhythms, controlled by neurons [89] thought to be located in the thalamus [90], are the basis for the normal generalized alpha (8-13 HZ), beta (20-22 HZ), and delta (3-4 Hz) rhythms of electroencephalography. Stereotaxic procedures demonstrate spontaneous activities from medical geniculate nuclei, inferior colliculus, mesencephalic reticular formation, and dorsal hippocampus. [91] Inherent rhythm of sympathetic nerve discharge, e.g., periodic leading to chaos, may originate in the hypothalamus [59,92-94]. A temporal relationship exists between intrinsic rhythms of central and peripheral autonomic nervous systems. [59] Characterization of LSP supports the concept of closely related central and autonomic rhythmic activity and its role in maintaining homeostasis. When stable LSP was lost, both precipitous mean arterial blood pressure changes and the incident of ECG changes occurred more frequently, suggesting LSP, either by its mere presence or by the rhythm at which it occurs, may play a role in the origin of autonomic dysfunction and contribute to SUDEP. [55]

Studies demonstrate acute neurogenic pulmonary edema and, central nervous system mediated respiratory changes are possible contributory risk factors for SUDEP (Table 2). Acute pulmonary edema can occur during a clinical seizure and lung weights increase in victims of SUDEP. [98] Seizures in a sheep model produce acute pulmonary edema and a neurogenically induced increase in pulmonary microvascular pressure with an accompanying prolonged change in endothelial conductance to protein. [45] In addition to neurogenic pulmonary edema, seizures are also associated with central nervous system induced apnea. [46,47] A potentially fatal event is avoided, most of the time through good fortune, while less

frequently SUDEP may occur consequent to an adverse fatal combination of neurological and cardiopulmonary events. Given the varying degrees of epileptogenic activity in animal models, it is theoretical possible that in a given person with epilepsy during a particular aberrant epileptogenic discharge, the extent of contribution of dysfunctional nonuniform peripheral autonomic discharge may vary so that during some cerebral discharges the epilepsy patient may exhibit an arrhythmia, yet not continue on to have a fatal event. [12-16] The same patient may be at risk for SUDEP during another event characterized by a different, more malignant, aberrant pattern of peripheral cardiac autonomic neural nonuniform discharge that predisposes to or actually elicits a fatal event. Sudden death could result when an increased risk for arrhythmias is combined with acute hypoxemia associated with the occurrence of neurogenic pulmonary edema [45-47] and/or associated central apnea. Differences may exist in the functional and interactive status of the autonomic nervous system at various times and during different combinations of circumstance among individuals and also within the same individual in persons with epileptogenic activity.

The book EPILEPSY AND SUDDEN DEATH [99] reviewed all pre-clinical and clinical knowledge related to SUDEP and emphasized that, despite a wealth of data on this subject, there was (and still is 18 years later) a disturbing paucity of understanding of operant risk factors and mechanisms of death. In this book, Quint et al [100] discussed the use of power spectral analysis to assess autonomic factors related to risk factors for SUDEP. Following the unique summarization of data on SUDEP contained in this book [99], other investigators applied time-frequency mapping of R-R intervals during seizure activity to assess autonomic dysfunction and cardiac arrhythmias [101-103] while others [104] developed studies to examine proposed mechanisms, including cardiac dysrhythmias, by which SUDEP may occur. The increased awareness of the importance of risk of SUDEP focused attention of the FDA, practitioners and pharmaceutical manufacturers on the question of whether use of anticonvulsant drugs contributes to or diminishes the chance of SUDEP.[105] The ongoing need for consideration of the risk of SUDEP when developing new anticonvulsant drugs was emphasized by the panel of scientists and clinicians assigned to review data associated with use of Lamotrigine for risk of SUDEP. Newer anticonvulsant drugs have FDA required warning labels with data on the relative risk of SUDEP associated with use of each drug. The proliferation of published papers on SUDEP since publication of EPILEPSY AND SUDDEN DEATH in 1990 indicates increased interest in the topic, as evidenced by organization of international conferences dedicated wholly or in part to SUDEP, and by an expansion in the number of investigators who have devoted themselves to this problem throughout the world.

The original epidemiological study of Leetsma from the Cook County Coroner's Office [98], has been supplemented by numerous other studies in various populations [106-122], including children [120] and confirm that SUDEP is one of the most common causes of death in persons with epilepsy. [121,122] SUDEP risk increases in proportion to refractoriness of the seizure disorder, presence of localization related generalized tonic clonic epilepsy, being a young male, sub-therapeutic anticonvulsant levels, and use of multiple antiepileptic drugs [123,124]. Other less defined risks, such as acute stress, may be involved. [125] Overall risk of death in persons with epilepsy can be 24 times greater than in the general population. [126] The overall incidence is about 1:680/year but may be as high as 1:100/year in populations with severe seizure disorders.

Sudden Infant Death Syndrome (SIDS) occurs in neonates and infants. The cause of death in SIDS during sleep likely involves apnea, failed arousal, and/or failed autoresuscitation (Table 2). Possible risk factors include genetic predisposition, neurotransmitter receptor defects, persistent fetal cardiovascular reflex responses in neonates, e.g. amplified inhibitory cardiorespiratory reflex responses, reduced excitatory cardiorespiratory responses, and a prone sleeping position. The presumption that multiple subtle abnormalities interact to lead to sudden death emphasizes the difficulty of ante-mortem identification of infants at risk for SIDS. However, the empirical observation that having infants lie supine rather than in a prone position during sleep has had a major impact on reducing the risk. [127]

Table 3. Syncope

Symptoms and/or Changes	Mechanisms of Sudden Death
Psychogenic syncope and Psychogenic seizures are common disorders but difficult to identify. Head-upright tilt table testing evaluates vasovagally mediated syncope and convulsive syncope. In 8 patients with syncope and/or tonic clonic motor activity, without changes in blood pressure and heart rate, transcraneal Doppler cerebral blood flow velocity and EEG monitoring, was in all instances psychogenic or malingering.	Conclusion: Patients who pass out or convulse during head-upright tilt without any change in physiologic parameters can be presumed psychogenic in origin and may be referred for psychiatric evaluation without further expensive diagnostic studies. [174]
Syncope. Isolated cardiac rhythm abnormalities noted in 21 patients, but none were symptomatic and no definitive arrhythmias occurred. Isolated EEG abnormalities noted in 11 patients, 5 of whom had EEG abnormalities consistent with seizure disorders. Simultaneous EEG and ECG abnormalities seen in 4 patients. In 2, a previously unsuspected etiology for syncope was found: seizures in 1 patient with heart disease and sinus pauses in another thought to have a seizure disorder.	Combined ambulatory EEG/ECG monitoring may prove useful in evaluation of some patients with syncope. [129]
Syncope is a loss of consciousness and postural tone. Although arising suddenly from prolonged recumbency or returning from weightlessness to Earth's gravity can result in syncope from orthostatic or vasovagal effects, there are many other possible causes. Cardiac causes are more likely to occur in the elderly; noncardiac causes are more common in the younger population. Cases described illustrate often unexpected mechanisms of syncope in otherwise healthy individuals.	Most important screening tool in identifying mechanism(s) of syncope is a detailed history emphasizing a search for underlying disease, specific associated circumstances, and pre- and post-event symptoms. Type of diagnostic studies, i.e., cardiac or neurologic, undertaken should be based on historical data. Seizures must be considered as a possible mechanism of otherwise unexplained loss of consciousness in nonelderly persons, including air crew members. [130,175]
Vasovagal syncope. Much of natural history is unknown. Study determined whether patients presenting for care had a recently worsened syncope frequency.	Many syncope patients present for care after a recent worsening of their frequency of syncope. [176]
Insufficient cerebral perfusion. Ultimate common cause leading to loss of consciousness with a critical reduction of blood flow to reticular activating system. In neurally mediated syncope, a paradox ictal reflex can occur that induces an increase in cerebrovascular resistance and contributes to the critical reduction of cerebral blood flow.	Outlines anatomic structures involved in cerebral autoregulation, its mechanisms in normal and pathologic conditions, and noninvasive neuroimaging techniques used to study cerebral circulation and autoregulation. Emphasis placed on description of autoregulation pathophysiology in orthostatic and neurally mediated syncope. [128,177]

Table 4. Genetic/Structural Mechanistic Factors

Associated Changes	Mechanisms of Sudden Death
The long QT syndrome (LQTS) is a genetically transmitted cardiac arrhythmia due to ion channel protein abnormalities, affecting transport of potassium and sodium ions across the cell membrane. Patients with LQTS may present with syncope, seizures or aborted cardiac arrest. LQTS is also an important cause of unexplained sudden cardiac death in the young.	Diagnosis of LQTS depends on ECG showing prolonged QT interval. Establishment of LQTS registry and discovery of genetic mutations causing LQTS contribute greatly to understanding this condition and provide an impetus to understanding other inherited cardiac arrhythmias. Genotype-phenotype correlation studies allow risk stratification of LQTS patients. Life style modification to avoid triggers for malignant cardiac arrhythmias, and use of beta-blockers, pacemakers and implantable defibrillators, help treat symptoms and reduce mortality in these patients. [133]
Congenital long QT syndrome is a rare inherited condition characterized by prolongation of action potential duration (APD) in cardiac myocytes, prolongation of QT interval in electrocardiogram (ECG), and increased risk of syncope and sudden death due to ventricular tachyarrhythmias.	Mutations of cardiac ion channel genes that affect repolarization cause majority of congenital cases. Despite detailed molecular characterizations of mutated ion channels, complete understanding of how individual mutations may lead to arrhythmias and sudden death requires study of intact heart and modulation by autonomic nervous system. Reviews studies of molecularly engineered mice with mutations in genes known to cause long QT syndrome in humans and specific to cardiac repolarization in mouse. [178]
Cardiac hypertrophy is an independent predictor of cardiovascular morbidity and mortality, predisposing patients to heart failure, QT interval prolongation and ventricular arrhythmias.	Cardiac Ang II overproduction leads to long QT syndrome resulting from an IK1 potassium-dependent prolongation of action potential duration through modulation of channel subunit expression. [159]
Inherited arrhythmia syndromes, 'channelopathies'	Long QT syndrome, short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, Brugada syndrome and overlapping phenotypes; established connections between these syndromes and idiopathic ventricular fibrillation. [179]
Cardiac hypertrophy associated with a dramatic change in gene expression profile of cardiac myocytes. Many genes important during development of fetal heart but repressed in adult tissue are reexpressed, resulting in gross physiological changes that lead to arrhythmias, cardiac failure, and sudden death. One transcription factor thought to be important in repressing expression of fetal genes in the adult heart is the transcriptional repressor REST (repressor element 1-silencing transcription factor).	Continued REST expression prevents increases BNP (Nppb) and ANP (Nppa) genes, encoding brain and atrial natriuretic peptides, in adult rat ventricular myocytes in response to endothelin-1 and inhibition of REST results in increased expression of these genes in H9c2 cells. Increased expression of Nppb and Nppa correlates with increased histone H4 acetylation and histone H3 lysine 4 methylation of promoter-proximal regions of these genes. Deletions of individual REST repression domains showed combined activities of two domains of REST required to efficiently repress transcription of Nppb gene while a single repression domain is sufficient to repress Nppa gene. Data provide some insight into molecular mechanism important for changes in gene expression profile seen in cardiac hypertrophy. [160,180]

Syncope results from acute cerebral hypoperfusion and must be differentiated from epileptic seizure in cases where convulsive activity is observed during the syncopal episode (Table 3). The pathogenesis of loss of consciousness is insufficient cerebral perfusion and reduction of blood flow to the reticular activating system. Brain circulatory autoregulation system keeps cerebral blood flow constant over a wide range of systemic blood pressures. With intact autoregulation a drop in blood pressure results in reduction in cerebral vascular resistance, in an attempt to prevent cerebral hypoperfusion. However, in neurally mediated

syncope, autoregulation can also be harmful, being actively implicated in a paradoxical reflex that induces an increase in cerebrovascular resistance with reduction of cerebral blood flow. This differentiation is important because of the possibility that so-called convulsive syncope could be misdiagnosed as a seizure disorder. [128] The possibility of fatal syncope masking as SUDEP has not been investigated. The occurrence of recurrent syncopal episodes is associated with an increased risk of sudden death. The type of diagnostic studies, i.e., cardiac or neurologic, undertaken should be based on the historical data. Evaluation of patients with syncope often includes a battery of noninvasive tests. Based upon history, combined ambulatory EEG and ECG recordings may be indicated in the evaluation of loss of consciousness. In one study, 45 patients (26 with suspected neurologic and 19 with suspected cardiac syncope) were evaluated with simultaneous 24-hour electroencephalographic (EEG) and 2-channel electrocardiographic (ECG) recordings. Isolated cardiac rhythm abnormalities were noted in 21 patients, but none of these was symptomatic and no definitive arrhythmias occurred. Isolated EEG abnormalities were noted in 11 patients, 5 of whom had EEG abnormalities consistent with seizure disorders. In 2 cases, a previously unsuspected etiology for syncope was found: seizures in 1 patient with heart disease, and sinus pauses in another thought to have a seizure disorder. [129] The occurrence of recurrent syncopal episodes is associated with an increased risk of sudden death. Identifying the mechanism(s) of syncope requires a detailed history searching for underlying disease, the specific associated circumstances, and pre- and post-event symptoms. [130] The type of diagnostic studies, i.e., cardiac or neurologic, will be based on the historical data.

Identification of asystole is important since antiepileptic drugs and cardiac pacing may be necessary in order to prevent recurrence. Bradycardia and/or asystole can occur during an epileptic seizure. If the person demonstrates loss of muscle tone or bilateral asymmetric jerky limb movements during a seizure one must clinically consider the possibility of ictal asystole. Ghearing et al [131] recommended video monitoring of EEG and ECG in patients with epilepsy to determine if ictal asystole is present.

Long QT syndrome (LQTS) is a genetically transmitted cardiac arrhythmia associated with protein abnormalities of ion channels affecting membrane transport of potassium and sodium ions. Establishment of LQTS registry and the discovery of genetic mutations causing LQTS have contributed greatly to the understanding of the role of genetics in explaining these conditions, while providing an impetus to understanding other inherited diatheses for potentially fatal cardiac arrhythmias (Table 4). With early premorbid diagnosis, beta-blockers, pacemakers and implantable defibrillators can help to treat symptoms and reduce mortality [132,133]. Patients may present with syncope consequent to arrhythmia induced cerebral hypoperfusion, associated aborted cardiac arrest and, on occasion, seizure activity. LQTS is also an important cause of unexplained sudden death in young individuals. While clinical diagnosis of LQTS depends on ECG with prolonged QT interval, findings may not be consistently seen on routine studies, but manifested at the time an arrhythmia is observed. LQTS predisposes to convulsive syncope in association with potentially fatal malignant ventricular arrhythmias. The characterized phenotypes relate risk for arrhythmia to specific biophysical defects in various sodium ion channel functional disturbances [134,135]. These phenotypes also carry significant prognostic information regarding risk of dying from an arrhythmia. Occurrence of bradycardia and/or complete heart block with apnea is another

example of cardiac disease that mimics epilepsy [136]. Postmortem findings of microscopic cardiac lesions have been reported in persons with epilepsy [137,138]. It is important for physicians not to misdiagnose in order to avoid inappropriate or even harmful therapeutic interventions. Since to our knowledge no studies are extant in persons with epilepsy that look for genetic mutations predisposing to potentially fatal cardiac arrhythmias, we speculate only about the possibility that epileptiform discharge related cardiac autonomic neural imbalance would aggravate a predisposition to perturbations of cardiac autonomic balance and cardiac rhythm regulation in patients with epilepsy. Despite detailed characterizations of the mutated ion channels at the molecular level, we do not know which individual mutations lead to arrhythmias and sudden death. Soliciting a detailed family history of cardiac related deaths in relatives of persons with epilepsy could be an important first step in identifying cardiac risk factors in persons with epilepsy who might be susceptible to cortical discharge induced destabilization of cardiac neural regulation. Patients with a positive family history represent important subjects for future investigation into prevention.

Ictally related disruption of cardiac neural regulation might be a factor in persons with epilepsy who also are predisposed for Burgada syndrome (Table 4). The Brugada Syndrome is a clinical entity associated with increased risk for sudden death. It is thought to be an autosomally inherited disorder affecting the cardiac sodium channel, predisposing to ST segment elevation in right precordial leads and malignant ventricular arrhythmias. Meregalli et al. [139] suggest Brugada syndrome is not a monofactorial disease, but rather one with various pathophysiological mechanisms in the individual patients at risk.

The connection between cardiac and central nervous system mechanisms for sudden death, whether SUDEP or cardiac sudden death, supports the proposition that pathological interactions between brain and heart underlie occurrence of deaths in some, but not for all patients in both groups. There are crossovers between groups as exemplified by patients who present with epilepsy that masquerades as cardiac arrhythmias [140,141] while others present with heart disease that masquerades as epilepsy. [142-144]

Hypertension, cigarette smoking, diabetes mellitus, hyperlipidemia, and obesity are major risk factors associated with development of age related advanced cardiac disease and/or sudden cardiac death. [145,146] However, sudden unexpected death often occurs in young asymptomatic patients. While deaths in young persons may occur as a consequence of ventricular tachyarrhythmias arising in an electrically unstable myocardial substrate, the mechanism of death is unknown. [147,148] Necropsy studies demonstrate that while macroscopic heart features were normal in nearly one-third of young cardiac sudden death victims, many have subtle histological findings of focal inflammation, cardiomyopathy and conduction system diseases [147,149]. Supporting the hypothesis that incompletely penetrant genetic defects initiating idiopathic ventricular arrhythmias may underlie at least some of the unexplained deaths in young people is the finding of a history of parental sudden death as an independent risk factor. [148]

The electrocardiogram pattern of RBBB and ST segment elevation in leads V1 and V3 (Brugada Syndrome) is associated with high risk of sudden death in patients with a “normal” heart (Table 4). [150] Natural history of the disease is not well established nor is the approach to stratifying patients according to risk. Some patients do not consistently exhibit the characteristic ECG pattern, which may be apparent only intermittently or after provocation

with ajmaline or intravenous flecainide. [151] Molecular genetics may explain some mechanisms that underlie sudden cardiac death in young persons with structurally normal hearts. Genetic mutations affecting cardiac ion channels may disrupt the balance of action potential currents, predisposing to malignant ventricular tachycardias. [134,135]. The cardiac sodium channel gene, SCN5A, is involved in two arrhythmogenic diseases, i.e., Brugada Syndrome and one form of long QT syndrome (LQT3). Brugada syndrome mutations reduce sodium channel activity current while LQT3 mutations are associated with the opposite effect. [150] Both conditions result in an electrical gradient between the endocardium and epicardium setting the substrate for dispersion of repolarization and genesis of arrhythmia [152]. Studies to date illustrate how subtle changes in channel biophysics exert significant and distinct effects and provide evidence of the importance of understanding molecular changes to better treat cardiac disease.

Another under-appreciated risk factor is presence of familial cardiomyopathies, emphasizing the importance of clinical and genetic screening (Table 4). [153] In persons with risk factors for sudden death, but in whom symptoms are minimal or subtle, prophylactic use of beta-blockers, statins, angiotensin-converting enzyme inhibitors, and/or aldosterone antagonists may reduce risk of sudden death. [154] Familial hypertrophic cardiomyopathy is an autosomal dominant inherited disease caused by genetic mutations involving at least 5 to 7 chromosomal loci coding for sarcomeric proteins [155,156], suggesting substantial genetic heterogeneity is present. Major risk factors for fatal events in persons with familial hypertrophic cardiomyopathy include a survived prior cardiac arrest, history of ventricular tachycardia, family history of sudden death, unexplained syncope, asymmetrical ventricular hypertrophy, especially of the intraventricular septum, and prolonged intraventricular conduction. [157,158] Genetically determined cardiac hypertrophy is another independent predictor of cardiovascular morbidity and mortality in younger patients, since it predisposes to heart failure, outlet obstruction, QT interval prolongation, and ventricular arrhythmias. Routine cardiac evaluation of persons with epilepsy would help to screen for this subtle predisposing risk for sudden death. Cardiac Angiotensin II overproduction has been demonstrated to lead to emergence of long QT syndrome resulting from an IK1 potassium-dependent prolongation of the action potential duration through modulation of channel subunit expression. [159] Molecular data indicate cardiac hypertrophy is associated with a dramatic change in the gene expression profile of cardiac myocytes. Many genes are important during development of the fetal heart but repressed in adult tissue and are reexpressed, resulting in gross physiological changes that lead to arrhythmias, cardiac failure, and sudden death. One factor important in repressing expression of fetal genes in the adult heart is the transcriptional repressor REST (repressor element 1-silencing transcription factor). [160]

Wolf Parkinson White syndrome can, in the presence of atrial fibrillation, lead to ventricular fibrillation and sudden death in otherwise healthy young adults. [161,162] Predictors of risk of death include the shortest R-R interval in atrial fibrillation and the anterograde refractory period of the accessory pathway. Another group that defies explanation is that of young athletes with no prior cardiac history and no cardiac pathology who drop dead during competition. [163] Any association of syncope, mitral valve prolapse, arrhythmias and sudden death is still subject to debate. [164]

Table 5. Risk Factors for SUDEP in a Swedish Population [182]

1. Higher number of seizures per year (relative risk of 10.16 in patients having more than 50 seizures/year compared to those with up to two/year);
2. Increased number of antiepileptic drugs (9.89 for three antiepileptic drugs vs. monotherapy);
3. Early vs. late onset epilepsy (7.72);
4. Frequent changes in antiepileptic drug dosage vs. unchanged dosage (6.08).
5. Risk and early onset, and SUDEP risk and seizure frequency was weaker for females;
6. Frequent dosage changes had a stronger association in females.
7. Early age of onset and male sex.

We are not aware of any studies that screened persons with epilepsy for any of the above discussed material nor for genetically determined cardiac predisposition for potentially fatal arrhythmias.

Risk Factors for SUDEP

A review of risk factors for SUDEP [181] concludes that strong risk factors include being a young adult male, having generalized tonic seizures, and lying in bed, presumably asleep. Weak risk factors include the prone posture, sub-therapeutic AED blood levels, being in a bedroom but not in bed, and having a structural brain lesion.

A nested case-control study by Nilsson et al [182] investigated association between clinical variables and SUDEP in an effort to identify risk factors in a Swedish population. They found 91% of the 57 SUDEP cases studied had autopsies performed. This unusually high rate of post mortem examination lends considerable credibility to the data. The associated risk factors for SUDEP are summarized in Table 5. In addition, it is commonly acknowledege that SUDEP is most likely to occur in sleep.

A multi-center prospective cohort USA study of incidence and risk factors in SUDEP in three epilepsy referral centers and found SUDEP accounted for 18% of epilepsy related deaths. [183] Lack of required autopsy limited diagnostic certainty of SUDEP in most cases. In contrast to most other studies, data in this study indicate women are at greater risk than men (1.45/1000 vs. 1.21/1000). Independent risk factors for SUDEP were occurrence of tonic-clonic seizures (only in women), treatment with more than two AEDs, and a full scale IQ less than 70. Cerebral structural lesions and psychotropic drug use prior to SUDEP were not risk factors. Sub-therapeutic AED levels were just as common in the control group as SUDEP victims. SUDEP was not associated with use of any particular AED.

A prospective study of risk factors for SUDEP in coroners' cases in Australia [184] found that being a young adult, sleep, and evidence of a terminal seizure to be risk factors. There was no association with use of any particular AED, nor with seizure frequency. A retrospective study in the Netherlands [185] of all patients at an epilepsy referral center found SUDEP risk of 1.24 per 1000 patient years. SUDEP victims were younger than control group of non-SUDEP deaths and had an earlier age of onset. Other risk factors including male sex,

generalized tonic clonic seizures, high seizure frequency, specific AED use, AED polypharmacy, mental retardation, psychiatric illness, and psychotropic drug use did not correlate with SUDEP risk. Differing data about SUDEP risk factors found in these recent studies suggest that variability in study design contributes to inconsistencies. The most valid data will come from prospective multicenter collaborative studies from referral center and general epilepsy populations. Most importantly, autopsy performance must be done on all persons dying with a history of epilepsy that do not have an obvious cause of death, with a fixed protocol for detailed gross and microscopic brain, autonomic nervous system, and heart examinations.

Table 6. Pharmacological Risk Factors

Symptoms and/or Changes	Mechanisms of Sudden Death
Antiepileptic Drugs (AEDs) Newer AEDs, including topiramate and lamotrigine, developed for chronic focal and secondarily generalized epileptic seizures. Efficacy of these drugs as anticonvulsants does not seem to be superior to that of traditional anticonvulsants such as phenobarbital.	Advantage of new drugs is a smaller spectrum of possible adverse events. Newer AEDs may or may not induce sedation and some may minimize noncompliance by reducing side effects of lethargy and cognitive impairment. Difficulty in achieving therapeutic dosage with some of the newer AEDs because of side effects makes one question whether some of these newer agents are "better" than the older AEDs. New AEDs do have less frequent interactions, leading to improved tolerability with comedication. [195]
Risk of SUDEP rates patients on lamotrigine, gabapentin, topiramate, tigabine, zonisamide are similar to those on standard AEDs.	Suggests SUDEP rates reflect population rates and not a specific drug effect. FDA requires warning labels on the risk of SUDEP in association with use of each of mentioned drugs. [194]
QTc-prolonging drugs and risk of SUD Torsades de pointes is associated with early depolarization. Drugs that prolong QT interval :class III antiarrhythmic agents, antimicrobial agents - fluoroquinolone and macrolide antibiotics, antipsychotic and antidepressant drugs, agents used in general anesthesia, and antimycotics	Prolonged QT interval leads to increased risk for development of ventricular tachyarrhythmias, particularly polymorphic ventricular tachycardia (torsades de pointes). Polymorphic arrhythmia may rapidly develop into ventricular fibrillation and cause sudden death. [192]
Cardiovascular Effects of Antipsychotics Older antipsychotic literature primarily concerned with physiological consequences of muscarinic cholinergic antagonism, alpha(1)-adrenergic antagonism or receptors associated with cardiac conduction, but current literature recognizes that, for most antipsychotic-exposed patients, the more significant cardiovascular burden of treatment is mediated by metabolic adverse effects such as weight gain, dyslipidemia and diabetes mellitus.	Adverse cardiovascular effects of antipsychotic treatment: tachycardia, orthostatic hypotension and rarely, SUD; muscarinic cholinergic antagonism, alpha(1)-adrenergic antagonism or receptors associated with cardiac conduction, metabolic adverse effects of weight gain, dyslipidemia and diabetes mellitus. [186]
Chlorpromazine or thioridazine do not appear to produce arrhythmia or death via a central locus in an experimental cat model.	May be acting directly on myocardial conduction to produce arrhythmia and death. [187-191]

The role of cardiotoxic drugs and/or AEDs as a risk factor for sudden death has not been clearly elucidated, although some data exist (Table 6). Adverse cardiovascular effects of antipsychotic treatment include tachycardia, orthostatic hypotension, muscarinic cholinergic antagonism, alpha (1)-adrenergic antagonism or receptors associated with cardiac conduction, metabolic adverse effects of weight gain, dyslipidemia and diabetes mellitus/ [186] In a cat study, chlorpromazine and thioridazine did not appear to produce arrhythmia or death via a central locus and may be acting directly on myocardial conduction to produce arrhythmia and death. [187-191] Drugs that prolong the QT-interval are associated with increased risk of SUD. [192] Polytherapy for AEDs, frequent dose changes, and high carbamazine levels were identified as risk factors for SUDEP in unstable severe epilepsy. [193] It is unclear whether high carbamazine levels per se represent a risk factor or just reflect having severe epilepsy. [193] Data suggested a need for further detailed analyses of the possible role of AEDs in SUDEP in larger cohorts and indicate that closer monitoring of the drug therapy may be useful to reduce risks. In 2003 Walczak [193] raised the question of whether AEDs play a role in SUDEP, noting there was little information other than on phenytoin and carbamazepine. The incidence of SUDEP found for gabapentin, tiagabine, topiramate, zonisamide, and lamotrigine clinical development programs is in the range found in other populations with refractory epilepsy, suggesting these individual antiepileptic drugs are no more likely to cause SUDEP than AEDs in general. [194] The risk of SUDEP can be decreased by aggressive treatment of tonic-clonic seizures with as few AEDs as necessary to achieve complete control. The new AEDs do have less frequent interactions, leading to improved tolerability with co-medication. [195] Prospective studies of patients need to be done to determine what characteristics are valid in determining whether a person with epilepsy is a candidate for SUDEP and to identify the AED or combination of AEDs that will provide best protection for a given patient.

Stress and Sudden Death

Psychological factors in epilepsy include stress and anxiety. Arrhythmogenic effects of efferent sympathetic drive precipitate cardiac arrhythmia and sudden death (Table 7). [125,196-199] Patients with preexisting heart disease are especially at risk. Generation of proarrhythmic activity patterns within cerebral autonomic centers may be amplified by afferent feedback from a dysfunctional myocardium. An electrocortical potential reflecting afferent cardiac information indicates individual differences in interoceptive sensitivity (awareness of one's own heartbeats). [198] Ventricular arrhythmias occurring in the setting of anger are more likely pause dependent and polymorphic, suggesting that in predisposed populations anger may create an arrhythmogenic substrate susceptible to more disorganized rhythms and may serve as a possible mechanism linking emotion and sudden death. [199] Emotional stress of anxiety and/or depression is an acknowledged risk factor for sudden death in patients with cardiac disease [125,150, 196,197,200-203]. The potential as a risk factor for SUDEP is not known. [194] Epileptic seizures are associated with neurogenic cardiac arrhythmias [136,141,203] Diagnosis of seizure disorder is associated with observation of microscopic cardiac pathology such as perivascular and interstitial fibrosis

Table 7. Psychological Factors

Symptoms and/or Changes	Mechanisms of Sudden Death
Scared to Death. A 21-year-old student had generalized tonic-clonic seizures induced by mental image of human pain. One ictal event occurred while listening to a description of suffering, as read from Fox's Book of Martyrs. While again listening to the offending passage during EEG and ECG monitoring, had 25 s of asystole terminating in electrocerebral silence and a generalized tonic, tonic-clonic seizure. A 24-hour ambulatory monitor recorded episodes of progressive sinus bradycardia concomitant with PR-interval prolongation and Wenckebach atrioventricular block. Sinoatrial conduction times and sinus node recovery times were normal on atrial pacing.	Since implantation of a permanent pacemaker, has been asymptomatic. Patient demonstrates advantages of reproducing the circumstances associated with an unexplained loss of consciousness while monitoring EEG and ECG. [196]
Emotional trauma and psychological stress Stress response is associated with increased sympathetic activity and catecholamine levels that may be associated with increased risk of cardiac arrhythmias, especially in context of epileptiform cerebral discharges.	Arrhythmogenic effects of efferent sympathetic drive precipitate cardiac arrhythmia and sudden death. Patients with preexisting heart disease are particularly at risk. Generation of proarrhythmic activity patterns within cerebral autonomic centers may be amplified by afferent feedback from a dysfunctional myocardium. An electrocortical potential reflecting afferent cardiac information, reflects individual differences in interoceptive sensitivity (awareness of one's own heartbeats). [198]
Stress is associated with changes in autonomic neural function, but its role as a potential risk factor for SUDEP is not known. Association of epilepsy with cardiac abnormalities, such as neurogenic arrhythmias and microscopic perivascular and interstitial fibrosis, and with depression and anxiety indicates emotional stress should be evaluated as a potential risk factor for SUDEP.	Impact of adverse emotional states on autonomic control of cardiac rhythm is a known important factor leading to cardiac dysrhythmias in humans and other species. Interaction between emotional factors and arrythmogenic potential of epileptiform discharges and possibility of benefit from stress management intervention need to be investigated. [125]
Stress and anger: compare morphology and initiation pattern between ventricular arrhythmias that are triggered by anger and those that are not. At the time of shock, patients with ICDs recorded levels of defined mood states preceding the shock in a diary. [199]	Ventricular arrhythmias occurring in setting of anger are more likely pause dependent and polymorphic. Suggests that in predisposed populations anger may create an arrhythmogenic substrate susceptible to more disorganized rhythms, a possible mechanism linking emotion and sudden death.

[137,138] and high levels of anxiety and depression. [204-209] Voodoo death is associated with over whelming stress or fear [210]. Voodoo death may result from acute stress or fear without an associated coronary artery predisposition. [210] Interaction of such neurological, cardiac, and emotional factors to increase the risk of SUDEP is unknown. Little investigation to date exists on the relationship between epileptiform discharges, cardiac factors, and emotional factors. Sudden cardiac death in older persons is generally associated with extensive coronary atherosclerosis. In younger individuals without a history of cardiac disease or epilepsy [211] unexplained deaths occur in correlation with no disease or with subtle microscopic pathology evident only on meticulously detailed microsopic autopsy. [212] Sudden death in the elderly and young may be associated with a genetic predisposition, dietary deficiencies, sleep disorders, and stress as likely factors in development of fatal arrhythmias. [76, 110-113] Another group that defies explanation is that of young athletes

who drop dead during competition with no prior cardiac history and no cardiac pathology. [163]

A state of anger, with enhanced adrenergic activity, may also contribute to risk of sudden death (Table 7) [201,213-216], while acute stress evoked by fear may contribute to occurrence of sudden death if there is a history of coronary artery disease [217]. Chronic stress linked with a history of heart disease suggests a need for stress management interventions, especially since myocardial infarction patients with depression are 3.5 times more likely to die [218]. Syncope can also be associated with the occurrence of sudden death, especially in conjunction with emotional arousal and psychological uncertainty in conditions that simultaneously activate fight-flight and conservation-withdrawal responses.

Prevention of Sudden Death

The role of stress and sudden death in patients provides a common explanation for adrenergic-related arrhythmias, leading to death in different conditions such as epilepsy, heart failure, exercise-induced death and also possibly sudden death in schizophrenia. Zigelstein [219] discusses the role of acute emotional stress and cardiac arrhythmias, and emphasizes that episodes of acute emotional stress have significant adverse effects on the heart and may produce left ventricular contractile dysfunction, myocardial ischemia [220], or disturbances of cardiac rhythm. Even though these abnormalities may only be transient, consequences can be gravely damaging and sometimes fatal. Asymmetric brain activity may make the heart more susceptible to ventricular arrhythmias during stress. The heart may be stimulated asymmetrically, producing areas of inhomogeneous repolarization that create electrical instability and facilitate development of arrhythmias. In the setting of emotional stress, a beta blocker should be given in the presence of ischemic heart disease to those who have survived an episode of sudden cardiac death. Localization related epilepsy, the most common type with adult onset, is associated, at least initially, with asymmetric epileptiform activity. Further work needs to be done on the possible benefit of stress and anger reduction programs. The risk/benefit of greater use of psychotropic medication in persons with epilepsy who are in the higher risk categories for SUDEP, e.g., young adult males with frequent seizures who need multiple AEDs with frequent dose adjustments, must be determined.

Engel [221] described eight precipitating circumstances that preceded sudden death including (1) illness or death of a close person, (2) acute grief, (3) threat of loss of a close person, (4) mourning or anniversary of a death, (5) loss of status or self-esteem, (6) personal danger or threat of injury, (7) relief from danger, and (8) reunion, triumph, or happy ending. The precipitating event was one that was impossible for the victim to ignore because it was abrupt, unexpected, or dramatic or because of its intensity, irreversibility, or persistence.

Owada et. al. [213] recommend that it would be helpful to identify individual patient's subjective symptoms for the purpose of planning interventions to relieve such stress and presumably reduce the risk of sudden death. They reported on autopsies of sudden death cases in Japan from May 1994 to February 1998 and reviewed medical records for 271 cases with interviews conducted of victims' close family members. Out of the 271 cases, 176 patients 20 to 59 years old were classified as cases of sudden death in the working

generation. Of these 176 cases, 91 (52%) could be analyzed by telephone interviews of close family members. In these sudden death cases, 29 were due to coronary artery disease (31.9%), 18 to acute cardiac dysfunction (19.8%), 6 to other cardiac diseases (6.6%), 4 to acute aortic dissection (4.4%), 4 to cerebrovascular disease (4.4%), and 30 to other diseases (32.9%). Risk factors identified included long-term stress, history of heart disease, hypertension, chest symptoms, autonomic disturbance, short-term stress, and a smoking habit. Short-term stress, autonomic disturbance and a smoking habit increased the risk of sudden death due to coronary artery disease. Long-term stress was associated with increased risk of sudden death due to acute cardiac dysfunction. Autonomic disturbance and stress were related to occurrence of sudden death.

A large spectrum of cardiovascular disorders appeared to be the most common organic cause for most sudden deaths in one population, although more than one in twenty cases of sudden death in this young adult population was not explained by structural risk factors. Two hundred cases of sudden death in persons less than 35 years of age were examined for the Veneto region in Italy. [163] Fifteen cases (7.5%) were due to cerebral causes, 10 to respiratory (5%), and 163 to cardiovascular etiologies (81.5%). Unexplained deaths occurred in 12 cases (6%). For cardiovascular sudden death, obstructive coronary atherosclerosis was found in 23% of the cases and arrhythmogenic right ventricular cardiomyopathy in 12.5%. Mitral valve prolapse occurred in 10%, conduction system abnormalities in 10% and congenital coronary artery anomalies for 8.5%. Myocarditis was reported for 7.5%, hypertrophic cardiomyopathy for 5.5%, aortic rupture for 5.5% and dilated cardiomyopathy for 5%. Non-atherosclerotic acquired coronary artery disease was found for 3.5%, postoperative congenial heart disease for 13%, aortic stenosis for 2%, pulmonary embolism for 2%, and other causes for 2%. Sudden death was unexplained in 6% of the cases.

Sudden unexplained death claims over 4000 young persons between ages of 1 and 22 each year in the United States. Almost half of the pediatric sudden death victims have a normal structural autopsy. Thus, possible approaches to risk reduction include identification of children at risk for cardiac arrhythmias as a cause of seizure-like events and optimal seizure control measures in those at risk for seizure related cardiac arrhythmias. [222] Many studies suggest assessment of medical histories in combination with cardiovascular and EEG evaluation of surviving family members may clarify possible risks for various categories of sudden unexplained death. [146,213,218,219,223,224]

The genetic basis for potentially fatal arrhythmia associated with the inherited long QT syndrome may be a factor. A 17-year old sudden death victim’s mother was challenged with epinephrine and a potential defect in the phase 3 potassium current encoded by the gene KVLQT1 was identified. A 5-base pair deletion was identified in the genetic material recovered from the decedent’s paraffin-embedded heart tissue. [223] These isolated cases indicate ability to perform molecular autopsies on achieved necropsy material may transform forensic evaluation of sudden death. Combination of catecholamine provocative testing in surviving family members and a postmortem LQTS gene analysis may unmask families with "concealed” LQTS and establish cause of previously unexplained sudden death, including, SUDEP. Whether or not presence of such a genetic defect in combination with epilepsy is a risk factor for SUDEP is not known. As with adults, mechanisms of SUDEP in the pediatric age group is unclear, but quite possibly is associated with seizure related cardiac arrhythmia

and/or respiratory insufficiency. Although children with epilepsy have an increased risk of death, SUDEP is rare, i.e., 1 to 2 /10,000 patient years versus 1/100 to 750 patient years in adults.

Emotional stress associated with worry, anger, frustration and anger are commonly associated with increased frequency of seizures. [225] Mechanisms involved in emotion associated seizure activation are not known, but multiple factors may be operating, including activation of neural networks, sleep deprivation, noncompliance, alcohol use, and hyperventilation. (Table 7) Even though there often is no immediate temporal relationship, in that seizures do not occur at the moment the patient has the negative emotional experience, the patient is at increased risk for one or more seizures especially those originating from the temporal lobe. [225] Use of antidepressants and/or neuroleptics could also be associated with an increase in the chance of seizure recurrence. Nonetheless, drugs in either of these groups may be required to treat the patients' dysphoric symptoms, but also increase the chance of lowering seizure threshold. Many clinical studies demonstrated that poor seizure control is a major risk factor for SUDEP. [226] Interrelationships between an adverse emotional state and other related seizure inducing circumstances warrants further investigation, especially since there is an association between poor seizure control and increased risk of SUDEP. [227] The previous discussion emphasized the role of stress as a risk factor in various categories of sudden death, but the role may be compounded in the case of epilepsy.

Acute stress caused by emotions such as fear may be associated with an increased risk of sudden death in persons with coronary heart disease. (Table 7) Chronic stress may contribute to development of cardiac disease,[146] by promoting long-term development of coronary artery disease, indicating a potential role for routine use of stress management in standard cardiac rehabilitation programs. The distinction between Type-A versus Type-B personalities as risk correlates appears to be overly simplistic, in that psychosocial factors of depression, hostility, social isolation, anxiety, anger, and other stresses are related to increased cardiac death and illness in all groups with coronary heart disease. [228] All of these psychosocial risk factors may benefit from a bio-psychosocial model of intervention. Death can result from acute stress related to disasters as exemplified by the five-fold increase in atherosclerotic coronary artery events on the day of the Los Angeles earthquake in 1994. [229] Acute mental stress induced experimentallyis associated with ST-segment deviation and wall-motion abnormalities. [230] Mental stress needs to be considered as a greater risk factor than exercise-induced ischemia in increasing the rate of fatal and non-fatal cardiac events, [231] again emphasizing that psychosocial stress management treatment in a cardiac rehabilitation program reduces cardiac related mortality and morbidity. [232] Distress within the family and/or stress at work are strong predictors for developing stress-related disorders, and should require intervention. [233] Whether we can extrapolate management of stress factors in coronary artery disease as being helpful in diminishing the risk of SUDEP is not known, but since so many of these same factors come into play in persons with epilepsy makes it difficult to discount this possibility.

Depression and anxiety are common symptoms associated with epilepsy. [234] The established role of depression and stress as major risk factors in sudden cardiac death raises the question of whether the same risk exists in SUDEP. Epidemiological data on psychiatric morbidity in epilepsy is spotty. Having epilepsy is stress producing and stress increases

seizure frequency. The uncertainty of when a seizure can occur, consequences of having a seizure upon one's employment status and driving privileges are common stress producing circumstances with which the person with epilepsy must live.

The cardiology literature has long assumed a causal relationship among depression, stress, and increased cardiac mortality. Depression is considered to be a state of prolonged negative arousal or mental stress associated with a measurably higher risk of fatal cardiac events. Stress can result in histopathological changes in a previously normal heart while genetically determined and/or acquired dysfunction of the opioidergic, GABAergic, cholinergic, adenosinergic and other transmitter/modulator systems may interact to predispose to arrhythmias and sudden death. [235,236] The impact of emotional stressors on the autonomic nervous system ensures that psychogenic factors are important in leading to cardiac dysrhythmias and to coronary and non-coronary sudden death syndromes in humans and other species. [237] Prolactin levels at necropsy were examined as a marker of antemortem stress. [238] However, postmortem prolactin values differed according to the cause of death, with higher values found in postoperative deaths and in chronically ill patients. In persons with epilepsy, an elevated prolactin level after seizures is used as an indicator that a seizure actually occurred. The prolactin level is consistently elevated after a generalized tonic clonic seizure and is a less predictable marker of partial seizures. [239] This neuroendocrine response to seizures and the acute manifestations of autonomic dysfunction in association with seizures and interictal epileptogenic activity are evidence of stimulation of the hypothalamic-pituitary axis. The data suggest that concurrence of autonomic and neuroendocrine dysfunction could be considered as a combined hypothalamic-pituitary mediated stress response in association with epilepsy, but its role in SUDEP is unknown and warrants further exploration."

The physician has an important role as counselor about stress-related issues in the patient's life. Individualized recommendations for intervention can include referral to a clinical psychologist with expertise in stress reduction. If at all possible, contact with both internal and external stressors should be decreased. Treatment with anxiolytics, antidepressants, or neuroleptics certainly certainly can be helpful in conjunction with counseling. The long acting anxiolytics clorazepate and clonazepam are relatively effective as adjunctive antiepileptic drugs in selected patients. Paranoia, thought disorder, hallucinations, and extreme agitation require concurrent psychiatric consultation in addition to treatment with neuroleptics. When managing the patient, care must be exerted since a rapid change in levels of neuoroleptics, use of high doses, or induction of drowsiness may have the potential to worsen occurrence of seizures. Reduction in agitation, thought disorder and hallucinations usually exerts a calming effect and contributes to lowering the stress level and to restoring the patient's sense of well being.

Important issues above and beyond standard medical and phsychological intervention for the prevention/treatment of sudden death in cardiac patients or in patients with epilepsy at risk for sudden death has been raised [240], emphasizing the importance of lifestyle issues. The beneficial effect of nutritional aspects of Omega-3 fatty acid may decrease cardiac arrhythmias and sudden death (SUD) in patients with cardiac disease. Whether Omega-3 fatty acid deficiency is a risk factor for the relatively young population prone to SUDEP (mean age 32.5-43.5 yr. [241] is unknown. Unless someone has familial hypercholesterolemia with very

high levels of cholesterol at a young age, cholesterol is not a risk or predisposition to cardiac disease for the young population at risk for SUDEP. The beneficial cardiovascular effect of Omega-3 fatty acid to decrease sudden death in cardiac patients may be due to actions on cholesterol levels. Will this cardioprotective effect, independent of the effect on cholesterol levels, be of benefit for patients with epilepsy? There is certainly nothing bad to be said for including Omega-3 fatty acid in your diet to gain the long-term nutritional benefits.

Low temperatures may also be a risk factor for cardiovasular abnormalities and hence sudden death [240]

Many questions must be raised, including ours listed in Table 8.

Table 8. Low Temperature as SUDEP Risk Factor: To Be Answered

1. Exactly how does one define a low temperature?
2. What is the degree range used to define a low temperature
3. What is the duration at this low degree range?
4. Is there a dose response so that there is an increased risk of sudden death related to the lowest temperature?

If low temperatures are a risk factor for sudden death, one is unsure how to council patients to avoid cold. Should patients be advised to not ski, snow shoe, ice skate, or walk in the cold, to dress warmly, avoid hypothermia, or move to Houston, Florida, or Southern Spain? During the winter, increases in hemoconcentration (erythrocyte count, plasma cholesterol and plasma fibrinogen levels) occur and may contribute to arterial thrombosis. [242] It is essential to distinguish the pathological and normal response of the body for protection vs. the response to hypothermia. If the physiological changes noted above are normal defense mechanisms they may be difficult to modify except for moving to a temperate climate, an option not possible for most. Likewise we do not expect that patients living in a colder climate would cease participating in all outdoor winter activities. Additional studies are needed to confirm the basis of the cold theory. The cold theory has been challenged by several epidemiological studies, including the study by Kloner et al. [243]. They noted that even in the mild climate of Los Angeles Country, there are seasonal variations in the development of coronary artery death, with approximately 33% more deaths occurring in December and January than in June through September. Although cooler temperatures may play a role, other factors such as overindulgence or the stress associated with the holidays may also contribute to excess deaths during these peak times.

Beneficial effects of physical activity may be related to reductions in sympathetic activity since morbidity and mortality in cardiovascular disease are often associated with elevations in sympathetic nervous system activity. [240] Since increased physical action has a beneficial cardiovascular interaction, will increased physical action be of beneficial input if one assumes cardiovascular sympathetic dysfunction or insufficiency in persons with epilepsy? Exercise has no empiric downside, *assuming* the patient is cardiovascularly fit to undergo the type of exercise selected. If exercise is beneficial to prevent sudden death in persons with epilepsy it will be a great finding. Even if there is no protective or preventive effect for sudden death resulting from exercise, there is no reason for a patient with epilepsy to not

exercise. Prospective studies of patients need to be done to determine how to identify which persons with epilepsy are at risk for SUDEP. [244,245] Clarification of risk factors and establishment of the mechanism of SUDEP are important to establish preventative measures for SUDEP and emphasize the need to strive for full seizure control. [240] It is important to encourage patients with epilepsy worldwide to receive non-medical, life style modifying interventions that have generally accepted public health benefits even though there is as yet no consensus that they may or may not prevent sudden death.

The antiarrhythmic and anticonvulsant activity of beta-blocking agents pertinent to adrenergic mechanisms of SUDEP presents an interesting challenge pertinent to possible justification of trials testing effects of beta-blockers in SUDEP cases where resuscitation is possible. As early as 1980 Lathers [6] demonstrated that timolol, a beta-blocking agent initially approved for use in treatment of glaucoma in humans, exhibited antirrhythmic activity in the cat. This antiarrhythmic action was confirmed in humans in the BHAT trial. [246] Subsequently Lathers et. al. [26] administered timolol centrally and then peripherally to determine if it would have a beneficial effect on the risk of cardiac arrhythmias, epileptiform activity and changes in blood pressure and heart rate induced by pentylenetetrazol intracerebroventricularly (ICV) administered to anesthetized cats. Increasing doses of timolol administered intracerebroventricularly and intravenously not only significantly decreased elevation of mean arterial blood pressure and heart rate but also decreased and subsequently abolished incidence of cardiac arrhythmias associated with epilepiform activity. Pentylenetetrazol, trauma, inhibition of prostaglandin transport across the blood-brain barrier, or altered synthesis or metabolism of central enkephalins may lead to increased central levels of PGE2 and/or enkephalins. [27,28] The consequence of increased central levels of PGE2 and/or enkephalins may inhibit central GABA release, epileptogenic activity, increased blood pressure and heart rate, increased sympathetic and parasympathetic central neural outflow, and impaired or imbalanced cardiac sympathetic and parasympathetic discharge and arrhythmnia and/or death. These factors may be required to act together in various degrees and combinations in different susceptible individuals to initiate arrhythmias and/or death. Central (i.c.v.) administration of timolol partially suppressed the epileptiform activity and subsequently decreased the blood pressure and heart rate values elevated by pentylenetetrazol. Timolol may interfere with the central actions of PGE2 or enkephalins to reverse their known capabilities to induce epileptiform activity. Experimental studies are required to verify this possibility. Pharmacological agents capable of suppressing epileptiform activity and the sympathetic component of cardiac arrhythmias theoretically may be the best regimens to prevent interictal activity and associated cardiac arrhythmias that contribute to production of SUDEP [15,16,18,19,29]. Data indicate that timolol possesses components of both of these capabilities. Blockade of cardiac beta 1 receptors, a cardiac neurodepressant effect, and/or membrane depressant actions of beta-blocking agents may contribute to the antiarrhythmic action of beta-blocking agents [6,8,9,68-73]. Since pentylenetetrazol is an accepted epilepsy model and some drugs capable of suppressing pentylenetetrazol-induced epileptiform activity are anticonvulsant agents, the data suggest that timolol exhibited an anticonvulsant action. Although the data indicated that timolol can reverse the effects of pentylenetetrazol on the brain, this does not necessarily mean that timolol has intrinsic “anticonvulsant” properties separate from an ability to reverse the effects

of pentylenetetrazol. To answer this question, additional studies should be done to determine whether timolol and other beta-blockers will protect against seizures induced in other experimental models of epilepsy and in persons with epilepsy. It will be important to evaluate the capability of timolol to suppress interictal discharges and cardiac arrhythmias elicited in other in vivo experimental models not involving pentylenetetrazol. If timolol also suppresses both interictal discharges and arrhythmias in these models, this effect would provide additional evidence to support the possibility that timolol might be an effective adjunctive agent to use in epileptic patients to prevent sudden unexplained death.

Beta-blocking agents in general may have anticonvulsant action. [247-259] The anticonvulsant action of timolol [24] is similar to the anticonvulsant action of diazepam when employed in the swine model. [25,256,257] Intravenous propranolol was found to suppress significantly the seizure duration at one minute following pentylenetetrazol administration in a pig model.(Control 36.3 +- 4.8 minutes vs. iv propranolol 12.3 +- 5.1 minutes. Propranolol also decreased the basal heart rate and reduced the transient increase in mean arterial blood pressure elicited by PTZ compared to the untreated animals. No changes were effected on the basal mean arterial blood pressure. [24]

Proposed anticonvulsant mechanisms of beta blockers include decreased central serotonergic activity [248], monoamaine oxidase activity [247], and a membrane stabilizing effect [210] Another proposed antiepileptic mechanism of beta-blocking agents may include a CNS effect beta 2 receptor blockade. [249]. Although norepinephrine may have anticonvulsant effects, it may exacerbate seizure activity via activation of beta-receptors. Seizure susceptibility, but not necessarily seizure severity, in genetic epilepsy-prone rats may be the result of norepinephrine deficits in the hypothalamus/thalamus [261]. However, while severity and susceptibility can be determined by norepinephrine (NE) deficits in the telencephalon, midbrain, and pons-medulla, seizure severity but not susceptibility may be determined by norepinephrine abnormalities in the cerebellum. In the hippocampus the noradrenergic effect may not be uniform since selective activation of alpha or beta-receptors by NE in the hippocampus can produce either anticonvulsant or proconvulsant effects, respectively. [262] Beta-blocking agents can increase norepinephrine concentration in cerebral spinal fluid. [263] Another study suggested that establishment of beta blockade with timolol would increase the central NE concentration. [24] The protective mechanism for timolol and other beta blockers against seizures induced by PTZ maybe the result of a selective blockade of seizure-inducing beta receptors, allowing available NE to stimulate the anticonvulsant action of central alpha 1 receptors. The role of central postsynaptic alpha 2 receptors also deserves explanation. For example, activation of alpha 2 receptors decreases the excitability of CA1 pyramidal neurons [262,264]. Clonidine and 1-*m*-norepinephrine are more selective for alpha 2 than for alpha 1 receptors and inhibit epileptiform activity at low concentrations. However, the alpha 1 agonist l-phenylephrine is ineffective at high concentration, suggesting that central postsynaptic alpha 2 receptors may have a potentially greater anticonvulsant effect than the alpha 1 receptors in explaning the action of timolol [25].

Data from this cardiac arrest and resuscitation model [265-268] suggest that clinical trials to evaluate the effects of beta-blockers in persons at risk for SUDEP, i.e., those with poorly

controlled seizures and taking several AEDs. Propranolol [269], diazepam [270] and lorazepam [271] exhibited an anticonvulsant effect on PTZ-induced convulsions in swine.

The therapeutic approach to ischemic heart disease related to congestive heart failure and left ventricular hypertrophy, especially in the post infarction period, focus primarily on the use of beta-blockers, converting enzyme inhibitors, amiodarone [272,273] and implantable defibrillators [274]. While an arrhythmogenic right ventricular cardiomyopathy may be a cause of sudden death in young athletes, endomyocardial stripping, RV amputation, antiarrhythmic drugs, radiofrequency ablation, and implantable defibrillators have all been tried as treatment without success. [275,276] Measures for the prevention of SUDEP are also limited, and include achieving seizure control with a minimal number of AED's and/or with temporal lobectomy in appropriate patients [277]. Also to be considered in persons with intractable forms of epilepsy is the use of nocturnal respiratory monitors [121]. The prevention of sudden death in cardiac patients, just as in the prevention of sudden, unexpected death in persons with epilepsy [278], awaits further definition of the best combination of pharmacological and nonpharmacological measures. Finally, while the role of stress and/or depression as risk factors for sudden cardiac deaths is now widely acknowledged, their adverse effect upon the risk of SUDEP has had little investigation.[Table 7, 125, 218, 219]

Needed Studies

A fundamental question that needs to be addressed is that of the possibility of common risk factors for SUDEP and cardiac disease, especially related to central autonomic dysfunction, epileptiform discharges, and stress. [278] Unresolved issues in sudden unexpected deaths include the need for a better understanding of the risk for individuals; the mechanisms of cardiac arrest in individuals without previously identified structural heat disease, definition of the dysfunctional interaction of the CNS and the heart, the interaction of acute pulmonary edema and central apnea with cardiac autonomic neural and subtle anatomic/genetic factors as risk for SUDEP, development of preventive primary and secondary prevention of sudden death, and development of educational programs on preventive interventions.

One area of clinical investigation that is showing promise is that of spectral analysis of heart beat variability [100-103]. This method assists in understanding the relationship of the autonomic system to normal and abnormal conditions. Heart rate variability detects sympathetic-parasympathetic balance in the autonomic nervous system in persons with epilepsy at risk for sudden death and can be analyzed from data collected when persons with epilepsy undergo intensive monitoring with routine collection of ECG, EEG, and video data. While preliminary data suggested that subjects receiving phenytoin have more variability than to those given carbamazepine, the researchers were unable to determine whether differences in heart period variability were attributable to the drug alone. Pharmacological interventions aside, difference in the effects of heart period variability was found to be related to seizures within and between subjects. . Reduced power during the ictal events commonly was associated with episodes of tachycardia. [279, 280] Other changes included precipitous

or instantaneous heart slowing in the late ictal or postictal period, associated with extended R-R and normal QT intervals to the association of these latter changes with seizures were indicative of a measurable disturbance of cardiac autonomic regulation. Compared to ictal or postictal periods, decreased power occurred over the entire spectrum during seizures. This was jn agreement with previous observations of the autonomic effects of seizures being the very first manifestation of seizure activity [280,281].

Early autonomic changes preceding impending seizures can be used as biological markers to help elucidate the transition from interictal to ictal states in patients with epilepsy. Using these markers, complex partial seizures evoked early autonomic imbalance and tachycardia. Spectral power analysis found that the R-R intervals increased over the pre-ictal period, but fell rapidly over the 39 seconds before seizure onset, remaining reduced during seizure. These observations support the use of time-frequency analysis for autonomic activation hallmarks of impending clinical seizure onset. A rapid withdrawal of parasympathetic effect occurred approximately 30 seconds before seizure occurrence, while sympathetic activation peaks at seizure onset. These preictal autonomic disturbances indicate that the transition from interictal to ictal states is a prolonged event and that the associated subclinical autonomic changes are the first ictally related disturbance. [282]

Heart rate variability of epilepsy patients is observed to be lower at night than during the daytime, indicating subtle autonomic dysfunction at night, the time when the risk of SUDEP is greatest [144]. Persons having generalized tonic-clonic seizures, taking no AEDs, exhibited a higher standard deviation of all R-R intervals in 5 min recordings compared to normals. Using heart rate variability analysis, high frequency parasympathetic activity is found to be reduced and low frequency sympathetic values are found to be increased. Thus there is an increase in the sympathetically mediated heart rate in epilepsy patients who have generalized tonic-clonic seizures. These findings suggest that increased sympathetic activity may be a factor leading to increased risk of ventricular tachyarrhythmias in patients with epilepsy and possibly to sudden death. [283]

Presumably, heart rate is perturbed by alterations in neuro-autonomic function in clinical syndromes of sudden cardiac death, congestive failure, space sickness, and physiologic aging. The mathematical concept of fractals provides insight into such complex physiologic processes as heart rate regulation [284]. Fractal mechanisms as related to cardiac electrophysiology suggest that a subtle but functionally important loss of normal fractal complexity of interbeat interval dynamics, may not be detected using conventional statistics, and need to be analyzed using methods derived from the “chaos theory.” if we are going to be able to evaluate the loss of complex physiological variability in pathological conditions including heart rate dynamics before sudden death [285]. Cardiac chaos is prevalent in healthy hearts and a decrease of cardiac chaos occurs in abnormal states such as congestive heart failure [286]. Detrended fluctuation analysis of heartbeat time series may be helpful in distinguishing healthy from pathologic data sets [287]. Prospective studies of patients need to be designed to determine how we can identify which persons with epilepsy are at risk for SUDEP. [244,245]

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Chapter 14

Impact of Cardiac Rehabilitation, Exercise Training, and Fitness on Psychological Distress

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"It is Exercise Alone That Supports the Spirit, and Keeps the Mind in Vigor"
Cicero

The major risk factors for coronary heart disease (CHD) include smoking, hypertension, dyslipidemia, diabetes mellitus, a strong premature family history, as well as metabolic syndrome, and obesity.[1-3] Sedentary lifestyle and poor physical fitness are generally considered to have adverse affects on many of these established CHD risk factors, but may also independently increase the odds of CHD.[4-10] Although the importance of psychosocial risk factors in the development and expression of CHD and atherosclerosis has been debated for many decades, substantial evidence now exists that many components of psychological distress, especially depression, anxiety, and hostility, are also significant CHD risk factors that may also adversely affect recovery following major CHD events.[11-14]

Most of the evidence is focused on the high prevalence of depression in patients with CHD as well as the role of depression as a CHD risk factor and as a mean of predicting prognosis.[11-19] However, our research has also focused on the role that hostility [11,12,20,21] and anxiety [22,23] have to increase major CHD events. In fact, a psychosocial index incorporating many of these behavioral factors was used in the INTERHEART study from 11,119 cases of acute myocardial infarction (MI) and 13,648 controls in 52 countries. [24,25] This index has recently been demonstrated to be an independent risk factor for acute MI. [24,25]

Additionally these adverse psychological risk factors have been associated with several of the standard CHD risk factors, including dyslipidemia, hypertension, and obesity, [13] and psychological distress has also been associated with inflammatory biomarkers that are

associated with an increased risk of CHD events, as well as coronary artery calcification, coronary atherosclerosis, as well as peripheral vascular disease. [26-31] Therefore, this all supports that greater emphasis needs to be placed on psychological risk factors in the prevention and treatment of CHD.

Impact of Exercise Training

"Those who think they have no time for bodily exercise will sooner or later have to find time for illness."
Earl of Derby

Numerous studies have considered that regular exercise training is associated with marked reductions in the long-term risk of major cardiovascular (CV) events, CV mortality, and all-cause mortality. [4-10,32] In addition, many studies, particularly data from Blair and colleagues who have studied over 13,000 men and women at the Cooper Clinic, indicate that objective measures of overall fitness strongly correlate with total mortality as well as CV deaths and deaths from cancer. [33-36] Even in obese individuals or in people with many adverse CHD risk factors, high levels of overall fitness provide considerable protection against major CV events. In addition, improvements in fitness over time have correlated with reductions in CV and total mortality. [34,36,37]

Specialists in CV diseases have generally recommended exercise training in primary and secondary prevention of CHD (Table 1), [4] but substantial evidence suggests that regular exercise and increased fitness may also favorably modify various psychosocial risk factors, including depression.[6-10,12,13,15-17] In fact, cross sectional studies from patients with diseases as well as from otherwise healthy subjects have consistently demonstrated a direct relationship between depression and physical inactivity.[12,38] In addition, randomized controlled trials have demonstrated that exercise training also reduces depression. A randomized controlled trial comparing exercise therapy and the anti-depression medications sertraline hydrochloride was performed in 156 patients with depression, and exercise therapy was just as effective as medication for reducing depression with low rate of relapse in the exercise group.[39]

We and others have published the numerous benefits of exercise therapy following formal, phase II cardiac rehabilitation and exercise training (CRET) programs. [13,15-17,40-43] Patients generally enter these programs between 1-6 weeks following a major CHD event, and programs involve 12 weeks of 3 sessions per week (total of 36 sessions involving education and exercise.) Following these programs (Table 2), patients have marked improvements in exercise capacity and overall levels of fitness, reductions in obesity indices and risk factors for metabolic syndrome, [1,2,44] improvements in plasma lipids (especially high-density lipoprotein cholesterol or HDL-C as well as triglycerides), [45-48] inflammation (especially levels of high-sensitive C-reactive protein or CRP), [49] blood rheology and viscosity, [50] autonomic function, [51] parameters of ventricular repolarization dispersion (and therefore of the risk of malignant ventricular arrhythmias) [52, 53] and levels of homocysteine. [54]

Table 1. Potential Beneficial Effects of Regular Exercise

Benefits related to risk factors for coronary artery disease
Eases smoking cessation
Improves glucose metabolism
Raises serum high-density lipoprotein cholesterol level
Reduces arterial blood pressure
Reduces body weight
Reduces serum triglyceride and possibly low-density lipoprotein cholesterol level
Reduces stress
Hematologic benefits
Decreases hematorit and blood viscosity
Expands blood plasma volume
Increases red blood cell deformability
Increases fibrinolytic activity
Other benefits
Decreases atherosclerosis (proven in animals)
Decreases morbidity and mortality
Increases coronary collateral circulation (in many species)
Increases coronary flow reserve
Increases myocardial capillary density (in most species)
Increases tolerance of ischemia
Increases ventricular fibrillation threshold
Possibly increases epicardial coronary artery size

Reproduced with permission from Lavie CJ et al. Exercise and the heart: Risks, benefits, and recommendations for providing exercise prescriptions. *The Ochsner Journal* Oct. 2001:3(4):207-213. [4].

This therapy has also reduced subsequent hospitalization costs, [55] as well as major CV morbidity and mortality and all-cause mortality. [56] In addition, as we will review in this chapter, our CRET studies have demonstrated that this therapy results in marked improvements in behavioral and psychosocial factors, including depression, anxiety, and hostility, as well as overall health-related quality of life (QoL). [13]

Exercise Training and Psychological Distress

During the past 2 decades, we have performed numerous studies assessing behavioral factors with the Kellner Symptom Questionnaire. [57,58] For this Symptom Questionnaire (92 yes/no answers), patients are instructed to “Please describe how you have felt during the past week; circle the appropriate answer. Do not think long before answering. Work quickly!” This questionnaire is validated to assess behavioral characteristics, including

symptoms of depression, anxiety, hostility, and somatization, with a lower score indicating a more favorable behavioral trait (manual of the Symptom Questionnaire available on request; or P. Kellner MD, PHD, written and oral communication, 1986) based on prior studies of mean scores of healthy subjects [R. P. Kellner MD, PHD, unpublished data, January 1987; normal scores (scale scores between 1 and 2 standard deviations above the mean) for anxiety and hostility are 7 or less and for depression < 7; therefore, we chose 8 or higher as cut-offs to indicate anxiety and hostility symptoms and 7 or higher for depression symptoms. In addition to the Symptom Questionnaire, patients were also evaluated before and after formal CRET using the Medical Outcome Study 36-Item Short-Form Health Survey, [59] which is comprised of 36 short questions, and is validated for total QoL as well as several individual components (mental health, energy, fatigue, general health, bodily pain, well-being and functional status).

Table 2. Benefits of Cardiac Rehabilitation and Exercise Training Programs

• Improvement in exercise capacity and overall fitness
• Estimated METS: +35%
• Peak oxygen consumption: +15%
• Peak anaerobic threshold: +11%
• Improvements in lipids
• Total cholesterol: -5%
• Triglycerides: -15%
• HDL-C (nearly 15% increases in those with low baseline HDL-C): +6%
• LDL-C: -3%
• LDL/HDL: -8%
• Reduction in obesity indices
• Body mass index: -1.5%
• Percent fat: -5%
• Metabolic Syndrome: -37%
• Reduction in inflammation (hs-CRP – 40%)
• Improvement in autonomic function
• Improvement in blood rheology
• Reduction in homocysteine (-10%)
• Improvements in behavioral characteristics (depression, anxiety, somatization, and hostility)
• Improvements in overall quality of life and its components
• Reduction in hospitalization costs
• Reduction in overall cardiovascular morbidity and mortality, particularly associated with high psychological distress

METS = Metabolic equivalents
HDL-C = High density lipoprotein cholesterol.
LDL-C = Low density lipoprotein cholesterol.
hs-CRP = High sensitivity C-reactive protein.

Over a decade ago, we studied 338 consecutive CHD patients following major CHD events and found that 20% met criteria for depression symptoms based on the Symptom Questionnaire prior to the CRET program. [6] These depressed CHD patients have lower exercise capacity and physical fitness, reduced HDL-C and higher triglycerides, had lower scores for total QoL as well as for all 6 individual components of QoL, and had greater scores for anxiety, hostility and somatization compared with non-depressed patients. After the CRET program, depressed patients had impressive improvements in depression scores, the other behavioral scores, and in QoL and all of the components. In addition, they had marked improvements in exercise capacity as well as improvements in % body fat, triglycerides, and HDL-C. Many of these improvements were statistically greater in the depressed compared with the non-depressed patients following CRET. The prevalence of depression fell from 20% to only 12% following formal CRET.

Also over a decade ago, we demonstrated that patients with diabetes mellitus had a significantly higher prevalence of depression (26% versus 14%) compared with patients without diabetes, yet following the formal program of CRET, both groups had a prevalence of depression symptoms of only 9%. [7]

In another study of 268 elderly patients ≥ 65 years (mean 71 ± 5 years), the prevalence of depression symptoms was 18%. [8] Depressed elderly had significantly reduced exercise capacity and had lower levels of HDL-C than non-depressed elderly. In addition, the depressed elderly had significantly higher scores of anxiety, hostility, and somatization and had significantly lower scores for QoL and for each of the 6 components studies compared with non-depressed elderly. Following CRET, both groups had significant improvements in exercise capacity, obesity indices, HDL-C, as well as in behavioral characteristics and QoL and its subgroups. The prevalence of depression symptoms fell significantly from 18% to only 8% following rehabilitation. Although significant improvements were noted in depressed and non-depressed elderly, the depressed elderly demonstrated statistically greater benefits in anxiety, depression, total QoL, well-being, functional status, general health, energy and/or fatigue score, and mental health than did the non-depressed elderly group.

In a study of 83 women and 375 men, we demonstrated statistically similar improvements in all of the parameters studied in men and women. [60] Women with CHD, however, have a slightly higher prevalence of depression symptoms compared with men (23% versus 18%), and in women the prevalence dropped 12% following cardiac rehabilitation. [9] Moreover, in this study of 23 depressed women compared with 79 women without depression, the depressed women had statistically greater improvements in body mass index (BMI), HDL-C, total QoL, as well as well-being, pain, and mental health following formal CRET programs. We have also demonstrated significant benefits of cardiac rehabilitation program in very elderly ≥ 75 years of age, [61] as well as in elderly women. [19]

Although most of the emphasis has been directed toward depression as a major CHD risk factor, we have also focused on hostility or unexpressed anger, [20,21] and anxiety as risk factors. [22,23] In a study of 500 consecutive patients following CHD events, we noted that hostility symptoms were present in 13% at baseline prior to cardiac rehabilitation. [20] These patients with hostility symptoms were on average 7 years younger and had higher weight, BMI, total cholesterol, triglycerides, and other behavioral characteristics (anxiety, depression,

and somatization), and had lower levels of HDL-C, QoL (and several components) compared with patients with low hostility. Following CRET, the prevalence of hostility symptoms fell to only 8% and these patients had improvements in most of the CHD risk factors studied. Although both patients with and without hostility symptoms had improvements in most of the parameters studied following CR, those with high hostility score had greater improvements in hostility score (-45% versus +0%; $p<0.001$) and anxiety scores as well as 3 components of QoL (general health, mental health, and energy) and total QoL (+20% versus +15%; $p=0.07$). Subsequently, we demonstrated that patients < 50 years of age had a prevalence of hostility of 28% compared with only 8% prevalence in those ≥ 65 years; following CRET, the prevalence fell to 15% and 4%, respectively, in the young and older patients. [21]

In another study of 500 consecutive patients with CHD, we demonstrated that the prevalence of anxiety symptoms was 44%, 20%, and 24%, in patients < 55 years (n=121), 55-70 years (n=232), and those > 70 years (n=147), respectively. [23] As in our other studies of abnormal behavioral factors, patients with high anxiety were on average 4 years younger and had higher weight, % fat, BMI, triglycerides, and other behavioral scores and lower levels of HDL-C and QoL compared with non-anxious patients. Following cardiac rehabilitation, the entire group had a 56% reduction in the prevalence of anxiety and a nearly 70% reduction in the prevalence of severe anxiety. Additionally, the formal CRET programs significantly improved most of the CHD risk factors in both anxious and non-anxious patients. However, patients with high anxiety had greater improvements in anxiety scores (-56% versus -14%; $p<0.05$), depression score (-56% versus -17%; $p<0.05$) and total QoL score (+28% versus +14%; $p<0.01$) compared with patients without anxiety.

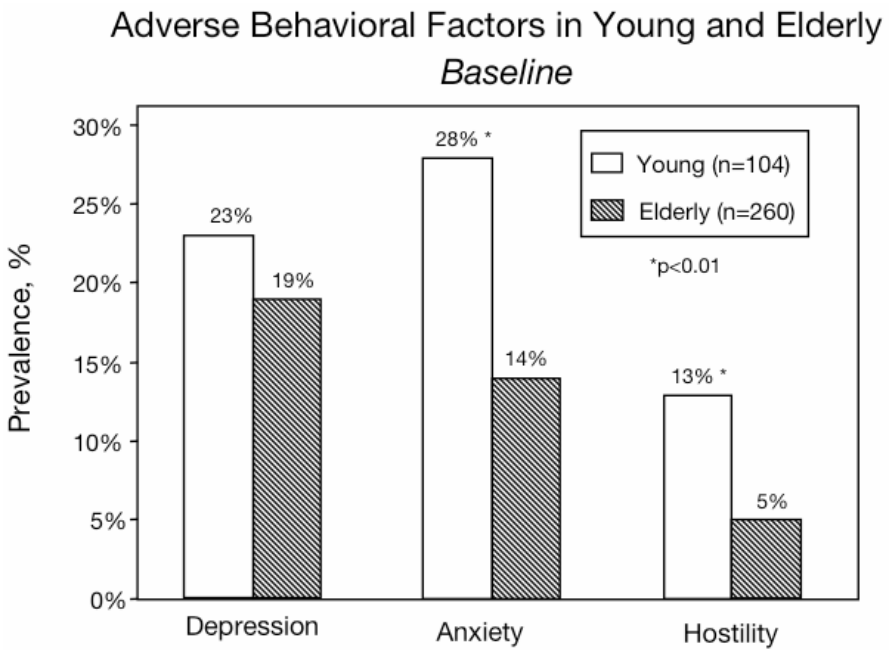

Figure 1. Prevalence of adverse behavioral characteristics in young (mean 48 ± 6 years) and elderly (mean 75 ± 3 years) patients with CHD. Adapted with permission from Lavie CJ, Milani RV. *Arch Intern Med* 2006;166:1878-1883. [62]

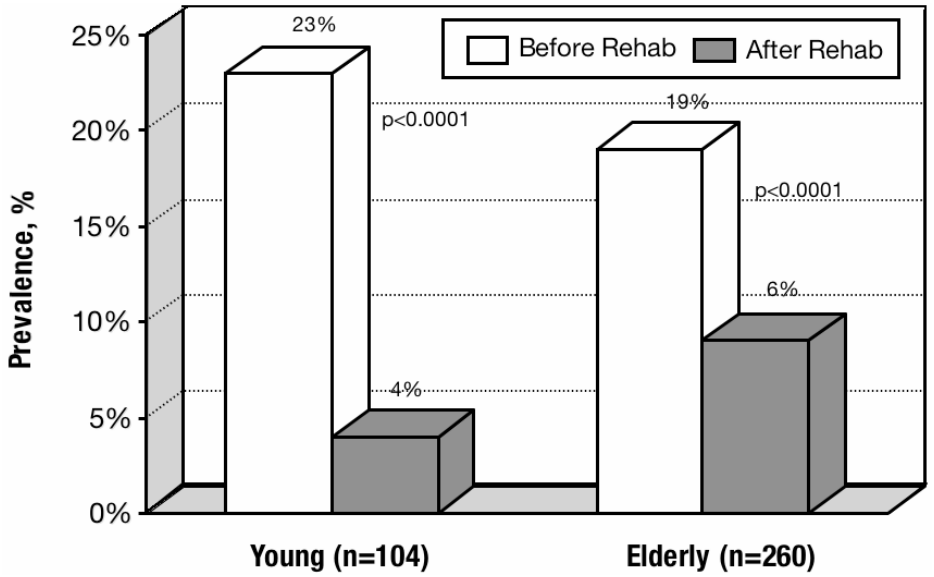

Figure 2. Prevalence of depression before and after rehabilitation in younger and elderly CHD patients. Data obtained with permission from Lavie CJ, Milani RV. *Arch Intern Med* 2006;166:1878-1883. [62] Reproduced with permission from Lavie CJ et al. *The Ochsner Journal*. 2007;7:167-172.[13]

Most recently, we studied a large cohort of 635 consecutive patients and specifically compared 104 patients < 55 years (mean ± 6 years) and 260 patients > 70 years (mean age 75 ± 3 years) to determine the prevalence of psychological risk factors as well as the response to cardiac rehabilitation (Figure 1).[62] We demonstrated that depression was slightly more prevalent in the younger patients (23% versus 19%), and that young patients had considerably higher prevalence of anxiety (28% versus 14%; $p<0.01$) and hostility (13% versus 5%; $p<0.01$) compared with older patients. Following the formal CRET program, both younger and older patients had considerable improvements in most of their CHD risk factors as well as improvements in depression, hostility, and anxiety (Figures 2-4) [13,62] as well as in QoL, but these improvements were even more impressive in the younger patients who had higher baseline prevalence of psychological distress.

Very recently, we also assessed 500 consecutive patients and utilized the composite Kellner Symptom Questionnaire score of psychological distress (combined scores for depression, hostility, anxiety, and somatization) and compared the highest quintile versus the lowest quintile. [63] We demonstrated that patients with high distress were younger and had a higher BMI, weight, triglycerides, and glycosylated hemoglobin but had lower levels of fitness and exercise capacity, HDL-C and QoL (in all 6 components of QoL) compared with patients with low distress. Following cardiac rehabilitation, both groups had improvements in most of the CHD parameters studied, however, the improvements noted in the high distress group were similar to or even greater than those noted in patients with low distress, further demonstrating the benefits of formal CRET programs in patients with higher levels of psychological distress.

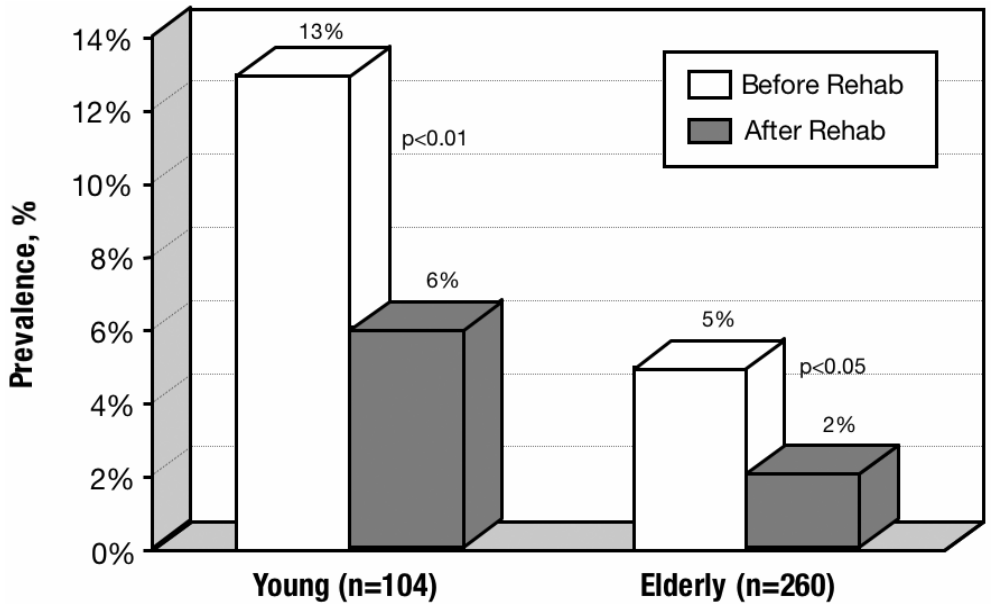

Figure 3. Prevalence of hostility before and after rehabilitation in young and elderly CHD patients. Data obtained with permission from Lavie CJ, Milani RV. *Arch Intern Med* 2006;166:1878-1883. [62] Reproduced with permission from Lavie CJ et al. *The Ochsner Journal*. 2007;7:167-172. [13]

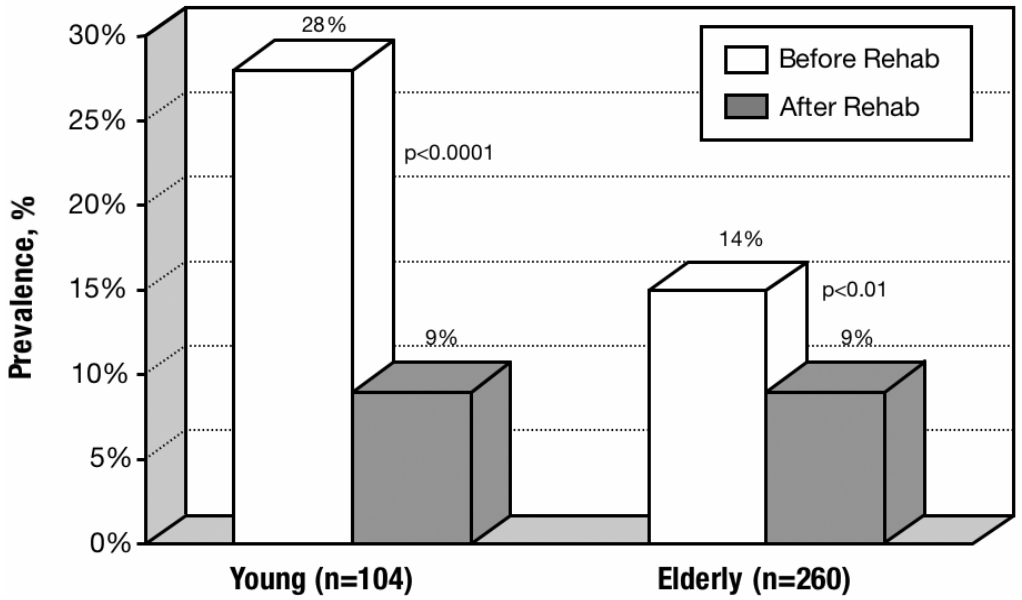

Figure 4. Prevalence of anxiety before and after rehabilitation in young and elderly CHD patients. Data obtained with permission from Lavie CJ, Milani RV. Arch Intern Med 2006;166:1878-1883. [62] Reproduced with permission from Lavie CJ et al. The Ochsner Journal. 2007;7:167-172. [13]

Psychological Distress and Mortality

"And is not bodily habitus spoiled by rest and illness, but preserved for a long time by motion and exercise?"
Socrates

Prior studies have demonstrated the increased risk associated with high levels of psychological distress, particularly depression, but also anxiety and hostility. [11-14,64] In our recent study of 522 patients who participated in formal cardiac rehabilitation and 179 CHD patients following major CHD events did not participate in formal rehabilitation and served as controls, we noted a 17% prevalence of depression at baseline that fell to only 6% following formal cardiac rehabilitation. [65] Most importantly, however, those patients who remained depressed following CRET had a 4-fold higher mortality (22% versus 5%; $p<0.001$) compared with those who were non-depressed (Figure 5). In addition, the controlled depressed group had a 30% mortality during a mean 3.5 year follow-up compared with an only 8% mortality in the "active" depressed group following formal cardiac rehabilitation (Figure 6). Finally, we noted that those patients who did not significantly improve their exercise capacity or parameters of physical fitness, as assessed by peak oxygen consumption assessed by cardiopulmonary stress testing, maintained a high prevalence of depression as well as mortality risk, whereas those patients who had either a small or a marked improvement in fitness significantly reduced their risk of depression as well as its accompanying high mortality risk (Figure 7). These data suggest that one needs to improve physical fitness and exercise capacity only slightly in order to reduce depression and depression-related high mortality risk. Although our results were specifically attained in a CHD cohort following major CHD events, we believe that our data are also applicable for depressed patients in primary prevention, supporting the potential benefits of regular exercise training and increased levels of physical fitness with depression.

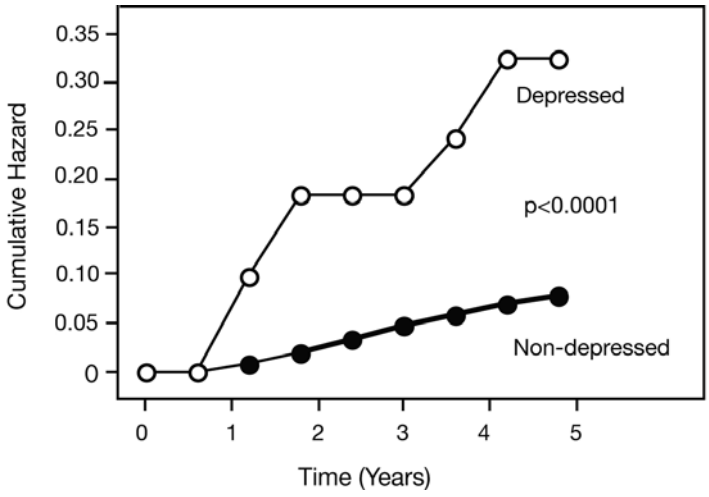

Figure 5. Cumulative hazard curves for mortality in patients who were depressed and non-depressed following formal CRET. Reproduced with permission from Milani RV, Lavie CJ. *Am. J. Med.* 2007; 120:799-806. [65]

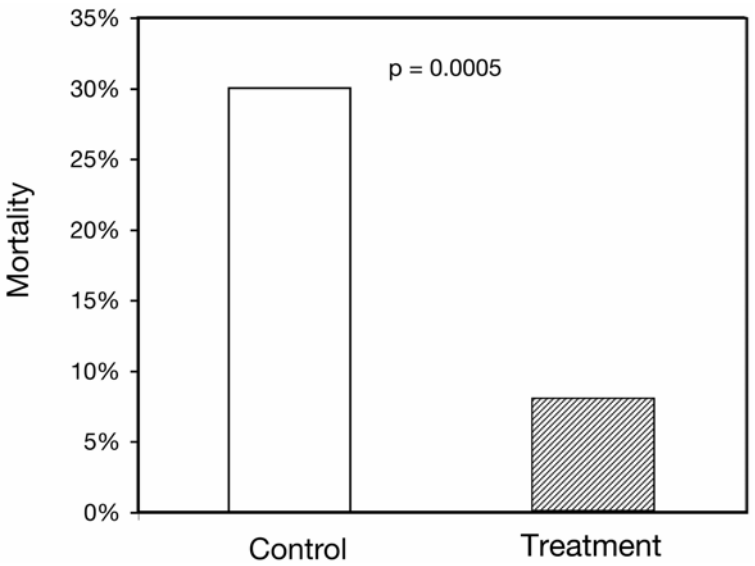

Figure 6. Prevalence of mortality during mean 3.5 year follow-up in control depressed (who did not attend CRET) compared with "active" depressed who attended CRET treatment. Reproduced with permission from Milani RV, Lavie CJ. *Am. J. Med.* 2007;120:799-806. [65]

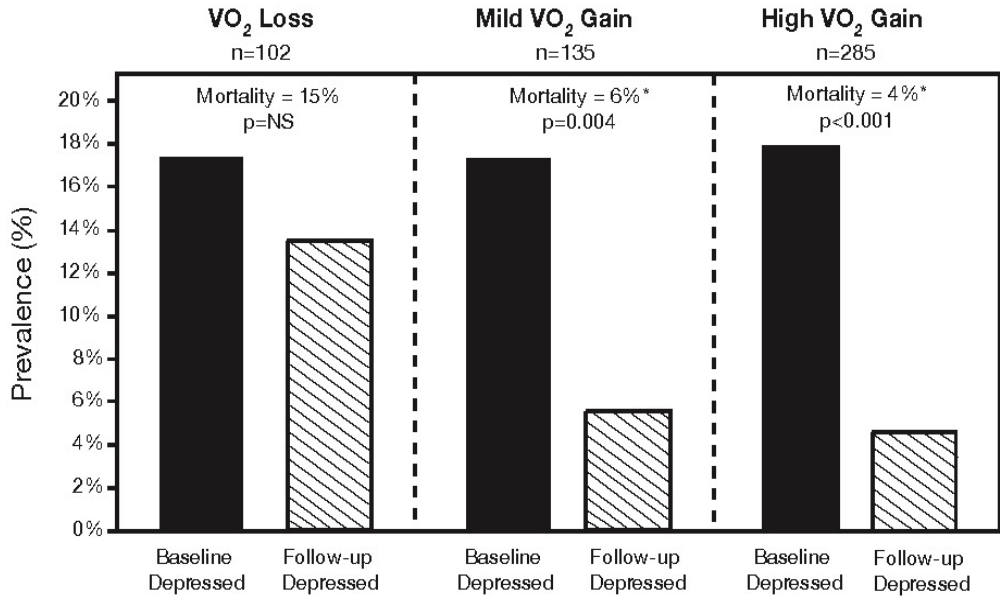

Figure 7. Prevalence of depression and mortality in patients who did not improve exercise capacity (VO_2 Loss), those with mild improvements in exercise capacity (Mild VO_2 Gain) and those with high improvements in exercise capacity (High VO_2 Gain) following CRET. Reproduced with permission from Milani RV, Lavie CJ. *Am. J. Med.* 2007;120:799-806. [65]

Most recently, in a preliminary analysis of 53 patients with high psychosocial stress compared with 469 CHD patients with low psychosocial stress, mortality was lower in those high stress patients with higher improvements in peak exercise oxygen consumption (at least

increases of 10%) compared with low change in peak exercise capacity (0% versus 19%; $p<0.01$). [66] In contrast, there was no significant improvement in mortality in the high versus low fitness change patients within the low stress group (4% versus 8%; $p=0.14$). These preliminary results suggest that most of the mortality benefits following formal CRET are due to mild improvements in psychosocial stress in patients with high levels of baseline stress.

Mechanisms

The mechanisms by which psychological and behavioral factors may predispose to premature CHD is unclear, but it is likely multifactorial, including worsening atherosclerosis risk factors, as suggested by our data and others, and may directly contribute to atherosclerosis, [26-28] enhanced platelet reactivity, [67] inflammation, [28] increased catecholamines [68] and coronary vasoreactivity and vasoconstriction, [69,70] all of which may increase the risk of major CHD events. Hostility and anxiety may also increase sympathetic activity, reduce vagal tone, and increase the risk of malignant ventricular ectopic activity, all of which may increase the risk of sudden CV death.[11,12,20-23]

The improvements in various psychological risk factors noted in our patients following formal, phase II CRET programs are also likely multifactorial. Specifically, cardiac rehabilitation is centered around progressive exercise training therapy, which is known to exert salutary effects on certain emotions and autonomic tone. [71,72] We have demonstrated that this therapy not only improves variables of blood rheology, such as viscosity, [50] but also has significant beneficial effects on the autonomic nervous system that may be related with behavioral and psychosocial factors. [51] Recent data have also focused on the effects of exercise therapy on cognitive function and brain plasticity. [73] Additionally, education of the patient and the patient's significant other may also be important by increasing understanding of the underlying disease process and its manifestations, thus empowering patients to modify their own recovery. This process of patients becoming more involved in their own personal health care is called "information involvement," [74] which may enhance coping, as well as the social and emotional recovery process. In fact, socialization and bonding with other patients who are at various stages of recovery following major CHD events and cardiac rehabilitation probably contribute to the favorable effects seen on the adverse psychological risk factors and overall CHD risk. [75] Importantly, we believe that the benefits obtained in our program are noteworthy, especially because this was accomplished through group sessions for the entire cardiac rehabilitation population and individual counseling directed at the specific high-risk behaviors was not included. However, our data indicate that patients with persistent depression or psychosocial stress post cardiac rehabilitation continue to have particularly high CV risk and mortality risk, [65,66] and potentially these high-risk patients may benefit from more tailored behavioral and/or pharmacologic interventions.

Other Psychological Interventions

The usefulness of organized psychosocial intervention has been typically assessed by evaluating their incremental impact upon prognosis among patients referred to formal CRET programs. [12] Linden et al [76] performed a meta-analysis of 23 randomized controlled trials that evaluated the impact of additional psychosocial intervention for standard cardiac rehabilitation programs. During the first 2 years of follow-up, psychosocial intervention was associated with lower risk of MI and mortality. Dusseldorp et al [77] observed differential effects depending on the effectiveness of the particular psychosocial intervention. With effective reduction of psychosocial stress, recurrent MI and mortality were reduced, but when no reduction in psychosocial stress occurred, mortality was actually higher in the intervention than in the control cardiac rehabilitation patients. Additional data also suggest that failure to respond to psychosocial intervention with reduction in psychosocial stress identifies a subgroup of patients with a high propensity for subsequent clinical events. [78]

Conclusion

Numerous studies indicate that various psychosocial risk factors increase the risk of CHD and also adversely affect recovery of patients following major CHD events. Our research has demonstrated the potential benefits of formal cardiac rehabilitation and exercise training programs and improvements in overall physical fitness on CHD risk factors in various groups of patients following CHD events. We have demonstrated the benefits of formal, phase II CRET programs to not only improve most of the established CHD risk factors, but also to dramatically reduce the adverse psychological risk factors, including depression, hostility, and anxiety, as well as total psychosocial stress. In addition, this therapy significantly improves all components of quality of life in patients with CHD. Therefore, we believe that our data supports 3 major conclusions: 1) Psychological risk factors should be assessed in patients with established CHD or high-risk of CHD; 2) formal cardiac rehabilitation programs should be routinely utilized as secondary CHD prevention; and 3) exercise training and increased levels of physical fitness should be emphasized to reduced depression, hostility, anxiety, and high levels of psychosocial stress and to reduce the high mortality risk associated with these psychological risk factors. Finally, our data support the fact that both small and large improvements in overall fitness are equally beneficial to improve psychological risk and the high mortality associated with this risk. This may have substantial public health implications in prevention and treatment of psychosocial stress as well as in the primary and secondary prevention of CHD.

> "Healthy exercise is valuable not only for the maintenance of good physiologic functions of the body, but also mental clarity, and the feeling of good health."
>
> *Paul Dudley White, MD*

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Chapter 15

Common Presenting Psychosocial Problems for Implantable Cardioverter Defibrillator Patients: A Primer for Consulting Professionals

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Abstract

The implantable cardioverter defibrillator (ICD) has been shown in clinical trials to achieve significant mortality reduction for both primary and secondary prevention applications in patients at risk for potentially life threatening arrhythmias. Psychosocial challenges for patients and families may present themselves in the forms of specific device related apprehension, anxiety and depression, and/or quality of life concerns. The purpose of this chapter is to review common patient concerns and the assessment and treatment approaches for consulting clinicians to assist ICD patients. The empirical basis for device specific approaches continues to evolve and utilization of multi-disciplinary care teams appear warranted.

Introduction

The implantable cardioverter defibrillator (ICD) is the treatment of choice for patients with potentially life-threatening cardiac arrhythmias due to their improvement in mortality compared to patients who take anti-arrhythmic medications alone [1, 2]. Both primary and secondary prevention trials have confirmed the beneficial risk reduction of the ICD [2-5]. This successful biotechnology has prompted new challenges for patients and mental health professionals, as what was previously an acute, terminal medical event (cardiac arrest) is now

a chronic disease state (long-term management of arrhythmia risk). Therefore, adjustment issues may present patients with emotional costs; specifically, approximately 25% of ICD recipients experience diagnostic levels psychological distress [6-9]. Consulting mental health professionals may view patients with a range of adjustment aspects including adjusting to a disease, a treatment device, medication adherence, and behavioral changes. The purpose of this chapter is to provide clinicians with a knowledge base of the common adjustment issues that ICD patients are prone to experiencing after implantation. Second, we will review recent developments in specific assessment tools and treatments for ICD patients.

Survival and Quality Of Life Outcomes with the ICD

Sudden cardiac death presents a major health problem, accounting for 300,000 to 400,000 deaths in the United States per year [10, 11]. As noted above, several large-scale clinical trials have demonstrated the mortality benefit of the ICD over anti-arrhythmic medication alone. The implantable cardioverter defibrillator (ICD) therapy in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II demonstrated a reduced risk of all-cause mortality of 31% in patients who were implanted with an ICD after experiencing myocardial infarction (MI) and having an ejection fraction of 30% or less [2]. Further, investigators in the landmark SCD-HeFT Trial [1] found that the ICD was superior to amiodarone, as the ICD alone was related to a 25% overall reduction in all-cause mortality.

The success of the ICD in preventing mortality has prompted greater attention to the quality of life (QOL) aspects of the technology. Reviews of QOL research have concluded that the ICD is at least equal to, or better than anti-arrhythmic medications on most indicators of QOL [12]. More recently, Groeneveld and colleagues [6], confirmed this assertion in comparing ICD patients vs. anti-arrhythmic drug treated patients on QOL. Further, these authors suggested that ICD patient-reported QOL scores were not as high as the reports of the general public or of pacemaker patients. Additional research by Groeneveld et al. [13] concluded that QOL outcomes were equivalent, regardless of indication of implantation (primary vs. secondary prevention). The experience of shock has been the single most scrutinized predictor of QOL. Early research confirmed that shock was associated with diminished QOL [14] with attention being focused on a threshold of shock tolerance between one and five shocks before QOL was reduced [15, 16]. More recently, shock was associated with a statistically significant decline in QOL in a group of ICD patients with non-ischemic cardiomyopathy but the decline was interpreted as clinically insignificant until the threshold of five shocks was met [17]. The absolute shock-QOL link may be increasingly diminished due to improved management of patients with arrhythmias using device and medication advances. Specific developments in using the diagnostic and painless therapies (e.g. anti-tachycardia pacing) available in current devices can reduce the chances of shock and increase patient perception of increased safety and improved quality of life vs. feelings of life threat.

Common Presenting Concerns for ICD Patients

The current section reviews common presenting problems for ICD patients for consulting mental health professionals. Although good general consultation skills are still needed, specific presenting problems for ICD patients are reviewed below to increase the precision of consultation for the unique concerns of ICD patients. We organize the following conditions into common cognitive concerns and common behavioral concerns and outline them in Table 1.

Table 1: Common complaints of ICD patients and recent, related studies

Common Issues Experienced by ICD Patients	Recent Studies that Highlight these Issues
Reliability/Device Acceptance	Burns et al., 2006; Sears et al., 2006
Death Anxiety	Dougherty et al., 2005; Vazquez-Sowell et al., 2007; Sears et al., 2006;
Shock and Storm	Kuijpers et al., 2002; Kamphuis et al., 2003; Prudente 2005; Prudente et al., 2006; Schron et al., 2002 Connolly et al., 2006; Irvine et al., 2002; O'Brien et al., 2005; Wallace et al., 2002; Sears et al., 2005; Lampert et al., 2002; Burg et al., 2004; Gehi et al., 2006; Chevalier et al., 2006; Sears and Conti, 2003; McMullan, 2007; Davis, 2007
Body Image	Vazquez-Sowell et al., 2006; Walker et al., 2004; Davis et al., 2004
Recall	Stutts et al., 2007; Cuculi et al., 2006; Kapa et al., 2007
Avoidance Behaviors /Learned helplessness	Lemon et al., 2004; Goodman and Hess, 1999
Sexual Dysfunction	Steinke et al., 2005
Depression	Bilge et al., 2006; Whang et al., 2005; Pederson et al., 2005; Crow et al., 1998; Newall et al., 2007; Kohn et al., 2000;
Anxiety	Bilge et al., 2006; Pederson et al., 2004; Vazquez-Sowell, et al., 2007; Kuijpers, et al., 2002; Crössman et al., 2007; Pederson et al., 2005; Pauli et al., 1999; Crow et al., 1998; Godemann et al., 2004; Godemann et al., 2001; Newall et al., 2007; Sola and Bostwick, 2005; Kohn et al., 2000;
PTSD	Neel 2000; Hamner et al., 1999
Type D Personality	Pederson et al., 2004; Pederson et al., 2007; Pederson et al., 2008
Overall reviews (last 5 years)	Pedersen et al., 2007; Bostwick and Sola, 2007; Stutts et al., 2007; Groeneveld et al., 2006; Edelman et al., 2003; Sears et al., 2004; Ezekowitz et al., 2007

Common Cognitive Concerns

Living with Technology: Reliance and Acceptance

A principle feature of psychological adjustment to a biomedical device entails acceptance of the device as part of oneself, one's self-care, or one's future. Patients' perceptions of their intimate relationship with biomedical technology are powerful factors in their adjustment. For many patients, ICD implantation documents the heart's need and reliance upon assistance from a device to ensure survival [18]. However, without proper education, patients may falsely conclude that their reliance on an ICD marks their heightened risk for disease progression and eventual death. Essentially, patients with this mindset are prone to overlook the life-saving capabilities of their devices. Negative device appraisals may fuel a patient's rejection of device technology and his/her need for it. Such negative views may be associated with low treatment satisfaction with ICD therapy [19].

Conversely, patients who make positive appraisals of their use of a cardiac device demonstrate enhanced psychological adjustment or patient acceptance [20, 21]. The term "patient acceptance" refers to the psychological accommodation and understanding of a device, as well as its benefits upon biopsychosocial functioning [22]. It connotes a construct that is intended to reflect disease or device specific adjustment. A patient who demonstrates high device acceptance likely understands and acknowledges the benefits of safety and protection provided by ICD-therapy and engages in a fully appropriate lifestyle post-implantation. Burns, Sears, and Sotile et al. [21] demonstrated an inverse relationship between device acceptance and depression, anxiety, and illness intrusiveness. These investigators also found that device acceptance was associated with increased quality of life in ICD patients [22]. Clearly, patient acceptance represents the initial efforts to understand a "patient-centric" view of the psychological and behavioral outcomes of biotechnology and warrants further theoretical and empirical testing.

Death Anxiety

The generic goals of biotechnology are to increase longevity, reduce pain and suffering, and improve quality of life. Yet the fear of death is present in both acutely and chronically ill populations managing serious medical illness. Death anxiety is a multidimensional construct that includes aspects of cognitive and affective changes, physical alterations, and stress. The ICD patient population may present with newly experienced fears and concerns related to death. Most patients with an indication for ICD placement have either survived or have been informed of their high risk for sudden cardiac death. Being provided with such medical news is undoubtedly significant and unsettling. Patients who have a tendency for catastrophic thinking may fear that their need for an ICD makes their risk for sudden cardiac death increased or more immediate [23, 24]. Recent research has highlighted potential age and sex differences in death anxiety, such that younger women with ICDs reported the highest levels of death anxiety compared with other device-harboring counterparts [25].

Patients living with device technology encounter frequent reminders of their mortality, which may also increase their preoccupation with death. Unlike other cardiac surgeries, ICDs require patients to be implanted with a device that necessitates recurrent interrogation, device programming, and in some cases, re-implantation. The ICD also presents the possibility of

exposure to spontaneous, high-energy shock. The collective psychological and technological phenomena associated with the device may provide patients with perceived threats to their health and existence. Therefore, recipients of psychosocial interventions benefit from information and discussion about the relative threats of life and the security provided by the ICD.

Shock Concerns

The ICD can provide a life-saving shock when indicated by its programming and detection algorithms. The OPTIC Study demonstrated that the shock experience in the first year ranged from as low as 10.3% (when beta-blockers and amiodarone were administered) to as high as 38.5% (when beta-blockers alone were given), indicating that a significant percentage of ICD patients will experience a shock during the first year of ICD use [26]. The occurrence of a shock is the most unique experience of ICD patients relative to other cardiac patients. Patients have compared the experience of shock to a swift kick in the chest and have rated it as a "6" on a 0-10 pain scale [27, 28]. As noted above, recent research has changed the understanding of the psychological effects of shocks on ICD patients. Generally, shocks have been associated with increased anxiety and decreased mental QOL, but the magnitude of the effects are now being reconsidered [16, 17]. Irrespective of these findings, the experience and anticipation of shock is exclusive to the ICD patient population and should not be discounted.

Shock anxiety can be defined as the fear or anticipation of an ICD shock that often results in increased heart-focused anxiety symptoms, as well as the development and maintenance of avoidance behaviors to minimize patients' perceived risk of shock [29]. Examining shock anxiety further clarifies the need for a conceptualization and measurement of device-specific anxiety that is distinctly related to the ICD, as opposed to more generalized or trait anxiety. Interestingly, shock anxiety may also be prominent in family members of ICD patients, as some studies show that spouses of ICD patients experienced higher levels of shock anxiety than did ICD patients themselves [25, 30, 31].

Consulting mental health professionals may also occasionally be referred ICD patients who believe that they have received an ICD shock although the device's stored memory reveals no electrical output has been provided [32, 33]. This phenomenon is termed a "phantom shock" by many electrophysiology professionals. It is estimated that phantom shocks are experienced by 6-7% of persons with an ICD [32]. Patients have reported bright lights, a kick to the chest, or being jolted in a similar fashion to those that occur during an actual ICD shock [33]. Patients who experience phantom shocks tend to have higher levels of depression and anxiety than their counterparts who do not experience this phenomenon, suggesting that there may be an association between psychological disturbance and the development of phantom shocks [33]. Clearly, phantom shocks are an interesting manifestation of symptoms in the hypervigilant and over-aroused patient.

Changes in Body Image

The implantation of biomedical technology incurs body image alterations, which may be especially distressful to female patients. The majority of ICD placements involve creating a 3-4 inch incision in the sub-clavian area, in which a pocket is formed for device insertion.

This often produces a visible scar that may pucker or bulge as a result. Due to the upper body structure of male recipients, the implant may not be easily discernible; however, due to the physiognomy of women, the device is more visible and more physically intrusive to the female body image.

No studies to date have empirically explored the effects of an altered body image on ICD recipients, yet several negative effects have been hypothesized. Davis et al. [34] examined body image concerns with pacemaker recipients who experience similar scarring and device protrusion. When compared to male patients, females reported having significant concerns regarding the appearance of the scar, as well as the consequential fit of clothing and swimsuits. Due to these factors, Vazquez-Sowell, Kuhl, and Sears, et al. [35] speculate that women ICD patients are apt to have decreased body satisfaction, QOL, and adjustment to living with a device. Interdisciplinary consultation involving cardiology, nursing, plastic surgery, and psychology/psychiatry may be indicated for patients with specific concerns about appearance and ICD implantation.

Device Recalls

Due to the technological nature of the ICD, patients often exhibit concerns regarding device reliability and related device recalls. Advances in device functions, features, and intricacies have been accompanied by increases in device malfunctions [36]. Maisel, Moymayhon, and Zuckerman et al. [37] demonstrated that between the years of 1996 and 2002, ICD re-implantations due to malfunction increased in number to a rate five times that of pacemaker re-implantations. Device recall does not necessarily require that the device be extracted and returned to the manufacturer, yet if a patient is included in the recall, it will invariably entail notifying him or her. Patients who must consider and/or undergo re-implantation may suffer the distress of surgical procedures, as well as possible financial strain and legal encounters. While a natural level of fear and concern is invariably related to recall [38], studies investigating the presence of clinically significant psychological distress have been inconclusive. Early studies demonstrated an increase in psychological morbidity in response to recall [39, 40], while a more recent study demonstrated no upward trend in such problems [41].

Even ICD patients who are not included in recalls may be subject to the negative effects of this phenomenon [38]. The mere occurrence of a recall reminds patients of the imperfection of a device upon which their cardiac health relies. Recall announcements often pervade media sources, including the television and internet. One recent study demonstrated that 80% of patients received notice of a recall through the media, which was also rated by these patients as the least desirable source for revealing recall information [38]. These results might suggest that recall-related communication options be more fully considered with attention to more direct communications between patient and doctor groups, and even industry itself.

Common Behavioral Concerns

Avoidance Behaviors

Repeated avoidance of activities and stimuli associated with distress represents a hallmark response of anxiety. ICD patients living with arrhythmias and the ICD are apt to engage in avoidance behaviors in an effort to prevent or anticipate an ICD shock. Approximately 55% of ICD patients engage in regular avoidance of places, people, and activities in a perceived effort to prevent shock [42]. Some patients may have a stronger desire to evade highly physical activities that could cause the heartbeat to increase in speed. Others may keep their distance from people and places out of fear of embarrassment or helplessness should a shock discharge occur. Regardless, these reasons are often inhibiting in that they prevent the patient from re-engaging in life's activities post-implantation.

Sexual activities are a common area of functioning associated with fear following any cardiac event [43, 44]. The imagined prospect of transmitting shock to a loved one during sexual intimacy is potentially frightening but is not factual. In the chain of negativistic thinking to which patients may be prone, sexual activity may be equated with high physical exertion that causes the heart to accelerate and henceforth increase the chance of shock or sudden cardiac arrest. Recent research provides some insight into the nature of sexuality-shock concerns. Shiyovich [43] divided ICD patients into two groups related to shock history (shocked vs. never shocked). The results revealed that 71% of the patients who had not been shocked reported ICD-related sexual dysfunction versus 44% of those who had been shocked at least once. These findings suggest a protective effect of shock on sexual dysfunction, as patients who have experienced shock may have greater confidence in their ability to survive a discharge and thereby limit its intrusiveness in daily functioning. Moreover, a recent qualitative study described the nature of sexual concerns in the ICD population, including themes related to having varied interest in sexual activity after implantation, partner over-protectiveness, and fear of discharge during sexual activity [44]. These participants also endorsed a need for more information related to ICDs and sexual functioning and sexual counseling.

Beyond the Normative Experience: Psychopathology in the ICD Patient Population

Beyond normative complaints related to life with an ICD, a substantial minority of ICD patients have psychological morbidity. Specifically, research indicates that approximately 1 in 4 ICD recipients experience diagnostic levels psychological distress [6-9]. Psychological distress, including depression and anxiety, may arise from the impact of the actual ICD implant, as well as the impact of fear of potential shock. Many patients experience symptoms consistent with some form of adjustment disorder before those symptoms begin to lift at roughly three months post-implant [45]. Regardless of whether psychological morbidity is an antecedent or consequential variable of device implantation, research indicates that those with psychological distress have low treatment satisfaction and poorer treatment outcomes [19]. The following is a discussion of four common forms of psychological morbidity that

may develop or challenge one's adjustment to device-technology: depression, anxiety, posttraumatic stress disorder, and Type-D personality.

Depression

Rates of depression in all cardiac patients and among those with ICDs can be problematic, as depression diminishes one's ability to effectively cope with a disease state, adjust to the prescribed regimen, and effectively manage the disease [46]. Rates of depression in ICD patients have been consistent with cardiac patients in general [9]. More recent research has indicated that the impact of depression may include increased chances of receiving an ICD shock in prospective work [47, 48]. Results from the Triggers of Ventricular Arrhythmias Study (TOVA) found that in baseline assessments of 645 patients, 14% were at least mildly depressed and another 3.9% were moderately to severely depressed. In addition, increased severity of depression was associated with a greater number of shocks [48].

The development of depression in the ICD patient has prompted a variety of psychological, medical, and social theories of its etiology. Sears, Conti, and Curtis et al. [49] reviewed theories including classical conditioning, operant conditioning, and cognitive appraisal processes as central to the development of both depression and anxiety. Goodman and Hess [50] demonstrated how ICD shock can produce "learned helplessness" in patients, leading to poor coping amongst such patients. With patients who had no reported history of psychological morbidity, higher levels of shock were predictive of higher levels of current depression and anxiety. On the contrary, among patients with a previous history of psychological morbidity, shock levels were not related to their current psychological status. These findings lend credence to the theory of learned helplessness in ICD patients, whereby the experience of the aversive stimulus of unavoidable ICD shock is directly related to depressive symptoms [50]. Consistent with previous literature [9, 51], elevated depressive symptoms in a sample of ICD patients have been found to be associated with poor social support, poor physical functioning, a history of depression, and a greater length of time since ICD implantation [52].

Anxiety and Post-Traumatic Stress

Anxiety is the most significant psychosocial problem among ICD patients. Between 13-38% of ICD patients experience either general or ICD-specific anxiety [24, 51, 53, 54], which is consistent with other cardiac populations [16]. Early research identified anxiety as an important variable for ICD patients [55] and more recent longitudinal research has documented as many as 33% of patients developing problems with anxiety, depressed mood, and fear of symptoms associated with the fight or flight response [39]. Distinguishing between the anxiety related to ICD implantation and anxiety related to shock remains a research objective. Lemon and colleagues [56] demonstrated that higher levels of anxiety, depression, and stress were associated with anxiety sensitivity at pre-implant; however, this

association did not remain at post-surgery assessments. As Lemon and colleagues point out, among ICD patients there is potential that during stressful circumstances, anxiety sensitivity is related to distress, but the relationship diminishes once the perceived threat has passed. The authors go on to say that the comfort afforded by the perceived protection of the ICD may also reduce negative perceptions of symptoms, promoting psychological adjustment in the majority of patients.

Not all patients experience gradually diminishing levels of anxiety; rather, some remain anxious due to the threat of shock. Dougherty [30] observed that patients with ICDs who experienced shocks in the first year after implantation reported higher rates of tension and anxiety at the end of the year compared with those who had not experienced shocks. Several studies demonstrated that most patients appear to adjust well until they have experienced five or more shocks [4, 14, 15, 57].

Currently, an interesting debate is possible as to whether ICD related anxieties may represent posttraumatic stress disorder (PTSD). The majority of the aforementioned studies have focused on state, trait, and general forms of anxiety, rather than looking for specific anxiety diagnoses. It appears that only few studies explore the PTSD-ICD connection, including a literature review [58] and a set of case studies [59], which prompts speculation as to whether PTSD is a valid diagnosis for ICD recipients. PTSD has been given more attention in other cardiac populations with reports of 10-20% of cardiovascular patients having co-morbid symptoms of PTSD [60]. Further, Shemesh and colleagues [61] found that PTSD symptoms in post myocardial infarction patients were significant predictors of non-adherence to cardiac-related medications and an increased likelihood of cardiovascular hospital readmissions. While these and other studies suggest the significance of PTSD among those with heart conditions [60, 62-66], caution should be used when making diagnoses in ICD patients without evidence from both clinical interview and validated ICD-specific measures. It is hypothesized that ICD patients most likely to demonstrate PTSD symptomology are those who have experienced frequent shocks. Patients who have survived high shock quantities may be more prone to the belief that their lives are being threatened, a key component of the PTSD diagnosis. It is recommended that future research in this area involve patients whose devices have discharged several times.

Type D Personality

Some researchers have attempted to focus on personality factors as an explanation in the variations of outcome among ICD recipients. This research has indicated that Type D personality, also called the distressed personality, is a primary risk factor for poor psychosocial outcomes in cardiac and ICD patients [31, 67, 68]. Type D individuals tend to display negative affectivity and social inhibition, which leads to greater distress and a low likelihood of expressing difficulties to others [31]. Emotional and social problems and higher rates of morbidity and mortality are some of the associated consequences of Type D personality that have been recognized in patients with heart disease [68-71]. Further, Pedersen et al. demonstrated that Type-D personality, rather than ICD indication, was

associated with impaired QOL outcomes at both the time of ICD implantation and at a three month follow-up.

In future investigations, it may be important to include personality traits, such as Type D personality in studies, given the negative health impact of having a distressed personality [67]. However, as anxiety and depression are both highly associated with the Type D personality, targeting the actual distress may be more plausible. In hospital and primary care settings, assessing personality variables may lack practicality considering time constraints. Identification of personality traits are likely to be of benefit when the patient is referred for in depth psychological services.

Formal Assessment and Treatment for the ICD Patient

Assessment

Assessment tools are helpful in assessing and monitoring ICD patients' adjustment to device technology. While the presence of adjustment and psychological issues can be discovered using general psychological assessment measures, we advocate that anxiety in ICD populations be assessed with both generic measures and device-specific measures. ICD patients may appear more pathological than they actually are if assessed with general measures that compare them to non-device counterparts. For example, one question on the Depression Anxiety and Stress Scale (DASS 42) test asks respondents to provide a rating of applicability for the following statement: "I was aware of the action of my heart in the absence of physical exertion" [72]. ICD patients may rate the statement with a higher score, which could thereby mistake the natural act of being more cognizant of one's heart function as a pathological behavior.

Recently, device-specific measures have been created to provide clinicians with precision and to account for normative levels of adjustment expected in response to ICD implantation. To date, these tools measure the specific constructs of anxiety related to the ICD, patient acceptance, ICD knowledge, behavioral avoidance, body image concerns, anxiety related to shock, and general adjustment. All measures were investigator-developed out of an identified necessity to more adequately address psychosocial constructs specific to this population. Most of these tools demonstrate cost-effectiveness in clinical practice due to their free usage dependant upon contacting the respective author. See Table 2 below for a summary ICD-specific assessment measures. Clinicians can select tools that target their specific needs for each client and use the normative data available to interpret scores.

Addressing Patient Adjustment with Education

Adjustment to living with an ICD is partially dependent on the ability of healthcare providers to afford patients with information and guidance [73]. Unfortunately, the standard of care for patients post ICD implant may be insufficient in addressing concerns and daily functioning [74]. Patient education provides information to prevent psychological morbidity

and to support positive coping mechanisms following implantation [75]. Patient education should encompass information on one's device, possibility of device recall, day-to-day activities, and on shock-planning. Realistic expectations should be conveyed, as preparing patients for a variety of possibilities relevant to their devices may decrease feelings of surprise, alarm, and distress if and when they occur.

Table 2. Examples of ICD-specific assessment measures

Measure	Authors	Construct Assessed
The Florida Shock and Anxiety Scale (FSAS)	Kuhl, Dixit, Walker, Conti, and Sears (2006)	Shock anxiety
The Florida Patient Acceptance Scale (FPAS)	Burns, Serber, Keim, and Sears (2005)	Device acceptance
ICD and Avoidance Survey	Lemon, Edelman, Kirkness (2004)	Behavioral avoidance
The ICD Concerns Questionnaire (ICDC)	Frizelle, Lewin, Kaye and Moniz-Cook (2006)	ICD-specific concerns
The Implanted Device Adjustment Scale (IDAS)	Beery, Baas, and Henthorn (2007)	Adjustment to device
Cognitive Appraisal of ICD Discharges	Godemann, Butter, Lampe, Linden, Schlegl, Schultheiss, and Behrens (2004)	Cognitive appraisal of ICD shock

Expectations about returning to pre-implant activities, such as sexual intimacy and exercise, should be addressed, and patients should be given clear guidelines regarding resuming these activities (6 weeks post implant, in most cases). Providers must actively encourage re-engagement in life activities that were enjoyed prior to implantation, in order to prevent patients from developing maladaptive avoidance behaviors. As previously discussed, some patients may exhibit patterns of behavioral avoidance based upon fear of inducing ICD discharge, or upon activities that were performed when previous shocks occurred. For example, an ICD patient who was shocked while riding a bicycle may erroneously assume that his physical exertion triggered the shock; thus, he may avoid an activity that once brought pleasure. In such a case, providers are encouraged to address this phenomenon by informing patients that there are no known links between shocks and behavior.

Shock-planning is another important element of patient education. Experiencing a shock or observing a loved one receive a shock can be a frightening experience. While patients cannot control the occurrence of shock, they can control their response to a device discharge. To this end, patients and their families require a plan to respond to the event of shock to decrease uncertainty, panic, and anxiety. This may be accomplished by empowering the ICD patient through advocating for the use of a shock action plan as described below [76].

If a patient receives a single shock he or she should:

1. Immediately assess symptoms:

- If the patient feels fine immediately after shock, his/her cardiologist should be called to discuss or arrange appropriate follow-up care.
- If the patient experiences chest pain/pressure, shortness of breath, rapid heart beat, dizziness, confusion, or a general feeling of illness, medical attention should be sought immediately.

2. If a patient receives two or more ICD shocks within 24 hours he or she should seek medical attention immediately, regardless of how the patient is feeling.

Psychosocial Treatment

Some patients require a more comprehensive treatment plan to address heightened psychological issues. Such patients may not have been afforded proper education about living with device technology; henceforth, they may have developed perceptions that hindered their adjustment. Other such patients may have had risk factors such as younger age (<50 years of age), sex/gender (female), shock history, or a pre-morbid psychiatric history that predisposed them to having greater psychological issues following the distress of ICD implantation [9]. Regardless of the etiology of these problems, many comprehensive treatment programs have demonstrated the ability to decrease psychological distress, depression, and anxiety [45, 77, 78].

Pedersen, Van Den Broek, and Sears [79] conducted a review of nine randomized controlled psychological intervention trials following ICD implantation. The review evaluated numerous endpoints of the psychosocial intervention techniques employed, such as QOL, shocks, anxiety, depression, ICD-related knowledge, exercise tolerance, and adjustment, among others. Results indicated that psychological intervention was considered highly worthwhile in the ICD patient population. Effect sizes for changes in anxiety in participants in the intervention groups ranged from small to large, as compared to small in the standard of care group. Pedersen et al.'s review indicates that mixed-format or interdisciplinary programs combining elements of education, relaxation, CBT, support, and/or exercise are becoming increasingly popular and effective. This research also highlights the need for large-scale, multi-center, longitudinal randomized controlled trials to further corroborate these findings. Yet at present, the standard of care for patients post ICD implantation may be under-developed, thereby highlighting the need for efficacious alternatives based on empirical evidence. The key components and significant findings from Pedersen et al.'s [79] reviews and others are summarized in Table 3.

Conclusion

The implantable cardioverter defibrillator (ICD) effectively detects and terminates potentially life threatening arrhythmias. Research examining specific psychosocial challenges for patients and families indicates that adjustment to both the condition and to the device is a

Table 3. Key Components and significant findings of ICD-specific treatment studies

Active Ingredient	Techniques Employed	Representative Studies
ICD Specific Education	Educate patients on device mechanics, events that trigger shock, and how to respond to shock Educate patients on everyday functioning, such as occupational limitations, physical and sexual activity, driving, and electromagnetic interference Education delivery via face-to-face contact, telephone, and computerized technology	Sears et al., 2007 Lewin et al., 2007 Frizelle et al., 2004 Kuhl et al., 2007 Dougherty et al., 2004 Fitchet et al., 2003 Carlsson et al., 2002
Relaxation and Stress Management	Assist patients in reducing arousal via progressive muscle relaxation, guided imagery, and/or diaphragmatic breathing	Sears et al., 2007 Lewin et al., 2007 Frizelle et al., 2004 Kuhl et al., 2007 Chevalier et al., 2006 Sneed et al., 1997
Cognitive Restructuring	Utilize cognitive restructuring to teach patients to value the ICD and to perceive their device as a source of protection rather than a threat to their life and well-being Encourage activity planning and exposure-based exercises to teach patients to engage in activities that have been limited or avoided due to device Target distorted cognitions and catastrophic thinking	Sears et al., 2007 Lewin et al., 2007 Frizelle et al., 2004 Kuhl et al., 2007 Chevalier et al., 2006 Kohn et al., 2000 Sneed et al., 1997
Social Support/ Group Discussion	Provide patients with social support via nursing contact, patient calls, and support groups	Sears et al., 2007 Lewin et al., 2007 Kuhl et al., 2007 Dougherty et al., 2004 Sneed et al., 1997 Carlsson et al., 2002
Shock Planning	Provide patients with instructions on what to do following shock	Sears et al., 2005
Activity Level	Demonstrate safety of customized exertion via cardiac rehabilitation approaches	Frizelle, et al., 2004 Fitchet et al., 2003

necessary process for patients. Unique issues such as reliance on implantable technology for safety, responding to shock, body image changes, and manufacturer recalls result in ICD patient concerns that prompt consultation with mental health professionals. Effective ICD-

specific assessment and treatment entails knowledge of current paradigms including learning and conditioning theories as well as multi-factorial treatments to re-engage patients in activities of living. Multi-disciplinary teams are not typical, but may be indicated to achieve optimal quality of life outcomes for ICD patients.

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Chapter 16

Is Coronary Heart Disease Risk Underestimated in the Primary Care Setting? The Potential Importance of the Psychological Stress Assessment

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Abstract

Psychological stress and depression have for some time been recognised as playing an important role in the etiology of coronary heart disease and for over thirty years the notion of risk factors has played an ever increasing role in estimating the probability of this disease and its sequela. There appears to be little debate as to stress being categorized as a risk factor. What appears to be at issue is the relative importance of stress and depression compared to both traditional and other risk factors for coronary heart disease, and whether new risk factors are even needed, given the current protocol for risk assessment which is periodically updated to reflect new study results and is currently undergoing recalibration outside North America.

This chapter will examine the current debate over the need for employing new risk factors, evidence that the currently used protocol for risk assessment appears less than ideal, and that the addition of new risk factors or an entirely different approach may have considerable merit, with psychological stress being a prime example. The discussion will include research that attempts to position psychological stress in the hierarchy of coronary heart disease risk factors and in addition, the role of stress in the development of atherosclerosis and as well as the apparent failure of the traditional risk factors to account this critical aspect of coronary heart disease.

Introduction

Coronary heart disease (CHD) is a major contributor to morbidity and mortality throughout the world and in particular in developed countries [1]. Thus the task of identifying and quantifying risk factors has attracted much attention over several decades, in particular in connection with the question of setting thresholds for intervention in asymptomatic individuals [2,3]. The ideal approach in the primary care setting is an assessment protocol that is rapid and simple and has high sensitivity and specificity. Non-invasive screening procedures such as treadmill ECG or electron beam tomography are traditionally reserved for high-risk or symptomatic patients.

The risk factor concept has a longer history than some may realize. In fact, the initial application was not in medicine but by insurance companies who early in the last century already recognized that hypertension and obesity put individuals at higher risk for premature mortality and adjusted their acceptance criteria and premiums accordingly [4]. The actual term “risk factor” appears to have been coined by Dr. William Kannel, one of the pioneers of the famous Framingham Heart Study [5]. The term as it is generally used implies either causal or predictive properties or both.

Risk factors provide a snapshot of the current status or if recorded over time, an indication of change in perceived risk. CHD can be thought of as having an initiation phase, a progression phase and at some point in time, an acute phase. The chain of events which progresses through numerous physiologic pathways and processes to the development of end-stage heart disease as been described as the cardiovascular disease continuum [6]. But known and postulated risk factors do not uniformly apply over the entire natural history of the disease and the available data are highly variable and in some cases sparse. In addition, there are a very large number of risk factors including age, gender, genetics in general and family history of premature CHD in particular, diet, lack of exercise, smoking, insulin resistance and diabetes, inflammation and chronic infection, obesity, unfavorable blood lipid profile and blood lipid particle size distributions, hypertension, and as well, psychosocial stress and depression. Together these form a complex picture. A much longer list could be presented if all the proposed biomarkers and surrogate markers are included [7-9]. Biochemical individuality compromises the applicability of these risk factors, perhaps more than is realized. The challenge is to convert this whole picture into the best possible assessment of the risk of CHD or CHD events in asymptomatic individuals with the goal of primary prevention, all accomplished in the primary care setting. Once an individual is symptomatic or has experienced an adverse CHD event, it would seem that the challenge is both different and considerably more straight forward with interventions based in large part on randomized clinical trials.

The traditional risk factors are total and HDL cholesterol, hypertension and taking hypertension medication, smoking, and diabetes, some of which are weighted during risk assessment by both gender and age, the latter also being a stand-alone risk factor. In addition, current protocols count risk factors exceeding set thresholds and establish a LDL cholesterol threshold for the purpose of deciding on recommendations and interventions [2,3,10]. The presence of diabetes is generally taken as evidence of a high risk equivalent to having CHD. The traditional risk factors can be used to obtain 10-year risks of either a composite endpoint

which includes CHD and fatal or non-fatal CHD events, or a more limited endpoint of just the latter two. The association between atherosclerosis and traditional risk factors is somewhat indirect since sub-clinical atherosclerosis is not itself an endpoint. But in the context of primary prevention, the risk of or presence of atherosclerosis is obviously important.

The introduction of a new risk factor into CHD risk assessment in the primary care setting will probably only be successful if the factor is easily characterized, if possible quantified for use in algorithms, and if the evidence of the factor's importance is strong enough to motivate its general acceptance. At present, the system is simple and uses yes or no questions and several numbers taken from the blood lipid profile. The evaluation requires only minutes, and therefore one might expect considerable resistance to expanding the assessment protocol, especially with factors somewhat unfamiliar to the primary care community, psychosocial stress and its evaluation being a prime example. But primary prevention includes the control of risk factors including those associated with the initiation and early progression of the disease, and thus factors in addition to those currently used for risk assessment may in fact be of great importance in this broader context. With this in mind, this chapter will examine how successful the current CHD assessment protocol is, the likelihood that important and significant factors are being ignored, and the merits of adding psychosocial stress and depression to the risk evaluation process in the primary care setting. The discussion will be restricted to CHD with emphasis on primary prevention.

The Risk Factor Debate

The modern protocol widely used for CHD risk assessment was developed a number of years ago and is based on studies carried out in Framingham, MA, a small town in near Boston [11,12]. The study started in 1948 and has continued unabated [13]. The protocol subsequently underwent several revisions and the latest version in general use in North America is based on guidelines developed by the National Cholesterol Education Program, Adult Treatment Panel III (NCEP ATP III) which were published in 2001 [3] and which continue to be updated [2,10]. This protocol calculates a 10-year absolute risk of having a myocardial infarct (MI) or death from CHD. Some versions of the protocol start with determining the presence of diabetes or symptomatic atherosclerotic disease (angina, previous MI, major or minor stroke, revascularization or intermittent claudication). If this is the case the indication is a risk of > 20% for having an adverse CHD event within the next 10-years, and this automatically leads to the classification of high-risk. If the above indications are absent, the risk assessment proceeds with an algorithm based on age, total cholesterol (TC) level, HDL-cholesterol level, and systolic blood pressure which are assigned age and gender weighted points according to the numerical values that apply to the individual in question. In addition, smoking and taking medication for hypertension are introduced with points for yes or no, with age included as a stand-alone risk factor. Finally an absolute risk is calculated based on gender and the summation of points This is commonly called the Framingham Risk Score (FRS). Low risk is generally defined as < 9%, intermediate risk 10-19%, and ≥ 20% is regarded as high risk of an MI or CHD related death in the next 10 years.

In practice, this is done with a table, an on-line calculator, palm pilot or some other simple calculation aid. This protocol along with its stratification by risk categories is also widely used in studies of correlations between the FRS and various endpoints, for example the extent of atherosclerosis determined by electron beam tomography (ETB). The FRS has the advantage of being numerical, whereas the complete set of guidelines is not. Current clinical guidelines go beyond the simple risk score and include introducing family history of premature CHD, the presence of the metabolic syndrome, LDL cholesterol levels and the number of risk factors exceeding thresholds. The overall assessment then leads to specific recommendations regarding the advisability of lifestyle changes and pharmaceutical intervention.

In the 1997 Shattuck Lecture presented to the Massachusetts Medical Society, Eugene Braunwald remarked that fully half of all patients with CHD do not have any of what he termed the established CHD risk factors, of which he enumerated hypertension, hypercholesterolemia, smoking, diabetes, marked obesity and physical inactivity [14]. This "only 50%" view predated Braunwald's lecture by a number of years but the evidence for and the source of the claim are not well documented [15]. Nevertheless, it became embedded in the conventional wisdom and has been and is still widely used to indicate the existence of under appreciated, undiscovered or missing risk factors and the need for research in this area to characterize, validate and quantify them. However, in the last 10 years evidence has been accumulating that this figure may be low. In fact, in 2002 Beaglehole and Magnus [16] published a commentary in which they took the position that what they defined as the major CHD risk factors (high blood cholesterol, high blood pressure, cigarette smoking and physical inactivity) satisfy public health criteria for causality and explain at least 75% of new cases of CHD, and that attention should now be directed toward implementing prevention based on existing knowledge rather than searching for new risk factors. They termed this search as "occupational therapy for epidemiologists" which as might be expected, prompted critical responses. Subsequently several additional studies reported the presence of one or more major risk factors in up to 90-95% of individuals experiencing fatal and non fatal CHD events, non-fatal events only, or both [17-19]. Taken on face value, these results suggest that there are no significant risk factors unaccounted for. In the context of this chapter, this is obviously an important issue.

One of the papers cited above (Greenland *et al* [18]), which found much higher than 50% prevalence of major traditional risk factors in individuals with CHD or CHD events, was subsequently criticized with regard to a number of points. Root and Cobb [20] pointed out that based on the data presented, the "more than one risk factors" rule was only 33% specific, i.e. 67% of those who did not have an MI or die of heart disease had one or more risk factors. They also point out that risk of CHD is much lower in non-US populations despite their having similar major risk factors, a paradox which suggest there are still large gaps in the understanding of the causes of this disease. In addition, Weissler used the data of Greenland *et al* to calculate a positive likelihood ratio [21]. A ratio of 2.0 or less indicates low predictive power whereas a value of 9.0 or more denotes high predictive power. Both for men and women, Weissler calculated likelihood ratios of less than 1.5 for CHD death or non-fatal MI, suggesting remarkably low predictive power for the "one or more risk factors" criterion for predicting CHD events. He points out that the failure to account for the prevalence of a risk

factor in the event-free population can convey a significantly misleading impression of its clinical value.

There is additional evidence to support the suspicion that merely looking at the traditional risk factors in individuals with CHD or CHD events provides an incomplete picture. Using data from the Health Professionals Follow-up, Chiuve *et* al found that 62% of coronary events in a cohort of over 42,000 men age 40-75 years might have been prevented with better adherence to 5 healthy lifestyle practices i.e absence of smoking, BMI < 25, moderate to vigorous activity ≥ 30 min/day, moderate alcohol consumption of 5-30 g/day, and being in the top 40% of the distribution for a healthy diet score [22]. For a large cohort of women in the Nurses' Health Study [23], Stampfer *et al* found 82% of coronary events could be attributed to a lack of adherence to a low-risk pattern which was almost identical to that used by Chiuve *et al*. Emberson *et al* found that social class accounts for 22% of the CHD that occurs in a population of middle-aged British men [24]. That is, if it were possible to bring the CHD rates of men in the manual occupations (their way of stratifying by social class) down to those found for non-manual occupations, 22% of CHD death would be prevented.

There is an additional problem. Some studies related traditional risk factors just to fatal CHD events, but these events include sudden cardiac death (SCD). Two studies of predictors of SCD both found that high cholesterol was not a risk factor for SCD, but in studies that look at the importance of one or more traditional risk factors, high cholesterol is one factor used, sometimes only one of three [25,26]. This implies that risk factors for a significant proportion of fatal heart attack study populations are being incorrectly assigned and that some who are thought to have this risk factor in fact do not. It is estimated that as many as 50% of deaths attributed to CHD are in fact due to SCD [26]. Albert *et al* [25] found significant age and multivariate-adjusted relative risks for SCD to be diabetes, hypertension, smoking family history of premature MI and obesity.

In addition, a commonly used risk factor profile when the goal is identifying high risk is total cholesterol (TC) ≥ 240 mg/dL, systolic blood pressure (SBP) ≥ 140 mm Hg, smoking and diabetes [18,27]. For a 50 year old male, non-smoking, free of diabetes and having a HDL level of 60 mg/dL, presence of just high cholesterol or treated hypertension yields a Framingham 10-year risk of 6-8% even if the factor in question is set higher than the above values (i.e. TC=285, systolic BP=160). For a woman the corresponding numbers are 2 and 3%. The point is that the presence of either high TC or high blood pressure as a single risk factor still places one in the low-risk category if smoking and diabetes are absent and HDL protective.

In 2003, Akosah *et al* reported on a retrospective study of how well the ATP III guidelines performed in adults (age ≤ 55 for men and ≤ 65 for women) who had been admitted for acute MI. These guidelines incorporate LDL and involve counting risk factors as well as computing the 10-year risk using the traditional risk factors. The mean age was 50 years and 25% were women. Patients with a prior history of CHD or a CHD equivalent were excluded. Data necessary to estimate risk according to ATP III were collected retrospectively from medical records. Fifty percent of the total MI cohort had only 0 or 1 risk factor, and only 20% had 2+ risk factors and a 10-year risk of < 10%. Only 12% had 2+ risk factors and a 10 year risk > 20%. Only 25% would have met the criteria for pharmacotherapy according

to the ATP III guidelines, and for women it was only 18%. These results were interpreted to indicate that in spite of the new features in ATP III, the protocol appears to "under appreciate" the risk of disease and in particular first MI in young or middle-age adults [28].

In an editorial accompanying the paper by Akosah *et al*, Fredric Pashkow termed this "The Prudent Person's Paradox." He points out that we can all name a number of individuals we know who, despite conscientious effort on their part and the achievement of a normal risk factor profile, still experience an acute coronary event. He likens this to the antithesis of the "French Paradox" where the French have a much lower than expected incidence of CHD in spite of what appear to be high levels of risk [29].

Finally, it should be pointed out that when predicted (Framingham) vs. observed rates for CHD are compared outside the U.S. there is significant over prediction when the 10-year risk is low and under prediction only at high levels of risk, and this has prompted efforts at recalibration with the generation of new systems of assessment [30]. But in a study from the UK that introduced social status as measured by deprivation, the Framingham score seriously underestimated cardiovascular risk [31] and in a U.S. study of siblings of patients with premature coronary artery disease, the Framingham risk equation underestimated the 10 year incidence of total coronary artery disease events, especially for men [32]. Thus the Framingham-ATP III protocol and its risk factors emerge as forming a somewhat less than satisfactory system.

Even if the truth regarding the "only 50%" figure is that the actual number is higher for the presence of one or more risk factors in individuals experiencing CHD events, it can still be argued on the basis of the data presented above that there may be significant risk underestimation and that there may well be missing factors that might prove of value if included in future algorithms or taken into account in some other way. In fact, this is an active area of research. But in the context of primary prevention, as Nieto pointed out [33], there are other important issues such as the incidence and progression of atherosclerosis that must also be considered.

Evidence of Underestimation from Coronary Calcium Studies

The currently employed office protocols such as Framingham-ATP III for the assessment of CHD risk only indirectly infer the potential presence of subclinical atherosclerosis. But the intimate relationship between CHD and atherosclerosis makes it of considerable interest to more directly examine the correlation between atherosclerosis and the traditional Framingham risk factors (TRFs). Over the last decade, one of the most popular approaches to this question has been with electron beam tomography (EBT) which yields results generally presented as a coronary artery calcium score (CACS) or Agatston score which is taken as a measure of the extent of coronary atherosclerosis. Values for the CACS range from zero to over 400. In general, the EBT CACS is an independent predictor of coronary events and adds incremental information to the standard risk factors [34]. Studies have examined correlations between the CACS and the Framingham risk category (10-year risk), and also between CACS and individual Framingham and other risk factors. In this section the emphasis will be on the

relationship between the traditional Framingham risk factors (TRFs) and the extent and progression of atherosclerosis.

A recent study by Desai *et al* [35] examined 8549 asymptomatic individuals using EBT for coronary calcium assessment. The association of TRFs and coronary artery calcification (CAC) was examined in part by stratifying the cohort using three TRF categories for 10-year risk. The prevalence of advanced atherosclerosis was found to be 20% in the low-risk group and 27% in the intermediate risk group. Low risk was defined as ≤ 9% 10-year risk and intermediate risk as between 10% and 20%. Those classified as having advanced coronary calcification were in the ≥ 75^{th} percentile for the coronary artery calcium score. In addition, Desai *et al* present a scatter plot of log(calcium score) vs. the TRF 10-year risk score. A very low correlation coefficient (0.31) was obtained and visually any correlation at all is hard to discern. It is important to note that 47% of this study cohort had a TRF 10-year risk that did not exceed 20% and yet had advanced coronary calcification. The presence of significant underestimation, based on TRFs, is especially evident in the 20% of low-risk individuals with advanced calcification.

Similar results were reported from a study by Achenbach *et al* [36] who compared CACSs with three similar CHD risk estimates: (a) the risk estimated by the traditional Framingham factors plus the presence or absence of diabetes to predict overall CHD (angina, MI and coronary mortality); (b) the NCEP ATP III protocol for hard coronary events (MI and coronary death) which incorporated the traditional Framingham factors only; and (c) the Prospective Cardiovascular Münster (PROCAM) algorithm which also predicted hard coronary events and included triglycerides and family history along with the traditional Framingham factors. This study found the correlation between coronary calcification and the predicted cardiac event risk to be very low. In addition, 13% of patients with < 10% event risk according to ATP III were in the 90^{th} percentile in terms of the extent of coronary atherosclerosis as measured by the CACS.

In a study restricted to women (age 51 ± 7 years) with a family history of premature coronary heart disease, Michos *et al* [37] found that while 98% were at very low risk as estimated by the Framingham risk score (mean 10-year risks of 2% ± 2%) , 40% had detectable CAC, 12% had CACSs > 100 and 6% had CACSs > 400. Based on CAC score percentiles, 32% had significant subclinical atherosclerosis and 17% were above the 90^{th} percentile in CACS.

Other studies showed a similar pattern. In the Rotterdam Coronary Calcification Study [38], 29% of men and 15% of women without risk factors had extensive coronary calcification as indicated by a high calcium score. A study of asymptomatic Brazilian men revealed that the NCEP guidelines were limited in terms of identifying significant coronary atherosclerosis [39], and in another study CAC scores were found to improve risk prediction in the elderly [40]. The Prospective Army Coronary Calcium Project also found that conventional coronary risk factors significantly underestimated the presence of premature, subclinical atherosclerosis [41]. Shaw *et al* [42] found in a large cohort that 16% of men and 12% of women with low-risk Framingham scores had detectable calcium. For those with an intermediate-risk Framingham score, calcium scores > 10 were found for 31% and 43% of men and women, respectively. Taylor *et al* [43] studied a group with a mean 10-year Framingham risk for CHD of 4.6 ± 2.7, i.e. low risk subjects, and found coronary calcium in

22.4% of men with a mean CACS of 20 and in 7.9% of women with a mean CACS of 3. A multi-ethnic study of non-diabetic women aged 45-84 who were at low risk based on their 10-year Framingham score reported in late 2007. The presence of a CACS > 0 was found in 32% of the subjects and a follow-up over about 4 years yielded a significant hazard ratio of 6.5 for risk of symptomatic CHD or events in this subgroup compared to women with a CACS of zero. Differences in traditional risk factors between the group experiencing events and the no-event group were not significant [44].

The Framingham-ATP III guidelines were also found to underestimate cardiovascular risk in middle-aged asymptomatic adults (age 53 ± 10 years) as inferred by the presence of CAC [45]. In this study low risk was defined as having 0-1 risk factors and intermediate risk ≥ 2 factors plus a 10 year Framingham risk of < 10%. For those with a CACS of zero, 65% were low risk, 29% intermediate risk. The comparable figures for a CACS between 1 and 99 were 39% and 42%. For a CACS between 100 and 400, 25% were low risk and 39% intermediate risk with similar figures for CACS > 400. These results are consistent with those found in studies discussed above and underscore the presence of advanced and very advanced atherosclerosis in some individuals judged either of low or intermediate risk by the Framingham-ATP III guidelines.

The failure of commonly used CHD risk assessment methods to correlate with coronary calcium is also illustrated by results of other studies that examined CACS vs. individual risk factors. Examination of the results of a number of studies reveals poor or negligible correlation of CACS values and either total cholesterol, LDL cholesterol, or both [46-51]. One study illustrated the low correlation with scatter plots for CACS percentile vs. levels of LDL, HDL and the ratio total cholesterol (TC) to HDL [51]. The corresponding correlation coefficients were 0.0006, 0.11, and 0.06, respectively. In this study it was concluded that asymptomatic individuals with subclinical atherosclerosis defined by coronary calcification were not reliably identified by NCEP guidelines, and that TC, LDL, HDL, and triglyceride levels and the TC/HDL ratio correlated neither with the extent nor prematurity of the calcified plaque burden.

The relationship between risk factors and the progression of atherosclerosis as judged by increases in CAC is also of interest. Associations have either been absent or inconsistent in several studies. Wong *et al* [52] examined this question in over 700 subjects, mostly men, with two scans seven years apart. After adjustment for other risk factors, neither LDL cholesterol levels nor the control of LDL were related to the progression of CAC with CAC progression similar across categories of optimal, intermediate and higher risk LDL levels according to ATP III. However, higher levels of HDL (≥ 60 mg/dL) were associated with less CAC progression than those with levels ≤ 40 mg/dL. Other studies found similar but not identical results. Chironi *et al* [53] found CAC progression in asymptomatic men over 3.3 years to be independent of BMI, blood pressure, blood lipids, glucose, fibrinogen, smoking, and family history of CHD. Only lipoprotein(a) correlated positively with CAC changes. Yoon *et al* [54] examined progression of CAC over an average of 25 months and found that among the traditional risk factors, only hypertension and diabetes were significantly related to calcium progression. In addition, Houslay *et al* [48] found that statin treatment had no major effect on the rate of progression of CAC in spite of reduced systemic inflammation and reduced LDL levels. Finally, in a recently reported study, among the traditional risk factors,

only systolic blood pressure, taking anti-hypertensives, smoking and diabetes were significantly associated with changes in coronary calcium over time in a cohort aged 45 to 84 with an average of 2.4 years between scans. However, in connection with the incidence but not progression of CAC, HDL and LDL cholesterol were also significant risk factors [47].

Thus there appears to be growing evidence that there may still be significant and perhaps major so-called underlying risk factors missing from the Framingham-ATP III protocol in all of its various formulations when applied to the question of the presence or progression of atherosclerosis. In particular, serum levels of TC and LDL were seldom implicated. Even though it can be argued that the risk factor assessments such as Framingham emphasize event rates and the CACSs discussed above relate to the extent of subclinical atherosclerosis, there is a strong correlation between CACSs and the risk of CHD or CHD events and as well overall mortality [55,56].

Evidence of Underestimation from Autopsy Studies

Autopsy studies offer an opportunity to directly observe and measure the extent of coronary atherosclerosis. Typically, victims of violent or accidental death or suicide provide the cases. The first significant study appears to have been reported 1936. Two pathologists from New York University, K. Landé and W. Sperry, studied a large group of individuals who had died from violent incidents [57]. They examined the extent of coronary atherosclerosis observed at autopsy and found no correlation with serum cholesterol levels. Some dismissed these results by claiming that post mortem cholesterol values measured after death were not a reliable indication of levels while alive. But other studies enable one to discount this objection. A Canadian study examined a large number of veterans at death [58]. Adequate retrospective cholesterol data were available and while levels varied considerably among the individuals, for any given person, they were fairly constant. Autopsy studies on all the veterans who died revealed no connection between the degree of atherosclerosis and blood cholesterol levels. The same results were found in a study from India. Mathur and coworkers [59] studied the changes in cholesterol levels subsequent to death and found them to be stable for at least 16 hours. Thus samples collected shortly after death were representative of pre-death levels. Next, Mathur's group studied 200 individuals who had died in accidents but were free of any prior disease. No connection was found between cholesterol values and the degree of atherosclerosis. These studies involved what amounted to random selection of cases.

Similar results were obtained in other studies. The Framingham investigators found a very weak correlation expressed as a correlation coefficient of 0.36. Correlation coefficients of this magnitude generally accompany scatter plots where one can barely detect anything other than a random array of points. Also, in the Framingham cohort at that time, there were 914 deceased individuals, but the Framingham investigators selected only 127 (14%) for the purpose of studying atherosclerosis and cholesterol. This may not have been a random selection and the report did not describe the selection criteria. Two studies from Japan claimed a positive correlation, but correlation coefficients were even smaller than found in

the Framingham study, and in one study, the correlation appeared only in individuals with low or normal cholesterol levels, and in the other only in the elderly. Also, for those with very high cholesterol, the degree of atherosclerosis was the same whether they were young or old. In a study from Norway, many people with normal coronary arteries had cholesterol levels as high as those in whom all three coronary vessels were constricted, and those with two constricted vessels had lower levels than those with just one constricted artery [60].

A poor correlation (r = 0.35) between histologic coronary calcification and the Framingham risk score was also found by Taylor *et al* [61] in an autopsy study of victims of sudden cardiac death. Likewise, in an autopsy study of Greenlanders, there was no association between the extent of atherosclerosis of the left anterior descending or right coronary arteries and smoking, hypertension, high LDL + VLDL, low HDL, or obesity for either men or women. In this study the ages ranged from < 24 to 89 years and the cholesterol levels covered a very wide range [62].

Thus the autopsy studies either do not support the connection between circulating cholesterol or traditional risk factors and the degree of atherosclerosis, or they produce very weak correlations. The lack of correlation with cholesterol levels is important because LDL cholesterol levels play a central role in risk assessment for CHD or CHD events. Although the data are limited, the autopsy results are consistent with the CAC studies discussed above. The special case of very young individuals will be discussed below.

Other Imaging Evidence of Problems with Traditional Risk Factors

The METEOR trial [63] was designed to examine the impact of statin therapy on carotid intima-media thickness (CIMT) determined by ultrasound in low-risk individuals. The ATP III guidelines were used to define the low-risk study population. The criteria were 0 or 1 risk factors or ≥ 2 risk factors with a 10-year risk of CHD of less than 10%. Ages ranged from 45 to 70 years for men and 55 to 70 years for women. The investigators screened 5751 asymptomatic individuals and identified 984 who had substantial increased CIMT but met the criteria for being low risk for CHD according to the criteria used. Thus in this cohort, approximately 17% of those judged at low risk by applying ATP III guidelines in fact had what the investigators regarded as significant carotid atherosclerosis. In an editorial in the same issue of the JAMA, Lauer points that the METEOR results raise a number of medical and public health issues involving the merits of screening and potentially treating individuals deemed low risk by the Framingham based guidelines. He points outs that according to recent National Health and Nutrition Examination Survey data, among healthy adults between the ages of 20 and 79, 85% had low-risk Framingham scores while only 2% were at high risk [64].

While CIMT looks at a different vascular bed than does EBT of coronary arteries, it is interesting that the percentage of low-risk individuals who have significant CIMT is similar to the percentage of low-risk subjects in the EBT coronary calcification studies who had advanced atherosclerosis. In addition, a recent angiographic study of CAC found that of the CHD risk factors, only age, systolic blood pressure and family history were independently

related to CAC. No differences in the CAC severity were found associated with BMI, LDL cholesterol, diabetes or smoking habits [65].

The extent of atherosclerosis can also be examined with intravascular ultrasound. This technique provides transmural imaging of the entire arterial wall and allows both the detection of early stage atherosclerosis and cross-sectional and 3-dimensional quantification of plaques [66]. As part of the REVERSAL study [67], which compared the effects of 80 mg of atrovastatin and 40 mg of pravstatin, the relationship between risk factors and atherosclerotic disease burden at baseline was determined by both intravascular ultrasound and quantitative angiography. Hyperlipidemic patients between 30 and 75 years of age with a clinical indication for diagnostic angiography were enrolled. About 90% presented with angina, 35% with prior MI. When univariat predictors of the percent area of stenosis based on angiographic data were examined, only non-white race and prior procedures achieved statistical significance with the traditional risk factors of smoking, systolic blood pressure, total and LDL cholesterol, diabetes and hypertension all yielding large p-values associated with the β coefficients. In multivariate analysis of predictors of disease burden measured by intravascular ultrasound, among the traditional risk factors, smoking and diabetes were significant for percent plaque volume, diabetes for total atheroma volume and percent abnormal cross sections. In commenting on the observation that none of the traditionally measured lipid values were independently predictive of disease burden, the authors suggest that an interaction between lipid levels and other risk factors such as inflammation and genetic susceptibility may determine whether abnormalities in lipid metabolism are expressed as atherosclerotic disease [68].

Thus EBT, angiographic and autopsy studies of the association of traditional and other risk factors with the presence or progression of atherosclerosis do not reveal consistent correlations. This should focus attention on the possibility of missing risk factors.

Atherosclerosis and Young Individuals

It has been known for some time that atherosclerosis frequently starts at a young age. For example, autopsy studies between 1987 and 1994 revealed 5% of men studied who were between age 25 and 29 had an advanced atherosclerosis lesion that caused stenosis of 40% or more of the proximal left anterior descending coronary artery, and for men between 30 and 34, the figure was 20% [69]. Similar prevalence was seen in the Pathological Determinants of Atherosclerosis in Youth (PDAY) study which included subjects as young as 15 years [70]. In this latter autopsy study, which involved both males and females with an age range of 15-34, significant odds ratios associated with risk factors for the presence of target lesions in the coronary arteries were found to be age, non-HDL cholesterol, hypertension, hyperglycemia and obesity, the latter for men only. From these results the investigators developed a so-called Risk Score which had for the area under the receiver operating characteristic curve values of 0.75 and 0.84 for the predicting coronary artery and aorta target lesions, respectively. In a related study, this PDAY Risk Score was found to predict CAC up to 15 years before its assessment with EBT [71]. The PDAY risk score performed better than the

Framingham score for predicting CAC among young adults 15 years after assessment (areas under the receiver operating curves of 0.736 vs. 0.619).

The CARDIA project also looked at early adult risk factors and subsequent coronary calcification in a group with ages 18-30 years. Included were age, race, gender, cigarette smoking, LDL and HDL cholesterol, systolic blood pressure, BMI, and serum glucose levels. Only BMI and HDL cholesterol failed to yield significant odds ratios for having CAC at year 15 based on either baseline or year 15 assessments, with baseline values providing better prediction [72]. At year 15, the overall prevalence of any CAC was about 10% with only 1.6% having CAC scores greater than 100.

When these results are compared with studies discussed above of risk factors for the presence and progression of atherosclerosis in older individuals, it appears that the traditional risk factors are more successful in predictions for the young and very young and for predicting incidence. The data, however, are limited.

Stress and Atherosclerosis

Since the traditional risk factors for CHD and CHD events appear to poorly correlate with the extent of atherosclerosis, except perhaps in very young individuals, it is of interest to briefly examine the relationship between the extent or progression of atherosclerosis and psychosocial stress, a potential missing factor. Unfortunately, some of available studies are of cross-sectional design and are thus unable to examine the basic question of whether or not chronic stress over a number of years enhances the rate or extent of coronary calcification. Also, studies that have directly examined the connection between CAC and stress are limited and somewhat inconsistent. A recent cross-sectional study used EBT scanning to evaluate coronary calcium and questionnaires with validated scales to evaluate depressive symptoms, anger, anxiety and the chronic stress burden [73]. No association was found based on this one-time evaluation of psychological parameters. An earlier and much smaller cross-sectional study also reached the same conclusion[74]. The power of this latter study to detect the target association has been questioned [75].

The above negative results are to be compared with studies that found positive correlations. Koh *et al* [76] studied only anger and its relation to CAC in individuals with and without risk factors for coronary artery disease. Logistic regression analysis showed that only the total anger score was significantly associated with CAC regardless of the presence of risk factors. It was concluded that anger plays an important role in coronary artery calcification. Positive results were also obtained by Iribarren *et al* [77] who examined the association of hostility with CAC in young adults. This was a prospective study associated with the Coronary Artery Risk Development in Young Adults study (CARDIA). Hostility assessment was made three times over 10 years and then EBT scans were employed to determine the extent of CAC. Comparing those with hostility scores above and below the median resulted in odds ratios of 2.57 for having any coronary calcification, and 9.56 for having a CACS $\geq$ 20. Both results were statistically significant. In a cross-sectional study of the association between CAC and major depression by Agatisa *et al* [78], a group of healthy middle-aged women with a history of recurrent major depression were found to be more likely to have

CAC or CACSs in the high percentiles as compared with women with a history of a single episode or no depression. When compared with those having no history of depression or a single episode, odds ratios adjusted for cardiovascular risk factors were 2.46 for any calcification and 2.71 for high coronary calcification. Similar results were obtained by Tiemeier *et al* [79], but Matthews *et al* found in a study of women free of coronary disease, stroke or diabetes that there was no significant relationship between psychosocial factors and CAC except for aortic calcification [80]. Finally, Kop *et al* [81] found in a cross-sectional study that negative social networks such as being single or widowed were associated with CAC.

The level of education has also been associated with CAC. In one study, education was inversely associated with the prevalence of CAC in a graded dose-response fashion, although the association was partially explained by risk factors measured 15 years earlier [82]. In a cross-sectional study, educational attainment was associated with lower early stage atherosclerosis [83].

There is also evidence based on coronary angiography. In a cohort derived from the Stockholm Female Coronary Angiography Study, patients were enrolled who had been admitted to hospital for unstable angina or an acute MI. The degree of atherosclerosis was measured at baseline and three years later. Marital and job-related stress were determined by questionnaires. It was found that stress from work or at home accelerated the decrease in luminal diameter as compared to women who had a favorable stress profile [84]. This same group had reported earlier on an angiographic study of the association of progression of coronary atherosclerosis with depressive symptoms and social isolation which, for women with CHD, accelerated disease progression [85]. Likewise, Everson *et al* found that men who showed stress induced blood pressure reactivity and reported high job demands experienced the greatrest atherosclerotic progression in the carotid arteries [86]. Also, another carotid aretery study showed sustained anxiety accelerated the progression of atherosclerosis [87].

Indirect evidence of the association between stress and coronary calcification comes from a study of the behavior of cortisol levels throughout the day in individuals for which there was EBT determined CAC data [88]. This study, which was part of the CARDIA project, was based on the hypothesis that the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis is one of the pathways whereby chronic stress affects CHD risk [89-91]. Diurnal cortisol decline was used as a measure of this dysregulation and a positive association was demonstrated between stress and the risk of coronary atherosclerosis by this measure. Impaired cortisol response has also been found in patients with coronary artery disease (CAD). Nijm *et al* [92] found that compared to clinically healthy individuals, CAD patients had a higher 24-hour cortisol secretion and a flattened diurnal slope resulting at significantly higher cortisol levels in the evening. They suggest a dysfunctional HPA axis response involves a failure to contain inflammatory activity in CAD patients and this provides a possible link between stress, inflammation and atherosclerosis.

In fact, it was suggested a number of years ago that inflammatory action innitiated by psychological stress might play a role in the initiation and progression of atherosclerosis and also account for the significant number of atherosclerotic patients with no other known risk factors, and in the last few years this subject has received increased attention [93-95]. In addition, it is now recognized that there exists a strong possibility of a close relationship

between the stress induced response of the HPA axis and the systemic sympathetic adrenomedullary systems and the etiology of insulin resistance, obesity, atherosclerosis and type 2 diabetes, an association mediated mostly through inflammation [94,95].

Ranking Stress among the Risk Factors for CHD

In contrast to the rather limited data directly or indirectly linking the extent of atherosclerosis to psychological stress, there is extensive evidence regarding the association of stress with the risk of CHD and CHD events [96,97]. This will not be reviewed in detail in this chapter. The relevant question in the context of this chapter is how psychosocial factors rank with the traditional risk factors including diabetes. This question was addressed in a multi-center case-control study that may well be considered for landmark status. This was the INTERHEART study which examined the magnitude of risk factors associated with MI in 52 countries in 10 geographic regions including North America. In part of the INTERHEART study, an attempt was made to identify the major potentially modifiable risk factors associated with first acute MI [98]. Approximately 15,000 cases of MI and 15,000 controls were enrolled. Data was collected regarding smoking, history of diabetes and hypertension, waist/hip ratio, dietary patterns, alcohol consumption, blood apolipoproteins, total and HDL cholesterol (measured but not used in the analysis) and psychosocial factors. Odds ratios were calculated for the association between these factors and the risk of MI, and as well, their population attributable risks were calculated. Questionnaires were used to acquire data not obtainable from blood analysis or other clinical measurements. Psychosocial factors included depression, locus of control (the perceived ability to control life circumstances), perceived stress and stressful or traumatic life events. The details are provided by the authors in a related paper dealing only with psychosocial factors and MI [99]. Participant's ages covered a wide range. Because the apolipoprotein (Apo) concentrations were not influence by the fasting status of the participants, the ApoB/ApoA ratio was used in place of TC and HDL cholesterol [100].

An odds ratio (OR) of 2.87 was obtained for current smoking vs. never. Comparison of the top 4 quintiles vs. the lowest for ApoB/ApoA yielded an OR of 3.25. A history of hypertension, diabetes or abdominal obesity gave ORs of 1.91, 2.37 and 1.12 (top tertile vs. lowest) respectively. Finally psychosocial factors had an OR of 2.67. All were significantly related to the risk of a first MI and were noted in men and women, old and young and in all regions studied. When daily consumption of fruits and vegetables, regular consumption of alcohol and regular physical activity (all found protective) were included, the nine risk factors collectively accounted for 90% of the population attributable risk in men and 94% in women. In younger men and women, the figures were 93% and 96% respectively. While the main objective of the study was to examine the importance of these risk factors as they relate to the incidence of MI since they were potentially modifiable, in the context of this chapter, the most important result is the relative ranking of psychosocial factors which put them on a par with diabetes and smoking, both major risk factors in traditional assessments.

This study also examined the population attributable risk (PAR) associated with the risk factors considered. The PAR, which takes into account the probability or prevalence of

exposure, is useful in estimating the impact of preventive interventions in the context of overall public health. The following results were reported for the PAR values for the positive risk factors [98]: ApoB/ApoA 49.2%, smoking 35.7%, psychosocial factors 32.5%, obesity 20.1%, hypertension 17.9% and diabetes 9.9% . Thus the psychosocial risk comes out near the top and in this comparison is much more important than diabetes, a result which is due mainly to the much greater population exposure to the former (approximately 3 fold). Thus both the odds ratio and PAR views suggest major importance should be assigned to psychosocial factors.

The PAR values associated with psychosocial stress found in the INTERHEART study also varied considerably from country to country and by gender and age. For example, for men and women, the numbers were 23.7% and 67.1% for Western Europe, 31.6% and 17.2% for Australia and New Zealand, and 63.7% and 32.7% for North America, respectively. For young men ($\leq$ 55 years of age) the overall PAR was 39.7% whereas for older men it was 23.7%. For women $\leq$ 65 years, the PAR was 53.0% and for those $\geq$ 65 it was 30.6%. The potential public health benefit associated with psychosocial risk reduction is clear from these figures.

The INTERHEART study also examined in detail the contribution of individual psychosocial risk factors and the risk of MI [99]. Using a case-control design, Rosengren *et al* investigated this association for over 11,000 cases and 13,000 controls from 52 countries. Stress and depression status were evaluated in detail by trained staff who administered simple questionnaires. When compared to controls, the odds ratios for an MI, which all achieved statistical significance, were for (a) work stress in the previous year, 1.38 and permanent work stress 2.14; (b) several periods of stress at home, 1.52 and permanent stress at home, 2.12; (c) general stress that was periodic, 1.45 and permanent 2.17; (d) financial stress 1.33; (e) stressful life event 1.48; and (f) depression 1.55. These results were significant after adjusting for other cardiovascular risk factors and were consistent across regions, in different ethnic groups, and in men and women.

There is also an issue in that psychosocial stress probably acts in different ways and by different physiopathologic mechanisms during the development of atherosclerosis, starting potentially at an early age, and during symptomatic CHD or a fatal or non-fatal MI much later on in the natural history of the disease where triggering events becomes important. Thus the INTERHEART results were mainly concerned with the stress-CHD events relationship.

Thus the INTERHEART study strengthens the accumulated evidence that stress and depression, especially if chronic, make a major contribution to CHD risks. In addition, when judged against other risk factors, psychosocial stress appears to rank with diabetes in terms of importance, and since diabetes automatically places one in the high risk or “CHD equivalent” category according to some assessment protocols, this emphasizes the point that psychosocial stress perhaps should be considered a major factor and its inclusion could play an important role in reducing the underestimation of CHD risk.

The Challenge—Identification and Quantification of Stress in the Office Setting

There arises a serious problem associatged with evaluation if it is granted that psychological stress and depression may well together be a major and perhaps a very significant missing major factor in assessing CHD risk with the goal of high sensitivity and specificity, and that this might in part account for some if not many of the low Framingham risk individuals who have very high levels of atherosclerosis and as well the incidence of CHD events in individuals with no conventional risk factors or low 10-year CHD probabilities. In the INTERHEART study information was collected regarding stress at work and at home, financial stress, stressful life events, and locus of control. Depression was assessed by a general question concerning feeling depressed and if the answer was yes, with an additional set of seven yes or no questions. Thus there already exists a protocol which has been successfully employed, at least in the case-control setting. Also, there was a successful study of stress and CHD reported in 1991 that used only one question [101]. However, effort in developing and validating questionnaires appropriate to the office setting rather than the research setting appears to be largely absent although Lemyre and Tessier reported a simple 9-question survey instrument that has been used in industrial settings. But they do not provide detailed validation evidence [102]. However, it should be possible to develop a user-friendly and office setting-friendly questionnaire based on the protocol similar to that of the INTERHEART study that can be administered by office or nursing staff at the start of a visit. Since the results can presumably be quantified, there is the potential to introduce them into the commonly used algorithms for calculating 10-year risk. As the search continues for an approach to assessing CHD risk with high sensitivity and specificity, it may indeed prove desirable to explore this.

From what has been discussed above, and especially what the INTERHEART study demonstrated, if an individual presents with evidence of a high level of depression or chronic work and/or domestic stress, for lack at present of a protocol for assessment that would properly take this into account, the individual might with reasonable justification simply be put in a high-risk category equivalent to having diabetes. Whether or not screening for coronary calcium is indicated in those presenting with high levels of stress and/or depression but a low Framingham-APT III overall risk is of course highly debatable given the hazards of ionizing radiation, particularly in premenopausal women, and the possible morbidity associated with the follow-up [103]. It is interesting in this connection that the guidelines promoted in the Screening for Heart Attack Prevention and Education Task Force Report (SHAPE) recommend non-invasive screening for all asymptomatic men aged 45-75 and asymptomatic women age 55-75 except those deemed very low risk, i.e. no traditional cardiovascular risk factors, including diabetes. Thus according to this view, the presence of significant chronic depression or psychologically induced stress would constitute justification for screening if the risk was regarded as equivalent to having diabetes. EBT screening for CAC was one of the suggested possibilities in these guidelines [104].

In Search of the Best Protocol for the Identification of CHD Risk

There are fundamental problems that make this a difficult proposition. First, the risk factors should be independent. However, as Brotgman *et al* point out, independence is based on specific statistical models and depends on the set of risk factors included in the model, and these will vary from study to study. Thus while a given independent risk factor may have a significant statistical association with a clinical outcome and retains this significant association when other established risk factor are included in a model, the result is of necessity model dependent [105].

Screening tests in general deal with predicting events or symptomatic presentations in an asymptomatic population. The predictive value of a test depends on the prevalence of the condition in the population being tested and as well the sensitivity and specificity of the test. The influence of the prevalence of the condition in question appears to be underappreciated. This problem is addressed by Bayes' theorem which states that the greater the probability that the condition being screened for is present in an individual or population, i.e. the pretest probability, the greater the validity of a positive test and the likelihood that the result is a true positive. This becomes a serious issue when screening an asymptomatic population since if there is a low probability of the condition being present, this limits the value of a positive result in the sense that it is more likely to be a false positive. This point was recently emphasized and discussed by Pasternak *et al* in the introductory paper reporting on the 34th Bethesda Conference on Atherosclerosis Imaging Techniques and the Assessment of CHD Risk [106].

In addition, there is a problem with the biologic variation and temporal fluctuations of risk factors. Reynolds has modeled this using the variability of the continuous risk parameters systolic blood pressure, total cholesterol and HDL cholesterol. He found for the treatment threshold based on a 10-year CHD risk level of 20%, there was a 95% confidence interval of ± 6.0 percentage points and for the 30% threshold, it was ± 6.9 percentage points. For the Framingham threshold of 10-year 15% risk, the confidence interval was ± 5.1 percentage points. These numbers suggest the potential for day-to-day variations in risk factors being responsible for patients who needed treatment not receiving and as well, over treatment. His model showed that this situation could be improved considerably by triplicate measurements of these parameters [107]. But three separate office visits to establish the 10-year risk is probably unacceptable in the primary care setting.

One approach to finding an improved or even optimal protocol is to include in risk assessments a large number of additional risk factors over and above those included in Framingham-ATP III. Cobb *et al* [108] present an expanded list of 25 such factors and a potential algorithm that provides a hierarchy of categories. The list includes psychosocial factors in the category of predisposing risk factors. Cohn *et al* [109] have pursued a similar path in outlining a protocol for detecting CVD in asymptomatic individuals using 10 tests designed to detect early vascular and cardiac abnormalities and blood tests to identify potential targets for intervention. The fact that acquiring data for such comprehensive assessments would require considerable and in general probably unacceptable examination time and expense (EBT, ultrasound, exercise ECG etc.) makes it incumbent on proponents of

such an approach to provide justification of real benefit over simply including one or two additional factors to the assessment. But if an approach using a large number of risk factors develops credibility there will always be individuals who have both the time and financial resources and wish the best possible assessment. However, the problem of justifying thresholds for individual factors and overall scores will always plague such an approach given the large studies required to place a new protocol on a firm footing. Finally, work is ongoing developing prediction models that involve only a limited number of additional risk factors [110].

In the context of primary prevention, the goal of screening is to identify asymptomatic individuals who most benefit from advice on lifestyle modification, those who might benefit from drug treatment for hypertension, abnormal lipid profile, potential clotting problems, etc., and those who might benefit from referral for additional testing, for example EBT screening for coronary calcium. Low-risk and intermediate-risk asymptomatic individuals present the greatest challenge. In particular, as is widely recognized, there is a problem in false positives. But as illustrated above by the results of several coronary calcium studies, there is also a not insignificant risk of missing cases of severe atherosclerosis in individuals judged of low or intermediate risk by the traditional CHD risk factors. The low-risk group can be viewed from a different perspective by examining the lifetime risk along with the 10-year risk using the results of a recent study. In this type of analysis one risk factor can assume considerable importance and life-time risk can be used to argue for treating even one risk factor aggressively [44,111].

A commonly held opinion is that there is little merit in identifying risk factors if such knowledge does not lead to effective measures aimed at prevention. A somewhat pessimistic view has been introduced by a recent Cochrane Collaboration review of multiple risk factor intervention for primary prevention of CHD in general or in work-place populations of middle-aged adults. Pooled results suggested that multiple risk intervention had no effect on CHD related mortality or overall mortality. Risk factor changes were relatively modest. While the evidence suggested that such interventions have limited utility in the general population, the investigators found that high-risk hypertensive populations may accrue some benefit. According to the investigators, part of the explanation for the poor outcomes may be that the small risk factor changes were not maintained long-term [112].

These recent Cochrane results raise the following question. If multiple risk factor interventions are not very effective does this indicate that important risk factors are not being addressed or that assessment is not made early enough in the natural history of the disease? Two risk factors that are missing from of the studies included in their analysis are psychological stress and insulin resistance. Even if fasting glucose is used as a risk factor, it does not provide definitive information regarding insulin resistance, and the two-hour oral glucose tolerance test, which would be much more informative, will probably never be popular for routine physical exams [113,114]. With regard to insulin resistance, the inclusion of the metabolic syndrome, as it is defined in ATP III, may, according to Gerald Reaven, be both the wrong way to approach the insulin resistance problem and lead to the failure to treat individual aspects and attempt to reverse their impact on the development and progression of atherosclerosis [113].

Interventions to address stress and depression may also have limited effectiveness given that root causes may involve work or domestic situations that are frequently not easily modified. It may turn out that a potentially more effective approach will be to find ways to limit the resultant inflammation and the problems it can cause at all stages of the natural history of CHD.

It is interesting to speculate as to the success that might be achieved with a somewhat different approach in the context of primary prevention which would involve the early identification of insulin resistance and attempts to reverse it, perhaps with aggressive dietary intervention designed to significantly restore insulin sensitivity, raise HDL and lower triglycerides, the latter two being the only easily measured surrogate markers for insulin resistance [113,114], and in addition would involve identifying and addressing chronic stress and depression. Such a protocol would also include identifying and treating hypertension and advising against smoking, This approach would be consistent with the view that insulin resistance and psychological stress together have a broad and wide reaching impact, operating mostly through inflammatory mechanisms and the induction of the acute phase response, which lead down the path to atherosclerosis, adult onset diabetes, CHD and CHD related adverse events [94,95,115,116]. In fact, the poor correlations between traditional risk factors and the extent of coronary atherosclerosis as seen in the EBT coronary calcium and other studies should provide incentive to find and test new and different approaches to identifying and deal with CHD in asymptomatic individuals. Such an approach would also have the merit of perhaps more closely addressing causative factors than the present approach, and would represent a very significant departure from current guidelines with respect to asymptomatic individuals since the importance of total or LDL cholesterol is deemphasized. Nevertheless, successfully addressing the high triglyceride, low HDL presentation, a fairly good surrogate marker for insulin resistance, with exercise, diet and/or drugs would also have the potential for changing the LDL particle size distribution in a favorable direction, a change which may have a greater impact than lowering the actual LDL level [113]. This approach ignores the metabolic syndrome which has become one of the risk factors in the ATP III protocol. It has been argued that treating individual risk factors is better than diagnosing the syndrome, since many individuals who do not qualify for the diagnosis still have some of the factors that make up the set of diagnostic criteria [113,114,117]. In fact, Reaven has taken the position that diagnosing the metabolic syndrome has “neither pedagogical nor clinical utility” [110].

Conclusions

Significant problems appear to exist when one compares the estimated risk for CHD or CHD events and the extent of atherosclerosis as determined by coronary calcification. These problems reveal the potential for underestimation of risk, in some cases missing severe atherosclerosis. There also appears to be a problem in that the standard risk algorithms to some extent are also prone to underestimation. Even if a combination of standard risk factors and a CACS improves sensitivity and specificity [118], it seems clear that EBT screening as part of a routine physical exam probably will not happen soon [119]. There are also issues

associated with the high levels of radiation exposure associated with EBT. Given the sensitivity and specificity or the area under the receiver operating characteristic curves that the standard risk algorithms generate [118], it is difficult to deny that perfection is still somewhat elusive and that there are underlying risk factors that should perhaps be quantified and introduced into modified algorithms. Evidence is presented to support in some detail the merits of including stress and depression as assessed by validated methods into the estimation of CHD risk, using a protocol that can be adapted to the office setting and, ideally, quantified to the point where tables or online calculators can be used to obtain 10-year probabilities of both overall CHD risk and the risk of hard events. Furthermore, it is suggested on the basis of existing data regarding the relative importance in this context of stress vs. hypertension, smoking and diabetes, that unless this is done, underestimation may continue to be a problem, and along with this comes the failure to recognized the need for lifestyle changes and if indicated, stress reduction therapy. In other words, it appears that benefits should accrue if stress as a CHD risk factor evolves from being of academic interest to becoming a measured parameter in risk algorithms.

If psychosocial stress is to become an accepted and used risk factor, it presumably should meet certain criteria. Stampfer *et al* [120] have discussed this using points raised by Manolio [121]. They provide five criteria for evaluating novel cardiovascular risk factors:

- Does the factor add independent information on risk and prognosis?
- Does it account for a clinically significant proportion of disease?
- Is the factor reliable and accurate, i.e. is it reproducible?
- Does it provide good sensitivity, specificity and predictive value?
- Is the factor available and practical for widespread implementation?

In the context of psychological stress and CHD, some of these issues have been addressed in detail above. Others await future research.

Finally, one can not ignore the philosophy which downplays the importance of global assessment using risk factors and instead concentrates on aggressively treating individual risk factors independent of the global risk estimate. This is in keeping with the recognition of biochemical individuality and in addition would encourage attempts to modify the impact of stress and depression on the natural history of CHD even for those deemed low or very low risk by traditional measures. In addition, the recognition of stress as a major factor may help focus additional attention on inflammation as an important aspect of the etiology of atherosclerosis and CHD and encourage a move toward a paradigm shift which would concentrate on the many aspects of systemic inflammation with a focus on, for example, pro- and anti-inflammatory eicosanoids and cytokines, insulin and insulin resistance, cortisol, and in addition on the non-infectious chronic silent acute phase response. This would of course lead to a somewhat different emphasis associated with primary prevention, risk assessment and risk reduction than is currently popular. In fact, finding ways to reduce stress induced inflammation or its impact may be the only practical approach in situations where the underlying cause can not be eliminated, as could be the case in some, perhaps even many instances of chronic work-related and domestic stress.

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Chapter 17

Psychosocial Interventions in Women with Coronary Heart Disease

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Abstract

Coronary heart disease (CHD) is the leading cause of death in the world. Women are as much at risk to suffer from CHD as men. Because treatment modalities have improved and lead to better survival of cardiac patients, the number of patients who need continuous care has increased substantially. Thus cardiac rehabilitation and secondary prevention have grown to be more and more important in healthcare.

Women are about ten years older at the onset of CHD and they display more coronary risk factors, a lower functional capacity, greater disease severity at first diagnosis, more concomitant diseases and higher psychological distress than men. Women also differ from men in their reactions and coping behaviors. After MI they do not cope as well as men both physically and psychosocially. They experience more depressive symptoms and have more problems to be compliant, to attend cardiac rehabilitation programs or to maintain exercise training. Depression, lack of social support, stress from work and family additionally worsen women's outlook after an acute event of CHD. Women are at high risk because of their more common stressors, but also because the stressors convey a higher cardiac risk. In addition to the stressors which are relevant for men, the experience of stress from family ties is highly relevant in women. In fact in study groups, where women are gainfully employed to the same extent as men are, emotionally stressful marital relationships were found to worsen the prognosis and accelerate progression of CHD in women patients. However, women who experienced both work and family stress had the highest risk.

Cardiac rehabilitation has proved to be a useful tool in the treatment of coronary heart disease in women as in men. Given the beneficial effects it has even for women of higher age and with greater disease severity and functional limitations, women should be

more strongly encouraged to take part in cardiac rehabilitation programs and the programs should be designed to meet their needs.

Introduction

Coronary heart disease (CHD) is the leading cause of death and disability in both men and women in the world - it causes about 450,000 deaths in US, about 25,000 deaths in Swedish and about 75 000 in German women each year [1-3]. Women are as much at risk to suffer from CHD as men, but they get it about ten years later in life. The treatment of CHD is of great health-economic importance. Considering the general population development, which is leading to an increasing proportion of older people, it is going to be of even greater importance in the near future. Effective pharmacological interventions have been developed to reduce cardiac morbidity and mortality as well as to improve the patients` health related quality of life, but the choices for life style change are far from optimal. More studies are needed to identify which patient is most likely to benefit from various kinds of treatment.

In earlier times treatment concepts have been developed primarily for men and were based on studies predominantly conducted in male patients. It was assumed that they would be similarly applicable to women, despite the fact that women differ in several baseline characteristics: Women are not only about ten years older at onset, but they also present with more coronary risk factors, a lower functional capacity, greater disease severity at first diagnosis, more concomitant diseases, higher psychological distress and a lower quality of life [e.g.4,5]. Furthermore particularly younger women have been found to have a worse prognosis after myocardial infarction (MI) in terms of higher morbidity and mortality rates than men [6,7].

In more recent years awareness has grown that gender should be considered in the design of interventions. But nevertheless female patients are still underrepresented in published clinical trials and enrollment remains well below the proportion of patients with myocardial infarction [8]. A recent review revealed that women comprised only a fourth of the population studied in the Cochrane Systematic Reviews on CVD and that of those trials that included both men and women only a third examined outcomes by gender [9]. Due to this paucity of studies and information it is difficult to draw definite conclusions regarding the efficacy and safety of treatments for women. This chapter intends to summarize scientific findings regarding the effects of cardiac rehabilitation and psychosocial interventions in women with CHD. Certain characteristics of female patients with CHD will be highlighted and treatment recommendations will be derived.

Effects of Cardiac Rehabilition

Cardiac rehabilitation (CR) is a multifactorial discipline that aims at both the physical and psychological well-being of patients with cardiac diseases. Its main goals are to reduce risk factors, enhance psychosocial adjustment, improve exercise capacity, adherence to behavior changes and medical treatments, and consequently reduce recurrent events of

cardiac morbidity and mortality. It may involve a variety of therapies, including medical interventions, drug treatment, education about risk factors, exercise training, stress management trainings as well as other psychological interventions.

How CR programs are implemented varies across different countries. In Germany, for instance, the main element of cardiac rehabilitation is a three-week in-hospital treatment program that is targeted at the improvement of the functional capacity of the heart and a reduction of modifiable risk factors. Referral procedures are mainly standardized and participation is paid for either by retirement funds or by health insurance. In the US, in comparison, CR programs are mostly outpatient programs that differ regarding their main aims. Referral is less standardized and participation in certain kinds of interventions is not necessarily paid for. These differences in implementation affect the respective aims and components of the programs and may alter their effectiveness. Some of the following explanations, particularly the ones regarding program participation, focus on CR in outpatient settings. The conclusions might therefore be more true or relevant for some countries (e.g. the US) than for others.

A number of reviews and meta-analyses confirmed the benefits of cardiac rehabilitation in terms of reduced all-cause and cardiac mortality as well as reductions in coronary risk factors such as total cholesterol level or systolic blood pressure [10-12]. There is evidence that these findings apply to both women and men [5,10,13-15]. Research on the impact of exercise training on functional capacity for instance has consistently shown its beneficial effects in women: despite the fact that women present with a lower functional capacity at CR initiation, they achieve similar relative improvements as men. [5,13-15]. Hence, a current guideline for cardiovascular disease management in women recommends that women should be referred and encouraged to participate in CR programs [16].

However, the limited number of studies reporting gender-related effects makes it difficult to discern whether male and female patients experience the same overall improvements as a result of cardiac rehabilitation [9].

Predictors of Women's Participation in Cardiac Rehabilition

Evidence shows that CR programs are underutilized by cardiac patients in general and attendance is even lower for female patients with coronary heart disease [17,18]. As summarized in a review by Jackson et al. [19] participation rates are limited to 25-31% of all eligible and 11-20% of female patients. Additionally, when women participated in a cardiac rehabilitation program, compliance rates were even lower than in men [15].

The physician’s referral and recommendation has repeatedly been found to be the most important predictor of program uptake [17,20]. Furthermore, participation is influenced by medical factors such as baseline functional impairment as well as by other patient-related factors such as socioeconomic status (as defined by education or income level): Patients with lower socioeconomic status have been found to be underrepresented in cardiac rehabilitation [21]. The latter is in accordance with general findings concerning social gradients in health. A higher prevalence of cardiac diseases, for instance, has been found in low education or

income groups in Britain and the US [22]. Finally, participation is influenced by features of the program such as ease of physical access and transportation [23].

Most of these factors facilitate or inhibit program uptake in both sexes, but there are some factors that are more specific or more important for women and might contribute to their lower participation rates. First of all women are less often referred to cardiac rehabilitation [24] and physicians recommend CR more strongly to men than women [17]. CR programs are also often scheduled to meet the needs of younger male patients who are three to five times as likely as women to experience cardiac events under the age of 65 years. This sometimes makes participation more difficult and less attractive for female cardiac patients who are older and present with a lower fitness level, greater disease severity at first morbidity and more co-morbid diseases [17-20,25]. Furthermore, women tend to perceive their disease as more severe and less treatable than men. This was related to higher psychological distress and less engagement in health preventive behaviors [26]. From a psychosocial perspective women's early resumption of their role as a homemaker and their family obligations such as caring for dependent relatives interfere with participation. Finally more women than men don't have or drive a car, thus making program uptake sometimes impossible for them [17].

Effects of Psychosocial Interventions

Psychosocial treatments have long been accepted as a substantial part of cardiac rehabilitation. They can be targeted at a variety of objectives such as the reduction of different risk behaviors (obesity, smoking etc.) or reducing psychological distress (depression, anxiety), which is based on the assumption that psychological stress increases the risk and interferes with cardiac rehabilitation. It was found in earlier reviews and meta-analysis that additional psychosocial interventions had beneficial effects on the course of the coronary disease [27,28]. However, more recent studies have been less positive and some of them failed altogether to show any effect on cardiac morbidity and mortality [4,29]. Based on these results it was concluded that there is not just one kind of cardiac patient but different groups which need interventions that are tailored to meet their specific needs.

Female patients with coronary heart disease differ from male patients with regard to physical as well as to psychosocial variables [e.g. 25, 30] Studies analyzing the effects of psychosocial interventions separately for the two genders are rare, but the results of two recent large-scale studies suggest that men and women differ in their responses to and outcomes of psychosocial interventions as well [4,31].

Published in 1997 the M-HART trial by Frasure-Smith et al. [4] was one of the first to include adequate numbers of male and female patients and to report different effects with regard to gender. It was designed to assess whether a 1-year home-based nursing intervention could improve psychological well-being and cardiac outcome and prognosis for patients recovering from myocardial infarction. 1376 patients were randomly assigned to either the intervention program or usual care. The intervention group patients were telephoned on a monthly basis, screened for psychological distress and patients with high distress scores were contacted and visited by one of the study nurses. The median number of nurse visits was 4 for

men and 6 for women ($p<.0001$). Contrary to the positive results of an earlier study [32], the M-HART trial failed to show a significant impact of the intervention on psychological outcome and cardiac prognosis. For women, it even resulted in a worsened prognosis in terms of a higher 1-year cardiac mortality compared to the women in the control group.

Some years later, the results of the ENRICHD trial were published by Berkman et al. [29]. ENRICHD was the first clinical trial to test whether a psychological intervention which aims at reducing depression and increasing social support reduces clinical events after myocardial infarction. Patients were randomly assigned to either a usual care condition or to receive an individual cognitive-behavioral intervention supplemented by group psychotherapy. Antidepressant medication was given when needed. The intervention group patients attended a median of 11 sessions. As a result the intervention produced a significant effect on depression and social support, but failed to reduce recurrence of MI or mortality. Post-hoc analyses revealed that independent of baseline characteristics there might have been beneficial treatment effects for white men but there were no significant effects for women regarding cardiac mortality and morbidity. In contrast a trend towards higher morbidity in women was seen [31].

It is not fully explained yet, why the ENRICHD and M-HART interventions resulted in beneficial effects for men while they had either no or negative effects in women. However, the results suggest that male and female patients with CHD differ in their reactions to interventions and that women might require specifically tailored programs to meet their needs. So the question is: What are the needs of women with CHD that could be relevant for their effective treatment?

Characteristics and Needs of Women with CHD

Patients who are diagnosed with coronary heart disease face a major threat to their lives. They have to adjust to changes in body and mind, feelings of uncertainty and fear, changes in family, social and professional relationships and to the necessity of lifestyle changes [33]. Many patients have difficulties with this adjustment process resulting in reactions of denial and repression or negative emotions including anger, anxiety or depression, which in turn can interfere with adherence to medical treatment regimens.

Women with CHD differ from men in their reactions and coping behaviors. After MI they do not cope as well as men both physically and psychosocially [25]. They experience more depressive symptoms [34] and they have more problems to be compliant, to attend CR programs or to maintain exercise training [15,35]. Depression, lack of social support, distress from work and family additionally worsen women's outlook when they have an acute event of CHD. Women are at high risk because of their more common stressors, but also because the stressors convey a higher cardiac risk [36,37]. This is in part due to the women's older age and their worse medical condition but is most likely also influenced by the following interrelated characteristics that are specific to the recovery and adjustment process of female patients with CHD. Understanding these characteristics can be used to consider and design more appropriate CR programs and psychosocial interventions that are tailored to the needs of women.

Need for Emotional Support and Encouragement

Emotional support is part of the broader concept of social support, which has been shown to be related to prognosis of women with CHD [38]. Both emotional support and encouragement by family, health care professionals and fellow patients were repeatedly found to be some of the most important needs of female patients. [39,40]. Emotional support contributes to their emotional adjustment [41] and helps women to initiate and adhere to treatment regimens [40].

On the one hand women show good working and caring networks and receive more support than men [42] while on the other hand their use of these networks might sometimes be limited by their difficulties to express their needs: women do not want to involve and to bother their families with their heart problems [43]. Thus, despite the fact that women express a clear need for emotional support, they tend to avoid asking for it in their close relationships. It might be due to this fact that for female patients support by fellow cardiac patients and the opportunity for social interaction with other participants are highly appreciated aspects of CR programs [33,40]. Another explanation is, that women are more often living alone than men and do not have the same natural access to emotional support [44].

Information Deficits

Information has been found to be one of the most important needs of patients after myocardial infarction besides social support and encouragement [45]. A lack of information may affect the emotional adjustment as well as interfere with adherence or initiation of preventive health behaviors. A study by Stewart et al. [46] showed that patients who felt well informed about their disease reported less depressive symptoms, showed a higher level of self-efficacy and healthcare satisfaction and were engaged in more preventive behaviors.

Recent research has revealed that women are not aware of their risk for developing CHD and that they have a lack of knowledge about CHD and its risk factors. In a telephone survey of 1024 women only 46% of the respondents identified heart disease as the leading killer of women and only a minority was able to name major risk factors [47]. Furthermore, women have a lack of knowledge regarding their individual risk as well: Results from a study by Murphy et al. [48] showed that there was little correspondence between the actual and the perceived risk factors in women with a cardiac disease.

It has not been investigated yet whether female patients know less than their male counterparts. However, it seems that women receive less information and counseling about their cardiac disease and its management from health care professionals than men [33,46].

Minimization of Symptoms and Treatment Delay

Women seem to minimize their symptoms and to deny the severity of their disease. There is some evidence for instance, that women resume household activities early after hospital discharge thereby ignoring the fact that they should rest or ask for help [49]. In qualitative

studies women also reported that they minimized their symptoms at onset, because they did not want to disturb and worry relatives and caregivers. [33,43]. Quantitative studies concerning the question whether women seek care later than men have not yielded consistent results though. However, Dracup et al. [50] summarized in a carefully done review, that even if effects of gender on delay time were not detected in all studies, it was documented that whenever differences between men and women occurred, women had longer delays. This is of particular relevance as time to treatment after MI is directly related to mortality and prognosis. The delay in treatment seeking behaviors in women might again partly be explained by the women's older age or the fact that they are more likely to be living alone but it might also be influenced by their tendency to minimize symptoms, by the women's difficulties to recognize symptoms of MI and by their lack of knowledge regarding their own risk.

Family Obligations, Double Loads of Work and Family and Marital Stress

In addition to the stressors which are relevant for men early resumption of household duties is of great importance in the recovery process of women after MI and many women only reluctantly accept help from others and often feel guilty when family members help with home duties [49,51]. This behavior seems to help them regain a sense of control over their lives while not being able to perform their role as a homemaker generates emotional stress, including feelings of guilt and shame leading to a lowered self-esteem [41]. However, early resumption of household activities and reluctance to accept help und to involve the family in their heart disease can interfere with necessary lifestyle changes [33].

Findings concerning the effects of marriage on health and prognosis in CHD patients showed beneficial effects for married compared to unmarried men whereas the results for women were less consistent [52]. It seems that depending on the quality of marital interactions and the satisfaction with the relationship being married can sometimes even be harmful for women: Marital stress and low marital quality have been found to be associated with a worse prognosis in women with CHD as well as worse biological risk factors profiles and more atherosclerosis in healthy women [53-56]. Women who had to deal with a double exposure to stress from family and work were at even greater risk [56]. More recently the continual exposure to stressors was shown to increase progression of underlying coronary artery disease, suggesting a direct effect of stress on the female coronary arteries [36].

Conclusion and Recommendation

Cardiac rehabilitation has proved to be a useful tool in the treatment of coronary heart disease in women as well as in men. Given the beneficial effects it has even for women of higher age and with greater disease severity and functional limitations, women should be more strongly encouraged to take part in CR programs and the programs should be designed to meet their needs. However, the effectiveness of cardiac rehabilitation in women is limited by low attendance and compliance rates as well as by their lower response to psychological

treatments. The arising questions therefore are: How can program participation and adherence be improved and what can be done to tailor psychosocial interventions to the specific needs of women?

The literature has shown that the participation of female patients in CR programs is limited by a number of modifiable and unmodifiable factors and the physician's recommendation and referral seems to be one of the most important factors influencing patients' program uptake. Physicians should be aware of the critical role they play in encouraging female patients to make lifestyle-changes and to take part in CR programs. They should recommend attendance more vigorously . Recommendations should also be discussed with spouses and other family members to facilitate the necessary arrangements regarding transportation or conflicting family obligations.

Based on the scientific findings about the needs and preferences of female patients with CHD it can be assumed that earlier interventions might have failed because they may not have considered certain characteristics of women with coronary heart disease. For example they might not have met the women's emotional needs and their need for social interaction with fellow patients or they might have interfered with the women's specific coping process. The latter might have been caused by the use of more directive instead of supportive and collaborative approaches, as was suggested by Cossette et al. [57] in another reexamination based on data from the M-HART trial: Women seemed to benefit more from listening to their concerns while men profited more from educational interventions such as advice, which had in turn no or negative effects in women.

Summarizing the aforementioned results the following recommendations for the treatment of women with CHD can be derived:

- women need to be vigorously encouraged and referred to cardiac rehabilitation
- women need individualized information about their disease, risk factors and treatment options
- women need opportunities for social interaction in CR programs
- women need encouragement and emotional support by their families, by health care professionals and by other patients with similar experiences
- if possible, the family should be actively involved to facilitate necessary life-style changes and CR participation

These needs might best be met in cardiac rehabilitation programs that include supportive and educational groups as a supplement to exercise-based components. A group format might be more effective for educational purposes than individualized counseling. Furthermore our experience with group interventions in cardiac patients suggests that women might do better in same-sex groups than in mixed-sex groups [58,59] as was suggested by Burell and Granlund [60].

These recommendations are theoretically derived and there is still more research needed to confirm which kind of intervention is most effective in women with CHD. Research on the effects of cardiac rehabilitation should seek to include adequate numbers of female patients and to address the question of gender-related differences in response to interventions.

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Chapter 18

Effectiveness of Musical Stimulation during Intracardiac Catheterization

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Abstract

Background: Intracardiac catheterization is a routine physical examination. Due to psychological strains, several psychosocial interventions, including music therapy, have been proposed. The aim of the present study was to examine whether the preventive or adjuvant use of music therapy results in a reduction in both subjective and objective anxiety and thus leads to a reduction in sedative medication. Methods of Assessment: N = 83 patients (48 male, 35 female, 66 ± 11 yrs) waiting for scheduled cardiac catheterization were randomly allocated to a control group (standard care), an exposure group (music stimulation during the procedure), or a coaching group (additional music therapeutic coaching in advance of the procedure). Target variables were subjective anxiety, physiological parameters and medication. Results: Music intervention did effectively reduce subjective anxiety. Physiological values and medication did not differ between groups. Conclusion: The use of music stimulation during the catheterization has a relaxing and calming effect on patients. It seems to be extra beneficial in a subgroup of patients with higher-than-average psychological strains. Physiological parameters and medication were not influenced by music therapy. Some limitations of the study and future prospects (e.g. use of music therapy in secondary prevention) are highlighted.

Introduction

Cardiac catheterization, often in therapeutic combination with PTCA or stent implantation is one of the most frequently used diagnostic procedures in cardiology [1, 2].

Patients should fast for at least eight hours before the procedure. Premedication with a mild sedative is common; the examination itself is done under local anesthesia. Patients usually appear awake and are able to communicate clearly at all times.

Though these methods are very safe [3] and cardiologists feel confident in performing them, this procedure is still experienced as a potential life-threatening event for many patients: prior to catheterization the patient's quality of life decreases [4] and there is an transient increase in psychological symptoms, such as anxiety and depression [5] and in the use of medication [6]. During the catheterization frequently cardiovascular and psychological adverse effects occur, which can cause an acute deterioration of cardiac function and thus influence both the immediate course of the examination and the subsequent recreation phase. The ongoing behavior patterns are activated by character traits [7], like decreased self-attention [8] or insufficient affect regulation (so called type D- (= distressed) personality) [9]. Coping mechanisms, like information seeking vs. avoidance of information [10] or necessity of control [11], exert considerable influence on subjective experience of the catheterization.

Therefore interventions to reduce anxiety and stress reactions, that are efficient and easy to implement, should be developed and evaluated.

Music Therapy and Invasive Procedures / Music Therapy in Cardiology

The anxiolytic power of music has been used since the ancient times [12]. Several meta-analyses and controlled trials have proven the effective use of music both in connection with invasive procedures, with coronary heart disease and also with cardiac catheterization in particular.

The effectiveness of music therapy during medical interventions is rather heterogeneous, due to the broad field of medical interventions. Music seems to be most influential in reducing pain and anxiety [12, 13, 14] but there are also positive reports on regulation of physiological parameters such as blood pressure, oxygen saturation or respiration rate and a reduction in analgetic medication [15].

The use of music in patients with coronary heart disease has received considerable attention. A search of databases PubMed, PsychLit, Medline and Cochrane Library revealed five reviews/meta-analyses [16, 13, 17, 18, 19] and identified 13 studies of acceptable methodological quality addressing music therapeutic interventions in cardiology (see table 1). All of them used receptive music strategies, i.e. guided and structured listening to music, one study used supplementary video-music therapy support [20]), in one study patients were given additional instructions for muscle relaxation [21]. Usually the music interventions are one-time applications of 20 – 30 minutes duration; sometimes the patients are offered the opportunity to listen to the musical pieces twice [21] or trice [22]. Interventions typically take place with inpatients of coronary care units often with (presumed) acute myocardial

infarctions or during the early post-operative recovery phase after invasive procedures such as heart surgery [23] or coronary artery bypass graft [20, 24]. Outcome criteria are physiological parameters such as heart rate, respiration rate, blood pressure, oxygen saturation or temperature and qualitative patient evaluative data on psychological distress (pain perception, mood states, anxiety). Results indicate that music seems to be particularly effective in order to improve the patients' well-being and mood state and to reduce the subjective levels of anxiety and pain perception. Influence on physiological parameters however are very inhomogeneous seem to be rather marginal.

Music application during and after heart surgery could effectively reduce intubation time postoperatively [25]. The use of supplementary relaxation instructions on cardiac complications however could not be proofed as there were no group differences (music listening vs. relaxation).

Additionally the control group conditions have to be considered: Most studies compared music application to "standard care", "treatment as usual" or "silence". These studies reach an overall effect size of d' = 0,68 (large effect). If the control groups received some treatment (usually "scheduled rest", i.e. periods of uninterrupted rest with no nursing or medical care, but also relaxation instructions or music-video tapes), the effects fall short and reach an effect size of but d'=0,40 (medium effect).

Interestingly all studies used pre selected music, the patients had no or very limited influence on the choice of music. Furthermore it seems reasonable to conclude that if the impact of music listening alone has therapeutic value, the administration of music therapeutic strategies such as psycho-educative interventions or musically based counseling should have even greater effects.

Music Therapy and Angiography / Heart Catheterization

Several studies confirm the anxiolytic benefits of adjuvant music therapy before and during cardiac catheter examinations in both children [26; 27] and adults [28, 29, 30, 31]. Though the results regarding adult patients are sparse and heterogeneous, results indicate a possible benefit on both subjective anxiety and physiological values.

Based on a detailed compilation of both psychological traits as well as the subjective emotional state before the imminent examination, the German Center for Music Therapy Research designed a music therapeutic intervention and investigated its impact on patients undergoing cardiac catheterization.

Aim of the study was to examine whether the preventive or adjuvant use of music therapy results in a reduction in of subjective anxiety and normalization of physiological parameters (blood pressure, heart rate), and thus leads to a reduction in sedative medication.

Further hypotheses were that a preparatory coaching outperforms mere musical exposure during the catheterization and that patients with pronounced strains react to the catheterization in a different way than patients with low strains.

Table 1. Studies on music interventions in coronary units

Author	Year	Population	N	Study Design	Intervention	Duration of Intervention	d	Outcome Criteria	Result
Davis-Rollans & Cunningham	1987	CCU	24	Within Ss	music / silence	Alternating phases of music vs. silence	0,00	HR	decreased HR during music intervention
Bolwerk	1990	MI	40	Exp-contr	music / silence	3 x 22 min relaxing music (3 different classical pieces)	0,93	HR, RR, BP, anxiety	reduction in anxiety in music group
Updike	1990	patients in CCU	20	Exp-contr	music / silence	listening to music	1,25	physiological and psychological impact	improved well-being in music group
White	1992	MI	40	Exp-contr	music / silence	relaxing music vs. no treatment	0,75	trait and state anxiety ; HR, RR	significant reduction in HR, RR, and state anxiety scores in music group
Cadigan et al.	2001	CCU (patients on bed rest due to procedural sheaths or an intra-aortic balloon pump)	140	Exp-contr	music / silence	30-minute music intervention (Symphonic music paired with nature sounds) vs. silence	0,28	HR, BP, RR, skin T, qualitative patient evaluative data on psychological distress (pain, mood states)	reductions in BP, RR, and psychological distress in music group
Twiss et al.	2006	CCU (postoperative care)	60	Exp-contr	music / standard care	music during and after surgery	0,60	STAI, postoperative intubation time	less anxiety and reduced postoperative intubation time in music group
Chan et al.	2006	CCU (percutaneous coronary interventions with C-clamp)	43	Exp-contr	music / standard care	listen to relaxing music during the procedure	0,94	pain (VAS); HR, RR, BP, OS	significant reductions in heart rate, RR, BP, OS, pain in music group
Overall effectiveness							0,68		
Zimmerman et al.,	1988	MI	75	Exp-contr	white noise / music / silence	1 x 30 min session	0,00	STAI, BP, HR, and digital skin T	no significant difference among the three groups
Guzzetta	1989	MI	80	Exp-contr	relaxation / music / rest	three sessions over a two-day period	0,60	HR, peripheral T, cardiac complications, and qualitative patient evaluative data	lowering of HR, raising peripheral T, reduced cardiac complications in both intervention groups

Table 1. Studies on music interventions in coronary units (Continued)

Author	Year	Population	N	Study Design	Intervention	Duration of Intervention	d	Outcome Criteria	Result
Elliott	1994	CCU (unstable angina pectoris or MI)	56	Exp-contr	music / relaxation / silence	2 x 30-minute sessions; audiotaped light classical music or verbal instructions for muscle relaxation.	0,20	STAI, HADS, LAAS, BP, HR	No significant differences between groups for the psychological or physiologic variables
Barnason et al	1995	Coronary Artery Bypass Graft (early postoperative period)	64	Exp-Contr	music therapy / music-video therapy / scheduled rest	2x 30-minute intervention postoperatively	0,37	BP, HR, STAI, mood and anxiety (NRS)	significant improvement in mood in the “music” intervention; no group difference of physiological parameters (reduction in all groups)
Zimmerman et al	1996	Coronary Artery Bypass Graft (early postoperative period)	96	Exp-contr	music / music-video / scheduled rest	30 min intervention: music (choice of 5 tapes), videocassette of peaceful scenes accompanied by music, undisturbed rest	0,45	pain (VRS, McGill Pain Questionnaire) and sleep (Richard Sleep Questionnaire)	Pain: music better than control, no group difference for exp groups; sleep: video better than control
White	1999	Acute MI	30	Exp-contr	music / scheduled rest / standard care	20 min intervention: classical music vs. quiet uninterrupted rest	0,63	HR, RR, BP, STAI	Reduced state anxiety, HR and RR in music group; no difference in BP
Voss	2004	CCU (chair rest after open-heart surgery)	61	Exp-contr	music / scheduled rest / standard care	30 min of sedative music, scheduled rest (no interventions)	0,54	Anxiety, pain sensation, and pain distress (VAS)	reduction of all parameters in intervention groups, greatest in sedative music
Overall effectiveness							0,40		

CCU = Coronary Care Unit; MI = myocardial infarction, HR = heart rate, RR = respiration rate, NRS = Numeric Rating Scale, VAS = Visual Analogue Scale; oxygen saturation; T = temperature, LAAS = Linear Analogue Anxiety Scale, Exp – Contr = Experimental Group vs. Control Group; Within Ss = Within Subjects Design (each patient receives different form of treatment).

Music Therapeutic Intervention by the German Center for Music Therapy Research

Methods

Patients

At the SRH Zentralkrankenhaus Suhl an experimental study concerning the impact of different music therapeutic interventions on subjective anxiety and physiological parameters was conducted. Patients were eligible if they were admitted to the hospital for an in-patient cardiac catheterization for the first or second time, were able to speak and read German, cognitively oriented to person, place and time and had no major auditory deficits. Overall n = 90 patients were eligible due to inclusion criteria, signed the informed consent and were randomized to one of three intervention groups: the control, exposure or coaching group. N = 83 data sets (n = 27 control group, 15 male; n = 28 exposure group, 18 male; n = 28 coaching group, 15 male) were complete and entered data analysis.

Interventions

Participants randomized to the control condition received standard medical care, but no further verbal or nonverbal interventions. Only health personnel were present during the catheterization.

Participants randomized to the music exposure group were provided the opportunity to listen to preselected music via earphones. Music began as soon as the patients lay on the operating table, continued during the whole cardiac catheterization and ended just before the patient left the operating table. A trained music therapist was present during the catheterization. Loudness and fit of earphones were controlled by the music therapist to ensure that patients could easily follow verbal instructions by health personnel (cardiologist or nurses) during the procedure. The music therapist gave no additional verbal or nonverbal instructions.

Participants randomized to the coaching group received a music therapeutic coaching on the day prior to the catheterization. This coaching lasted for about 50 minutes and comprised three parts: 1) psycho-educative coaching with a cognitive-behavioral focus on the upcoming examination; 2) musically supported relaxation training; 3) breathing exercises. The structure of the coaching was standardized and identical for all patients. The reasons for the inclusion of breathing exercises were twofold: On the one hand the relaxing power of breath regulation is a common fact – and the additional use of music enhances this effect [32]. On the other hand it has the potential to shift the patients' attentional focus from their cardiac perception to different bodily experiences while focussing on respiration during the catheterization.

Educative Information

The psycho-educative coaching comprised general information on the upcoming cardiac cauterisation and tried to explore particularly frightening aspects of the examination. The specific benefits of the music therapeutic intervention in terms of relaxation and attentional control were highlighted. Due to the restricted duration of the coaching no psychotherapeutic interventions were possible.

Music Therapeutic Relaxation

The patients were provided with earphones and could listen to preselected relaxation music. The musical was identical for all patients. The preselected music was "Relaxation" by Martin Rummel, a piece of music designed for relaxation based on music psychological principles [33].

Breathing Exercises

The patients were advised that the breathing exercises offered the opportunity to anticipate some parts of the upcoming examination, as breathing instructions are routine part of the catheterization (such as "Draw a deep breath", "hold your breath", "breath normally").

The patients were asked to lie down on their back, to close their eyes and to feel comfortable. Then they were given standardised instruction to control their respiration. The instructions were synchronized with the patients' respiration as follows:

> …Breath normally, calm… in … out…with every exhalation you feel the bodily relaxation increase…now inhale and hold your breath awhile…and exhale, breathe again, in and out… every gasp releases more tension…ease can spread through your body…pay attention to your exhalation and feel the tranquillity and relaxation you can retrieve…if you want to terminate the relaxation, count backwards from 4 to 1 …open your eyes…

The patients were invited to listen to the relaxation music for another 10 minutes after having completed the breathing exercises, as the music should be used as reinforcer of relaxation during the catheterization.

Outcome Measures

Target variables were psychological traits, subjective anxiety and physiological parameters.

Main physiological outcome variables were heart rate (HR), systolic and diastolic blood pressure (BP) that were registered three times (at baseline, i.e. on the day prior to catheterization, before and after the procedure). The psychological target variables were obtained through psychological questionnaires. Main outcome variable was subjective anxiety as measured by State Trait Anxiety Inventory (STAI-S, [34]). Because it was assumed that immediate reactions to the catheterization depend on psychological traits, these traits were surveyed by the Symptom Check List according to Derogatis (SCL-90-R, [35]), a widespread and established measure for the subjectively felt interferences to a person caused by somatic and psychic symptoms within a period of seven days, the Hospital Anxiety and Depression Scale (HADS, [36]), an instrument widely used in somatic medicine to measure anxiety and depression, and a Visual Analogue Scale measuring well-being (from 0 = worst to 10 = best).

Additional information on medication, complications, outcome and duration of the procedure (sheath insertion to sheath removal) were obtained from the patients' records.

Results

Impact Groups

To detect the influence of personality traits on subjective stress and anxiety, baseline personality traits were combined to "impact groups" by use of a hierarchical cluster analysis. One group of patients (59 %) shows low values on all scales and one group (41 %) shows high values on all scales. Impact pattern distribution is identical in the three intervention groups.

Physiological Variables

Acquisition of physiological data was a matter of routine. Physiologic outcome data was recorded three times. At baseline, both heart rate (74 BpM) and blood pressure (134/79 mmHg) were within the normal range, though 90 % of the participants suffered from arterial hypertension. This finding is possibly to be attributed to pre-medication, which unfortunately had not been registered. Comparable studies report similar mean values for blood pressure (127/73 mmHg [21], and 135/74 mmHg [29] respectively) and heart rate ([21]: 75, [29]: 67).

Table 2. Values on the psychological scales in the two impact groups (mean ± standard deviation) and interrelation of impact and intervention groups

	Cluster 1:0 low impact	Cluster 2: high impact	Total	Reference values (normal population)
Baseline - VAS	7,8 ± 1,5	5,9 ± 1,2	7,1 ± 2,0	---
State-Anxiety (STAI-S)	39,9 ± 7,5	49,9 ± 8,4	44,8 ± 9,4	37,5 *
Trait- Anxiety (STAI-T)	36,6 ± 5,8	46,3 ± 5,0	40,7 ± 8,1	35,8 *
Global severity index (GSI – SCL)	0,32 ± 0,20	0,71 ± 0,35	0,55 ± 0,45	0,33 *
Anxiety (HADS)	4,1 ± 1,9	9,0 ± 2,8	9,4 ± 2,6	5,8
Depression (HADS)	3,5 ± 2,8	7,0 ± 2,5	10,9 ± 1,8	3,4 *
Control-Group	71,4%	28,6%		
Exposition-Group	52,4%	47,6%		
Coaching-Group	50,0%	50,0%		
Total	58,3%	41,7%		

* = differences "total" – "reference" highly significant as revealed by t-tests (all $p < .000$).

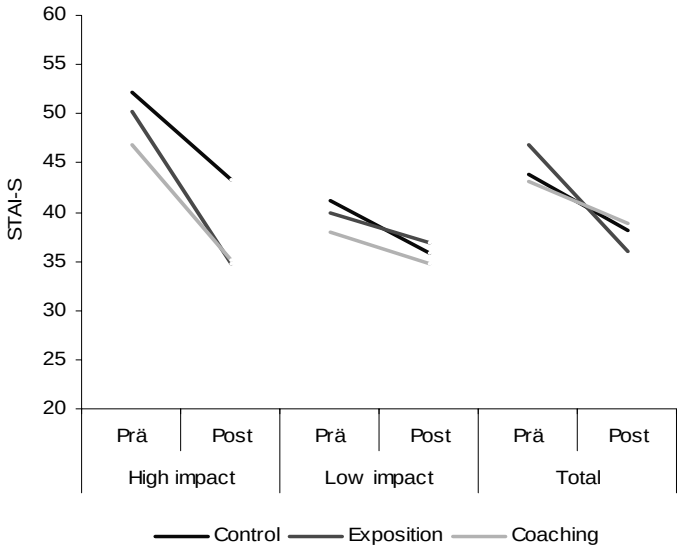

Figure 1. STAI-S scores pre-post by intervention and impact group.

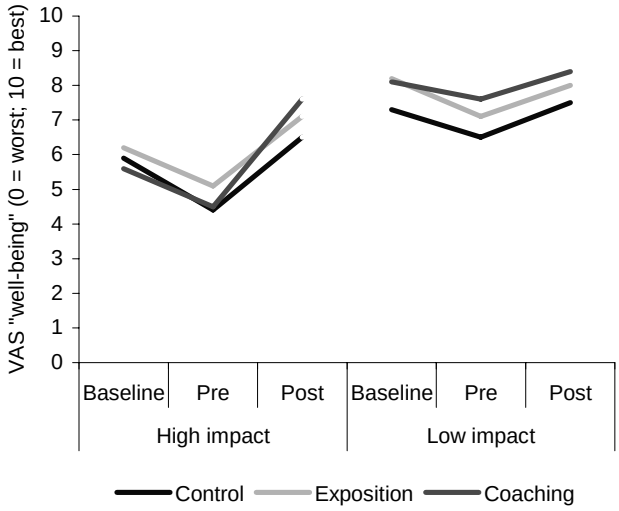

Figure 2. Well-being Scores (Visual Analogue Scale, range 0-10).

In the course of the examination, heart rate hardly changed (mean deviation was less than one beat per minute) and remained normotom. Comparable studies report similar variations (max. eight beats [21] and max. one beat [29] respectively).

Blood pressure increased from the baseline to the onset of the catheterization. While the systolic blood pressure persisted on this high level, the diastolic blood pressure leveled off to the initial value. Compared to similar studies rather distinctive variation in the systolic blood pressure values of 18 mmHg could be detected (max. 10 mmHg [21] and 6 mmHg [29]

respectively). Changes in diastolic blood pressure did not exceed 5 mmHg, which comes up to known results (max. 4 mmHg [21], max 3 mmHg [29]).

On the whole, music interventions led to a more distinct normalization in physiological parameters if compared to the control group with the exposition group outperforming the coaching group. There was no influence of psychological strains on physiological values as a further analysis by impact groups showed no group differences.

A limitation of the results may be the selective measuring times of the physiological values. Data acquisition was standardized so that the measuring times were identical in all patients. Still, blood pressure and heart rate oscillated rather heavily in many patients, leading possibly to biased results. A continuous recording of physiological parameters is desirable and would allow for more sophisticated analytic procedures such as time series analysis.

Psychological Variables

A trained psychologist obtained psychological data. On average, the patients reported noticeable psychological strains, especially somatic complaints as well as anxiety and depression. These findings are reconfirmed by relevant literature [7, 37].

Table 3. Characteristics of patients at enrolment

		Control group	Exposure group	Coaching group	Total
Age (years)	Mean ± SD Range	67,5 ± 14,0 28 - 83	65,8 ± 8,4 49 - 83	66,2 ± 9,0 44 - 80	66,5 ± 10,7 28 - 83
Sex	Male Female	15 (56%) 12 (44%)	16 (57%) 12 (43%)	16 (57%) 12 (43%)	48 (58%) 35 (42%)
Diagnosis at admission	CAD suspect Known CAD	20 (74%) 7 (26%)	18 (64%) 10 (36%)	17 (61%) 11 (39%)	55 (66%) 28 (34%)
Diagnosis after CC	CAD Coronary sclerosis Miscellaneous NAD	13 (48%) 6 (22%) 3 (11%) 5 (19%)	17 (61%) 8 (29%) 1 (3%) 2 (7%)	16 (57%) 8 (29%) 2 (7%) 2 (7%)	46 (55%) 23 (28%) 6 (7%) 8 (10%)
Access	Art. femoralis Art. brachialis	27 (100%) 0	28 (100%) 0	24 (86%) 4 (14%)	79 (95%) 4 (5%)
Actual procedure	Angiogramm only PCI	23 (85%) 4 (15%)	20 (71%) 8 (29%)	22 (79%) 6 (21%)	65 (78%) 17 (22%)
Duration	Mean ± SD	27 ± 18 min	26 ± 14 min	20 ± 10 min	24 ± 15 min

CAD = coronary artery disease, , SD = standard deviation, NAD = No abnormality detected, PCI = percutaneous coronary intervention.

Table 2 Physiological values (HR, BP) by group and time

		Control	Exposition	Coaching	Total
Heart Rate (BpM)	Baseline	77,8 ± 12,2	71,8 ± 10,1	71,2 ± 9,8	73,7 ± 11,1
	Pre	74,9 ± 9,8	72,4 ± 12,5	73,0 ± 12,5	73,5 ± 11,5
	Post	72,4 ± 17,2	74,3 ± 12,9	74,6 ± 13,9	73,8 ± 14,6
Systolic BP (mmHg)	Baseline	139 ± 20	129 ± 17	133 ± 21	134 ± 20
	Pre	149 ± 23	153 ± 24	155 ± 22	152 ± 23
	Post	152 ± 20	153 ± 21	147 ± 32	151 ± 25
Diastolic BP (mmHg)	Baseline	80 ± 10	78 ± 11	81 ± 14	79 ± 11
	Pre	79 ± 11	85 ± 15	87 ± 15	84 ± 14
	Post	78 ± 10	81 ± 9	79 ± 11	79 ± 10

Main psychological outcome criterion therefore was a reduction in subjective anxiety as measured by the STAI-S. All patients had a significant reduction pre-post in STAI-values by 7,3 ± 9,4 points or 18 %. This result is due to the advantage of the exposition group. Statistical analysis revealed an advantage of the music therapy groups as these interventions led to a stronger decline in STAI-values as compared to the control condition. Compared to a mean reduction by 7 points reported by other intervention studies [28], this result is further verified. The reason for this finding might be that the patients in the exposition group were effectively distracted resulting in lessened stress and anxiety. Coaching on the other hand may give the catheterization a serious aspect and emphasizes the symptoms. A more comprehensive and long-term preparatory strategy such as the music therapeutic coaching developed for patients on haemodialysis [5] seems to be more appropriate.

Consideration of the impact groups proves that music interventions significantly ameliorated subjective anxiety scores in the high impact group but not in the low impact group. Again the music exposure in particular seems to be beneficial for the high impact group. Further analyses revealed that psychological strains are different in two subgroups – one subgroup comprising about 40 % of the patients, with high impact on all psychological scales, and one subgroup comprising about 60 % of the patients with low strains. These two psychological impact groups reacted to the procedure in different ways: While the anxiety scores of the low impact patients remain constantly within the normal range, the scores in the high impact group were pathological previous to the catheterization but normalized after the procedure. Consequently, the interventions had different efficiencies depending on the impact of the patients. High impact patients could benefit from the music therapy, in particular from the exposition condition; low impact patients reported better results in the control group than in the music groups. One possible explanation may be different coping strategies employed by high and low impact patients. Davis [7] proposed two coping mechanisms during catheterization: “monitors” want to follow the procedure in detail; “blunters” prefer distractive strategies. The more information-avoidant strategies “blunters“ used, the higher

was the anxiety reduction. On the other hand, “monitors” reached the greatest reduction when utilizing information-seeking strategies. In the present study, patients belonging to the low impact group may be “monitors”, patients in the high impact group may be “blunters”. A more detailed clinical diagnostic focusing on coping strategies could answer this question. For clinical practice the claim for patient-focused treatments [38] is reinforced.

Discussion of the Study and Further Investigation

Demographic data indicates that the sample is representative for the population of interest. Group allocation was successful and equal. Most patients showed satisfactory compliance.

Implementation of the music stimulation during the catheterization was smooth and did not cause any disturbance of the routine examination. Both the patients and the personnel looked upon the music stimulation favorably. Some difficulties occurred in executing the coaching. Though the coaching lasted only for 50 minutes, the integration into the hospital routine turned out to be difficult sometimes, if patients were very busy with medical and nursing procedures.

As the average length of hospital stay in recent years has been reduced due to financial reasons, routine catheterizations are most often done on an out-patient basis: patients have a first date at hospital in order to receive information on the catheterization and for a medical check-up. On the day of their catheterization they enter the hospital early in the morning, get prepared for the examination. If there is no abnormality detected (NAD) during the catheterization, they get a compression dressing after the procedure and have to rest for about 6 ours but leave the unit on the same day. Otherwise they stay for further treatment (bypass graft, surgery…).

Therefore a follow-up study tried to compensate for this changes. As about 40% of all patients have marked strains, these patients should receive special attention. Aim of the second study was to implement the coaching procedure specifically for this high impact group. All patients with scheduled catheterizations were interviewed on their first admission. Only patients with marked strains (STAI > 35, rating of subjective well-being > 3 on a visual analogue scale ranging from 0 = no anxiety to 10 = extreme anxiety) were included and offered the opportunity to receive an additional music therapeutic coaching (coaching group, n = 23) or to listen to music during the catheterization (exposition group, n = 22). Results could confirm the relaxing effect of adjuvant music use, although the extended coaching procedure did not yield superior effects as compared to music exposure only (see Figure 3). Subjective reports of patients emphasize the importance of the preparation – if patients did not know the music they sometimes felt positively distracted but also secluded from the ongoing catheterization. If patients did know the musical piece from the coaching it was easier for them to both follow the catheterization and to divert themselves.

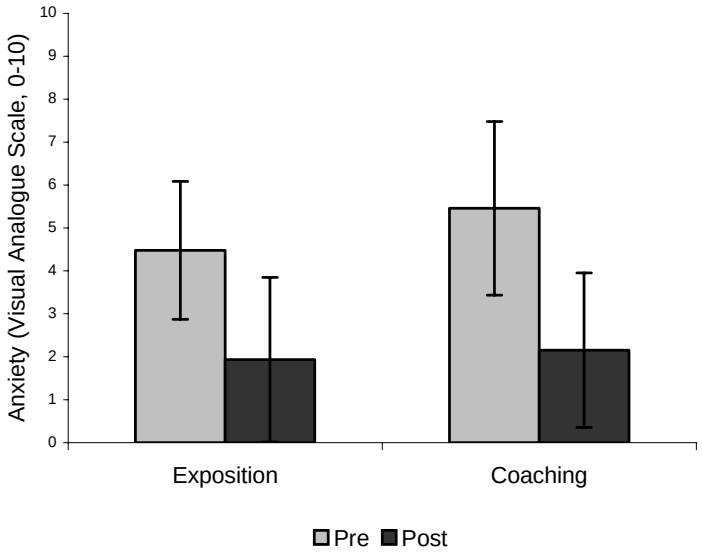

Figure 3. Anxiety Scores (Visual Analogue Scale, range 0-10) (study 2).

Conclusion

The present studies by the German Center of Music Therapy Research could implement a music therapeutic stimulation technique during intracardiac catheterization. The two music interventions led to significant amelioration in subjective anxiety (STAI-scores, visual analogue scale) with the exposition condition outperforming the coaching. Music intervention could effectively influence blood pressure, but not heart rate. However, the hypothesis that a preparatory coaching outperforms mere musical exposure during the catheterization had to be partly rejected. On the whole, patients in the exposition group reported near to normal blood pressure values and less subjective anxiety after the procedure and reached higher relative reductions in anxiety scores. This result is mainly due to the different baseline levels of anxiety. Patients with pronounced strains react to the catheterization in a different way than patients with low strains. The use of adjuvant music therapy as stimulation during the catheterization (exposition group) seems to be extra beneficial in a subgroup of patients with higher-than-average psychological strains. Patients with moderate to low strains are best off with no additional intervention.

Unfortunately, music intervention had no impact on sedative medication.

In summary it can be ascertained that music stimulation has a relaxing and calming effect on patients during cardiac catheterizations. Future prospects could be an extension of the coaching to a longer lasting preparatory strategy, comparable to the approach for patients on haemodialysis [39]. Music therapy has proven to be an effective means in cardiac rehabilitation [17]. Another approach lies therefore in the secondary prevention of CHD as proposed by the AWMF-guidelines [40]. One of the main problems in the post-operative treatment is restenosis. As some psychosomatic mechanisms aggravate this risk [41], a music therapeutic coaching might be an effective prevention in implementing health-oriented

behaviour and stress management. As the mere exposure to selected music does not have any impact on cardiac misconceptions or life style in patients with myocardial infarction [42], more comprehensive and longer lasting therapeutic interventions seem to be necessary.

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Chapter 19

Reducing CVD with the *Transcendental Meditation* Technique: Evidence and Theory

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Abstract

Researchers continue to report significant links between CVD and affective disorders. Recently, these links have been provided with plausible explanations in the context of psychosocial stress. Psychosocial stress is firmly identified as a factor contributing to CVD, and the same stress-response axes are engaged regardless of whether the stress arises from primarily physiological causes or from psychological causes such as depression and anxiety. Furthermore, an effective approach to stress reduction and psychological health, the Transcendental Meditation technique, is reported to reduce risk factors for CVD and to mitigate symptoms of established CVD. A thorough understanding of the nature and purpose of this technique and how it relates to psychosocial stress may shed light on the mechanisms underlying its CVD preventive and mitigating effects. The avowed purpose of the Transcendental Meditation technique is to facilitate the natural experience of a fourth state of consciousness, referred to as "transcendental" or "pure" consciousness, in which the thinking process is transcended and consciousness is left alone. Experience of this state is understood to have holistic normalizing effects on mind and body and to promote growth to yet higher states of consciousness. The normalization of adaptive systems distorted by chronic stress appears to be one of the transformative results of experiencing transcendental consciousness. These improvements in the functionality of critical adaptive systems may underlie the observed gains in physiological and psychological health, including the observed reductions in CVD risk and improvements in quality of life.

Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability in the industrialized world and approaches this status in developing countries [1-3]. Psychosocial stress is a significant contributor to CVD, and mechanistic explanations for this role are available in recent reviews [4-6]. The negative psychological states associated with certain affective disorders and personality types—mainly depression, anxiety, post-traumatic stress disorder, hostility, pessimism, and social isolation—all contribute to CVD morbidity and mortality [6-9]. Generally, these negative psychological states are considered "causes of stress," that is, "stressors," and psychological stressors are capable of enhancing CVD risk and CVD morbidity by the same mechanisms mediating the effects of other stressors [4, 6]. These mechanisms are thought to involve long-lasting changes in adaptive systems that can occur due to chronic or extreme stress [10-12]. The adaptive networks involved are the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic and parasympathetic branches of the autonomic nervous system, the immune system, and probably other neuroendocrine axes or physiological systems.

If stress plays an important role in CVD, as appears to be the case, then an effective means of reducing stress, or reducing deleterious effects of stress on adaptive systems, would be expected to reduce both CVD risk and CVD symptoms. The Transcendental Meditation technique appears to be one such approach to reducing stress and its effects. Psychopathologies as well as other CVD risk factors and symptoms have been reported to be positively affected by this technique in a range of populations. This chapter will review evidence that the Transcendental Meditation technique reduces psychological states related to CVD and reduces CVD morbidity and mortality. Because much of this evidence has been reviewed elsewhere recently, the current review is intended mainly to guide the reader to these more extensive treatments. The present review, however, also briefly describes the origin and essential nature of the technique and evidence that a regular routine of practice promotes a natural progression to higher states of consciousness.

Reducing Psychosocial Stress

Trait anxiety. The effect of the Transcendental Meditation technique on some common psychological risk factors has been studied quite extensively. For example, a quantitative meta-analysis of 146 studies of the effects of this and other techniques of meditation or relaxation on reducing trait anxiety found the Transcendental Meditation technique to be significantly more effective than each of the other techniques [13]. For studies of the Transcendental Meditation technique (n = 35), the Glass effect size [14] was .70. The effect sizes for studies of other techniques and placebo controls varied from -.003 (for concentration techniques, n = 6) to .41 for studies of Benson's technique (n = 12) and placebo (n = 6). This exhaustive meta-analysis also ran tests to control for a large number of other variables that might account for differences in effects, such as population, age, sex, experimental design, duration of the practice, experimenter attitude, type of publication, attrition etc., finding that none of these factors altered the overall outcomes and conclusions.

Addictions. Addictions to alcohol, tobacco, and drugs are behavioral expressions of another personality type or types associated with increased risk for CVD. In another large meta-analytical study, this one involving 198 individual studies of various techniques on addictions to alcohol, nicotine, and drugs, the Transcendental Meditation technique was found not only to show initial effects equal to or greater than those of other approaches to breaking the addictions but also to show that these effects continued to increase over time rather than to shortly succumb to relapse as with the other approaches [15]. The studies with Transcendental Meditation found the technique to be effective in individuals from a wide range of socioeconomic backgrounds and types of abuse. The populations studied included the general population, students, criminal offenders, drug users and addicts, elderly cigarette smokers, skid-row alcoholics, and Vietnam veterans with PTSD. The authors of the review concluded that the technique produced its effects by fostering significant improvements in physiological and psychological factors leading to substance abuse, thereby promoting primary prevention. In addition to this quantitative review, several qualitative reviews of research on the effects of Transcendental Meditation in the rehabilitation of addicts and criminals also are available [16-18].

Increasing psychological health. A more comprehensive approach to evaluating psychological effects of a treatment or technique is to examine the performance on tests of self-actualization, a widely-used measure of overall psychological health [19]. The concept of self-actualization was introduced by Abraham Maslow based on his studies of happy, successful people [20, 21]. The effect of the Transcendental Meditation technique and other forms of meditation and relaxation on self-actualization was studied in another quantitative meta-analysis, this one involving 42 independent treatment outcomes [19]. The effect size, in standard deviation units, of the Transcendental Meditation technique on overall self-actualization (.78) was triple those found for other meditation techniques combined (.26) and for relaxation techniques (.27), controlling for treatment duration and strength of experimental design ($p < .0002$). The average duration of the prospective studies used in these meta-analyses was 12 weeks, suggesting, as discussed later in this review, that the effect of Transcendental Meditation is due to something other than stylized relaxation, expectation, or other motivational factors whose effects tend to decline over periods of more than a few weeks.

Other measures of psychopathology. Effects of the Transcendental Meditation technique have been studied on other measures of psychopathology and psychological health as well, but these have been reviewed in other books and articles (see for example Glueck and Stroebel [22] and Alexander et al. [23]). As with the studies on addictions, these studies have involved disparate populations, and most have found improvements regardless of the population.

Reducing CVD Risk and Symptoms

Blood Pressure. Studies of the effects of the Transcendental Meditation technique on CVD risk factors and symptoms, like other studies on this technique, have included a wide range of subjects, from normal to clinical groups of different ages and ethnicities, and a wide

range of outcomes. Reductions in blood pressure, for example, are reported in normotensives as well as in those with prehypertension and essential hypertension, in youth as well as middle-aged and older individuals, and in populations of different ethnicities. The effect of the Transcendental Meditation technique on high blood pressure has been studied in more randomized, controlled trials (RCTs) than its effects on any other risk factors for CVD. These effects on blood pressure have been systematically and quantitatively reviewed recently in comparison to controls and to other techniques for reducing stress [24, 25].

The Anderson et al. meta-analysis [24] includes all locatable, full-length, published RCTs, up to the cut-off date of 31 December 2006, that used the Transcendental Meditation technique as the primary intervention and change in blood pressure as either a primary or a secondary outcome. A total of 9 studies met these criteria. Some of the studies involved hypertensive patients while others did not. Also, the authors developed an instrument for rating study quality that they consider more appropriate for studies on meditation than are other available instruments. By this measure, 3 of the studies were found to fall in the high quality range, 3 in the medium quality range, and 3 in the low quality range. The blood pressure results are summarized in Table 1 for all the studies combined, for those on hypertensives, and for only the 3 high-quality studies. It is noteworthy that the high quality studies showed the largest effects of the Transcendental Meditation technique compared to the total combined studies and the studies on hypertensives. Changes of the mean magnitudes observed in this meta-analysis are considered clinically significant [26].

The second recent systematic review and meta-analysis on reducing blood pressure compared the effect of the Transcendental Meditation technique with the effects of any other approaches to reducing stress that met the inclusion criteria for the comparison; these approaches included biofeedback, relaxation-assisted biofeedback, progressive muscle relaxation, and stress management training, in patients with elevated blood pressure [25]. The criteria used to identify well-designed trials for comparison were: 1) an RCT in prehypertensive and/or hypertensive patients; 2) adequate assessment of baseline blood pressure; 3) controlled for instructor attention; 4) study duration of at least 8 weeks; and 5) published in a peer-reviewed journal. Out of the 75 RCTs that were located in the literature searches, only 20 studies (with 27 treatment comparisons) met the inclusion criteria. The results of this meta-analysis were similar to those of the Anderson et al. meta-analysis for the 6 Transcendental Meditation technique studies that met criteria, but failed to reach significance for any of the comparison approaches (Table 2).

Table 1. Blood pressure change (TM group minus control group)

Grouping	Systolic Blood Pressure Mean (95% CL)	Diastolic Blood Pressure Mean (95% CL)
All studies	–4.7 (–7.4, –1.9)	–3.2 (–5.1, –1.3)
Hypertensives	–5.1 (–9.4, –0.8)	–2.1 (–5.4, 1.3)
High quality studies	–6.4 (–11.2, –1.6)	–3.4 (–6.2, –0.7)

Data are from Anderson et al. [24]; results are in mm Hg.
TM = Transcendental Meditation, CL = confidence limits.

Table 2. Change in blood pressure by stress reduction treatments (treatment group minus control group)

Treatment (No. of Comparisons, No. of Subjects)	Systolic Blood Pressure Mean (95% CL; P)	Diastolic Blood Pressure Mean (95% CL; P)
TM technique (6, 449)	–5.0 (–7.6, –2.3; .0002)	–2.8 (–5.0, –0.5; .02)
Simple BF (6, 141)	–0.8 (–4.1, 2.6; NS)	–2.0 (–5.1, 1.2; NS)
R-A BF (4, 98)	4.3 (–0.8, 9.3; NS)	2.4 (–0.7, 5.6; NS)
PMR (2, 171)	–1.9 (–6.8, 3.1; NS)	–1.4 (–4.3, 1.4; NS)
SM (5, 207)	–2.3 (–5.0, 0.5; NS)	–1.3 (–5.4, 2.7; NS)

Data are from Rainforth et al. [25]; blood pressure results are in mm Hg.

TM = Transcendental Meditation, BF = biofeedback, R-A = relaxation-assisted, PMR = progressive muscle relaxation, SM = stress management (includes relaxation), CL = confidence limits, NS = not statistically significant

Blood pressure reductions due to the Transcendental Meditation technique, as reported in these two meta-analyses, are equal to or greater than the reductions reported for the life style modifications recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) [26, 27]. For example, reductions in systolic blood pressure with these modifications were (in mm Hg): –5.0 for weight-reducing diet, –4.6 for aerobic exercise, –3.8 for alcohol restriction, and –3.6 for sodium restriction; the corresponding reductions in diastolic blood pressure ranged from –3.7 to –2.5 [26].

Other risk factors and symptoms of CVD. Aside from the psychological studies and studies on reducing blood pressure, other studies on the effects of the Transcendental Meditation technique in reducing risk factors and symptoms of CVD exist, but these are insufficient in number to permit meta-analyses. These studies have been reviewed elsewhere recently [28, 29]. Therefore, only the most salient ones will be summarized here.

One of the most critical questions concerning the long-term effects of the Transcendental Meditation technique, or of any other approaches purporting to reduce stress or to reduce CVD, is whether there is a change in mortality. A recent study examined the effects of the Transcendental Meditation technique on both cardiovascular mortality and all cause mortality [30]. This study used survival analysis to examine such effects in subjects over 55 years of age who learned the technique as part of earlier RCTs. Patient data were pooled from 2 previous RCTs in which the blood pressure effects of this technique were compared with those of other interventions and attention controls in 202 patients with systemic hypertension. Follow-up of vital status and cause of death covered a maximum of 18.8 years (mean 7.6 ± 3.5) and was based on information from the National Death Index. Compared with combined controls, the Transcendental Meditation group showed a 30% reduction in cardiovascular mortality (p = .045) and a 23% reduction in all cause mortality (p = .039). These results are highly suggestive and are consistent with shorter-term results obtained earlier [31, 32], but additional studies involving larger numbers are critical to further test the hypothesis that this technique reduces mortality.

Another recent study of considerable interest is one performed in patients with coronary heart disease (CHD) [33]. In this study, 103 patients with stable CHD were randomly assigned to learn and practice the Transcendental Meditation technique or to a health education control group. Duration of the study was 16 weeks. Main outcome measures included changes in blood pressure, lipoprotein profile, and insulin resistance, with the latter indicated by change in homeostasis model assessment (HOMA-IR). Change in cardiac autonomic system activity was indicated by change in heart rate variability. The Transcendental Meditation group had beneficial changes in blood pressure (included in the meta-analyses described earlier), in the HOMA-IR (–0.75 ± 2.04 vs 0.52 ± 2.84; $P = .01$) and in heart rate variability (0.10 ± 0.17 vs –0.50 ± 0.17 high-frequency power; $P = .07$) relative to the control group. The authors concluded that the observed changes indicated improvements in the blood pressure and insulin resistance components of the metabolic syndrome in the Transcendental Meditation group compared with the health education control. The trend toward improved cardiac autonomic nervous system tone in this group may reflect part of the mechanism of action of this technique that leads to mitigation of symptoms of CHD.

Two related earlier studies may reflect a further effect on prevention or reversal of CHD and CVD. These RTCs found evidence that the Transcendental Meditation technique alone [34], and in combination with other components of a multimodality traditional system of natural medicine, Maharishi Vedic Medicine [35], is capable of reducing carotid artery intima-media thickness (IMT), a surrogate measure of coronary atherosclerosis. The first of these studies was in 60 middle-aged African American subjects with hypertension [34]. It found a significant reduction of carotid IMT of –0.098 mm (95% CI –0.198 to 0.003 mm) in the Transcendental Meditation group compared with an increase of 0.054 mm (95% CI –0.05 to 0.158) in the health education control group ($P < .038$) after a 6-9 month intervention period. The second of these studies was in older (mean age 74) Caucasian American subjects who were of average health or better for their age. Of the original 57 subjects randomized to 3 treatment groups, 46 completed the 1-year post-test measurements. Carotid IMT (measured by B-mode ultrasound) decreased in a larger fraction of the multimodal Vedic medicine group that received the Transcendental Meditation technique in addition to Vedic exercise, dietary, and herbal food supplement components (16 of 20 subjects) than in the modern group (conventional dietary, exercise, and multivitamin approaches) and the usual care group (no additional treatment) combined (12 of 23 subjects; odds ratio, 3.7, $p = .05$) [34]. Furthermore, in a subset of subjects with multiple CVD risk factors, the Transcendental Meditation group showed a significantly greater reduction in IMT than either of the control groups [35].

Another recent study, a pilot study of the Transcendental Meditation technique compared to a health education, attention control group, examined the ability to reduce symptoms of congestive heart failure (CHF) in 23 African Americans with New York Heart Association class II or III CHF [36]. Patients who were randomly assigned to the technique showed significant improvements in the 6-minute walk test (the primary outcome measure; $p = .034$) and in secondary measures that included generic as well as disease-specific health-related quality of life scales and the Center for Epidemiologic Studies Depression Scale (CES-D) after the 6-month intervention, compared to the control group. The authors of this study intend to follow up on these encouraging results with a larger study.

Another pilot study has indicated that the Transcendental Meditation technique can be beneficial to patients with recognized coronary artery disease [37]. This study randomized 21 subjects to immediately learn and continue to practice the technique or to remain on a wait-listed control group until the end of the experimental intervention period (average of 7.6 months). Eligibility criteria included a history of chronic, stable angina pectoris for ≥ 6 months and documented coronary artery disease either by coronary angiography (≥ 70% stenosis in ≥ 2 arteries) and / or previous myocardial infarction. Single-blind, symptom-limited exercise tolerance testing was performed at baseline and again after the 7.6 month intervention period. Significant improvements (experimental versus control) were observed in exercise duration ($p < .013$), maximal workload ($p < .004$), ST depression onset ($p < .029$), and rate-pressure product at 3 min ($p < .016$), at 6 min ($p < .016$), and at maximum ($p < .016$). Although these results are striking, they have not yet been followed up by larger studies.

As seen in these examples, evidence that practice of this technique can reduce both the risk factors for CVD and the symptoms of existing CVD ranges from compelling to preliminary. There is little room for doubt that the technique has a wide range of effects on psychological as well as physiological risk factors, and to understand these effects demands a closer look at the nature and ancient origins of this technique.

Nature and Origin of the *Transcendental Meditation* Technique

The Transcendental Meditation technique comes from the ancient Vedic tradition in India [38-40]. It would be inaccurate to say that the technique, in its present form, has been around for thousands of years, but it is correct to say that its essential elements are ageless and have been used for similar purposes for millenia. The technique that exists today was introduced and first taught by Maharishi Mahesh Yogi ("Maharishi," as he was commonly addressed) in 1955. This introduction of the technique happened innocently and naturally a couple of years after the death of his spiritual teacher, Swami Brahmananda Saraswati, Shankaracharya (spiritual leader in the Shankara tradition) of the main center of spiritual learning in northern India, located at Jyotir Math. Maharishi gave credit for the technique to his teacher, whose life fully illustrated the vast reservoir of theory and practical technologies available in the Vedic tradition.

The meditation techniques that exist in different major traditions today are notably different from each other in procedure and frequently in their goals [41]. Direct comparisons, statistical meta-analyses, and cursive reviews report that different techniques of meditation differ also in their effects on various measures of results attributed to the practices [e.g. 13, 19, 31, 42, 43]. The Transcendental Meditation technique is held to be a natural, effortless procedure that promotes the direct experience of a state of consciousness referred to as "transcendental" or "pure" consciousness [38, 44]. In the practice, one sits comfortably eyes closed, and uses a special sound called a "mantra" in the manner instructed. (The standard course of instruction until recently involved seven steps led by a specially trained instructor. Six of these steps are given on separate days in meetings lasting about 1.5 hours each.

Currently, the course includes additional meetings periodically over a year's time after the initial seven-step instruction.)

Normal waking, dreaming, and dreamless sleep are considered to be three distinct states of consciousness due to their characteristic psychophysiological correlates and associated subjective experiences. Transcendental or pure consciousness is held to be a fourth state not only because its psychophysiological correlates appear to differ from those of waking, dreaming, and sleeping [45-49] but also for other reasons, including its reported uniqueness on the level of personal experience [38, 39, 44] and the existence of accurate descriptions of it in the ancient Vedic literature [see 38, 39]. Indeed, this state is difficult to conceive of or to relate to unless one has had the experience directly, and the direct experience of it appears to occur only rarely without an effective technique to aid the process [44]. Moreover, although this state shows the characteristics of a "higher" state of consciousness [50], it is not the highest state described in the Vedic tradition. In fact, three more states of consciousness are known and discussed, each fulfilling the characteristics required to be considered higher than the preceding one, including the full integration of all the states lower than itself [38, 50, 51]. Empirical (laboratory) evidence for these higher states is also beginning to appear [44, 50, 52-54].

From the very beginning of Maharishi's teaching, he held that it is the experience of transcendental consciousness during the practice of his technique that produces the wide variety of beneficial changes in mind and body that his initiates have experienced [39, 40]. The truth of this proposition is not easily tested objectively due to several factors, including the apparently short duration of the periods of this experience within each practice session for most individuals, at least in the beginning years of the practice [44-47]. However, even the earliest research on the Transcendental Meditation technique found evidence for a state of "restful alertness" during the practice that differed from ordinary eyes-closed rest or from sleep [48]. Thus, although the direct, objective evidence that this is the heart of the Transcendental Meditation technique is lacking, knowing the subjective properties of this state and how it may relate to the most advanced modern understanding of nature, it is reasonable to propose that the pure consciousness state is the "active ingredient" of the technique.

Concerning the subjective experience of transcendental consciousness, the results of a recent content analysis [44] of the self-reported experiences of 52 college students (half of them male and half female), who had been regularly practicing the Transcendental Meditation technique for an average of 5 years, are consistent with the characteristics attributed to this state. The students were asked to write descriptions of their most notable experiences during the technique using their own words. The content analysis showed that 68% of them referred to an experience of periods during which they were awake but without any awareness of space, time, or body sense. Thirty-two percent used the word "peaceful," and 20% used the word "unbounded" to refer to these most unique experiences. These reports are consistent with the ancient descriptions as a state of unbounded awareness, beyond space and time [44].

In recent years, the qualities and effects of this experience of transcendental, pure consciousness have been compared with those of the unified field of all the laws of nature described in the unified field theories of physics [38, 55-57]. To most scientists, this

comparison and proposed identity of the two may sound unlikely. However, not only is it consistent with the understanding of consciousness in the ancient Vedic tradition of Advaita Vedanta, from which the Transcendental Meditation technique derives [see 38], but it is upheld by dozens of quasi-experiments. These experiments purport to show societal effects of a supra-threshold percentage (i.e. >1%) of the members of a society practicing the technique in their homes or of a much smaller number (the square root of 1%) practicing the more advanced Transcendental Meditation and Transcendental Meditation-Sidhi programs together as a group [see for examples 56-59].

To attempt to deal adequately with such mind-bending ideas is beyond the scope of this chapter, and in fact would require a book. However, the notion that pure consciousness is a field underlying all matter and phenomena of the universe is not without merit. It certainly would help to explain some of the multitude of effects attributed to practice of these ancient Vedic technologies that Maharishi introduced to masses of people from both the East and the West during his 53 years of teaching. I will end this chapter by bringing this expanded view back to the topic of psychological influences and CVD.

As Alexander, Druker, and Langer point out in their introduction [60] to Alexander and Langer's book on higher human development [61], "What are the highest possible forms of human development? One's conception of the endpoint of development is fundamental, for it contains one's assumptions about the direction, possibilities, and dynamics of human growth." Not only do researchers' conceptions of the highest states of human development limit them in their exploration of this and related fields, but any individual's concept of his/her potential for growth is a formidable factor in deciding the "direction, possibilities, and dynamics" of their own growth. If indeed there is a unified field that underlies and gives rise to all material existence, including human thoughts and actions, then why is it so inconceivable that we could experience that field directly? The Vedic theory taught by Maharishi says that, to use the words of Shear, [38] "…when one's awareness settles down to the field of pure consciousness, one's body spontaneously attunes itself to this fundamental field, and this is held to explain why the body becomes more integrated both with itself and, functionally, with its environment." Is there evidence for this explanation of the results of the Transcendental Meditation technique in the area of psychological factors and CVD?

Other reviews of the effects of this technique have pointed out some possible explanations in terms of reducing stress and of balancing or readjusting the basic mechanisms for responding to stress [29, 62, 63]. In the example of the likely contribution of hyperactivity of the hypothalamic-pituitary-adrenal axis, and the consequent elevated cortisol levels, to hypertension and other risk factors or aspects of CVD, it may be relevant that cortisol level was found to decline significantly during an individual practice session of the technique [64]. Furthermore, both RCTs [see 65] and cross-sectional studies [66, 67] also are consistent with a normalization of the function of this axis due to the long-term practice of the technique. Such changes in the HPA axis conceivably might also mediate effects on other parameters such as insulin resistance and autonomic tone [68], and atherosclerosis [34, 35], but could they also explain the apparent reduction of free radicals [42, 69] due to the technique? Or for that matter, could changes in this or other neuroendocrine axes explain the apparently simultaneous reduction of trait anxiety [13] and increase in all around psychological health [19]? Going well beyond this, however, is the health-insurance evidence on 2000 regular

practitioners of the technique indicating reductions in all 17 major categories of disease delineated in the data [70].

Conclusion

In all, there are over 700 publications on the Transcendental Meditation technique, and these cover a wide variety of areas—physical, mental, sociological, and environmental. Here I have covered only a sample of the findings. As the number of repetitions of studies in different areas increases, the results are becoming more solidly established. If this trend continues, as I expect it will, it will strongly suggest that the ancient knowledge informing this and related technologies is far more advanced than the majority of modern thinkers have assumed.

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Chapter 20

Emotions and the Heart

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Abstract

Hundreds years ago, people knew about the relation between emotions and the heart. Most ancient cultures felt the heart was the seat of emotions because it reacted via its heart rate depending on the emotional state of the person. The effect of emotions on the pulse is well documented in the writings of celebrated physicians such as Galen and Avicenna. During the Renaissance, there occurred a renewed interest in the cause and effect of natural phenomena. Important development in studies of the relation between psychological factors and cardiovascular disease took place in the first part of the 20th century. For the past several decades attention to the psychosocial and behavioral factors in cardiovascular disease has increased significantly. As evidence has clarified how psychological factors affect the cardiovascular system, it is time now to focus on treatment interventions. It is to be hoped that the efforts of clinicians and researchers to prevent and to treat cardiovascular disorders related to psychological factors will be successful.

Introduction

Since ancient times, song, poetry, and literature have been replete with charming passages describing the close relationship between emotions and the heart [1]. Poets of all ages have reminded us of the close relationship between feelings and heart. In all languages "love comes from the heart," "people are soft-hearted," "warm- hearted," show "heartfelt sympathy," or they are "heartless," "cold-blooded," or even "stony-hearted." The heart may be "bursting with joy"; grief "gnaws at the heart" or "weighs on the heart;" one may even "die of a broken heart." Homer, an ancient Greek epic poet, regarded the heart as the seat of the emotions, intellect and will [2].

Ancient Times

Since ancient times, people have known about the relation between psychological factors and physical illnesses [3-6]. Nearly half a millennium B.C., Socrates came back from army service to report to his Green countrymen that in one respect the barbarian Thracians were in advance of Greek civilization: they knew that the body cannot be cured without the mind. "This," he continued, 'is the reason why the cure of many diseases is unknown to the physicians of Hellas, because they are ignorant of the whole." It was Hippocrates, the Father of medicine, who said: "In order to cure the human body it is necessary to have a knowledge of the whole of things." Paracelsus wrote: "True medicine only arises from the creative knowledge of the last and deepest powers of the whole universe; only he who grasps the innermost nature of man, can cure him in earnest."

Hundreds years ago, people knew about the relation between emotions and the heart [3-9]. Most ancient cultures felt the heart was the seat of emotions because it reacted via its heart rate depending on the emotional state of the person … thus a person was claimed to think and feel emotions with his or her heart. According to Traditional Chinese Medical Theory, the energy flow is the cause of hundreds of diseases [9]. The heart is the master of the five tsang (solid) organs, and the six fu (hollow) organs. Sadness and worry shake the heart (mind) and when the heart (mind) is shaking, the five tsang and six fu are all shaking. The five tsang and the five emotions are closely related, as anger hurts the liver, joy hurts the heart, worry (thinking) and over-concentration hurts the spleen the same as too much standing hurts the bones. Hebrews saw the heart as the seat of emotion [10]. To the ancient Hebrews the heart was the mind including all thoughts including emotions. The ancient Egyptians cited the heart as the center of feelings and emotions [8-10,12,13]. The Arab philosopher from Andalusia, Ibn Rushd (AD 1128 - 1198), who is known as Averroes in the West, stated in his book Kulliyat (General Medicine): "The brain is the master and the heart serves the brain with nourishment" [8].

"Some say that we owe our consciousness to our hearts and that it is the heart which suffers pain and feels anxiety. But this is not the case; rather, it is torn just like the diaphragm, and even more than that for the same reasons: for blood-vessels from all parts of the body run to the heart, and the heart encapsulates these, so that it feels any pain or tension occurring in a human being. Moreover, the body inevitably shudders and contracts when it feels pain, and likewise when it is overwhelmed by joy. This is why the heart and the diaphragm are particularly sensitive. Yet neither of these parts has any share in consciousness; rather, it is the brain which is responsible for all these." These words derive from the author of the Hippocratic work On the Sacred Disease, a medical text about epilepsy written in Ancient Greece c. 425 BC [5]. It reflects an early stage in a debate that was to have a long history, a debate between physicians, philosophers, scientists, psychotherapists, but also poets and other intellectuals about the location of the mind and the physical basis of personality and the emotions.

The 4th-century BC philosopher Aristotle advances a psycho-physical theory of emotions like anger, which he defines both as a "seething heat in the region of the heart" and as "a desire for retaliation": these two definitions are complementary descriptions of one and the same emotional state, the former referring to the physical, the latter to the psychological (5).

In Aristotle's view, the heart is the central part of the body, both spatially and in terms of hierarchy. It is the part that is formed first in embryological development. It is the source of bodily heat and thus primarily responsible for nutritive functions. And it is the primary seat of emotions and sensations, for it houses the 'central sense organ', a kind of coordinating center that processes the information derived from the peripheral sense organs (with which it is connected through the blood vessels) and that issues decisions to the limbs and other parts of the body involved in action and motion.

The effect of emotions on the pulse is well documented in the writings of celebrated physicians such as Galen (AD 130 - 201) and Avicenna (AD 980-1037) [14-16]. In one famous case, Galen treated a young woman who seemed to exhibit the signs of physical illness, but who upon closer examination, revealed no organic pathology [14]. After eliminating any possible "humoral" explanation, Galen identified the real, emotional cause of her somatic symptom: a hidden love interest. He used the sudden irregularity of her pulse as a crucial diagnostic clue. Likewise Avicenna one of the great Islamic physicians, described the effect of various emotions on the pulse: "Anger. . . pulse is large, rises high, swift and brisk. Delight. . . movement is gradual and outwards. . . volume is adequate and therefore, the pulse is slow and infrequent. Joy, the pulse is similar to [delight]. . . large in volume and soft, therefore slow and infrequent. Grief. . . pulse is small, weak, sluggish and slow. Fear. . . if of sudden origin, the pulse becomes quick, irregular, disorderly. Love. . . now the lover's pulse is variable and irregular, especially when he sees the object of his affections or hears her name or hears tidings of her"[16].

Renaissance

During the Renaissance (1500-1700), there occurred a renewed interest in the cause and effect of natural phenomena [17,18]. Many great thinkers of the time became involved in the dramatic changes that led to more scientific inquiry about man and his environment. The philosopher René Descartes (1596-1650) had a significant influence on the ancient mind-body relationship, by renouncing all formerly held beliefs and starting afresh. Descartes' famous phrase "I think therefore I am" gave substance to his logical explanation about the existence of spirit. Descartes wrote: "If, therefore, anyone wishes to search out the truth of things in serious earnest, he ought not to select one special science; for all the sciences are conjoined with each other and interdependent; he ought rather to think how to increase the natural right of reason, not for the purpose of resolving this or that difficulty of scholastic type, but in order that his understanding may enlighten his will to its proper choice in all the contingencies of life. In a short time he will see with amazement that he has made much more progress than those who are eager about particular ends, and that he has not only obtained all that they desire, but even higher results than fall within his expectation" [2].

The Twentieth Century

Important development in studies of the relation between psychological factors and cardiovascular disease took place in the first part of the 20th century [19-26]. Henry Head, in a comprehensive paper written in 1901, said: “A disturbed activity of the heart may alter the circulation to the brain or may change the character of the blood with which it is supplied. The delirium that accompanies a falling heart or pronounced vascular degeneration may be instanced as an example of a mental change dependent directly on altered vascular conditions” [19].

Von Wyss in an interesting article published in 1927 considers the heart as the organ of expression for all affects [20]. He wrote: “Psychic processes, especially emotions, have a bodily resonance and, vice versa, bodily processes have a psychic resonance. In other words, if affect, an affect contains not only a psychic experience, but also its motor expression in the outer world, and the resonance in the viscera, this latter representing a sort of language of the individual to himself. Since circulation is that function the cessation of which means instantaneous termination of life, the heart has become one of the most important organs of inner expression. It is for this reason that the heart has such close relationships with the emotional life and has become the symbol of what is really individual in man, the symbol of his virtues and vices. It is the study of these relationships which brings us to the borderland of our knowledge, to the question of what in the last analysis binds psyche and soma into a unity.”

In his book, “Der Herzkranke” published in 1931, Fahrenkamp suggested that depending on physician’s personal attitude, we still run the risk of error through overstressing in diagnosis and therapy either the somatically determinable element (X-rays and other physical methods) or the psychic element [21]. In our heart patients, psyche and soma are particularly closely intertwined. The case of the serious organic heart patient demonstrates the fact that the psychic condition is more important for happiness in life and subjective work-capacity than a perhaps seriously damaged circulatory system.

In 1964, in a very interesting article, Drazin described “the coronary way of life”: 1. Living by deadlines. 2. Ruthless competition. 3. Excess food, rich in saturated fat. 4. Excess smoking, especially cigarettes. 5. Excess coffee, tea and liquor. 6. Seeking status by conspicuous consumption. 7. Restlessness, seeking of power, wealth and possessions. 8. Speculation in the stock market, horse races, games of chance 9. Lack of repose, keeping emotions taut. 10. Driving at high speed, frequently recklessly. 11. Spectator rather than participant at sport events. Lack of exercise. 12. Deleterious effect on emotions by mass media [22]. Drazin writes: “The people who live this sort of life are, in my opinion, coronary prone. The tragedy is that these persons are productive middle-aged male Americans. They are the people who do the world’s work. This is characteristic of every industrialized state to a greater and less degree.”

More recently, it has been suggested that type A personality may be linked to the risk of cardiovascular disease [27-31]. Individuals who exhibit Type A behavior are characterized as being ambitious, competitive, impatient, and aggressive or hostile. Individuals lacking these characteristics are relaxed and patient, and are referred to as Type B [28]. Type A individuals experience a keen sense of time urgency, are more likely to be involved in conflict with

coworkers, more overloaded at work, and more likely to be overcommitted than Type B individuals [29-31]. Type A is a multi-dimensional construct that has differential relationships with other variables. Spence et al. [28] described two dimensions of Type A behavior. The first is labeled achievement strivings. Individuals high on the achievement strivings dimension are described as hard working, active, and as taking their work seriously. The other dimension is called impatience–irritability. Individuals high on the impatience–irritability dimension are characterized as impatient, irritable, and prone to anger. It is important to note that the studies disagree in the relationship between type A personality and coronary heart disease.

Recently, a new personality construct, the type D or 'distressed' personality, has been proposed [32-37]. This construct is a result of an investigation of coping styles in men with coronary heart disease. Type D personality subtype is characterized by the joint tendency to experience negative emotions and to inhibit these emotions while avoiding social contacts with others. In other words, the type D personality is a gloomy, anxious, and socially inept worrier. Type D individuals generally have fewer personal ties with other people and tend to feel less comfortable with strangers. Individuals scoring high on negative affectivity are not only dysphoric but have a negative view of self, report more somatic symptoms, and have an attention bias towards adverse stimuli. The inhibition of emotions has been associated with higher cardiovascular reactivity, lower cardiovascular recovery, lower heart rate variability, and, in the long term, carotid atherosclerosis, incidence of coronary heart disease, and cardiac mortality [38-43]. Social inhibition is a moderator: the prevalence of cardiac events for individuals who score high in negative affectivity but low in social inhibition is less than for that for individuals scoring highly in both components. In other words, the type D concept suggests that the way people cope with negative emotions may be as important as the experience of negative emotions *per se*. The observation that cardiac patients with type D personality are at increased risk for cardiovascular morbidity and mortality underlines the importance of examining both acute (e.g., major depression) and chronic (e.g., certain personality features) factors in patients at risk for coronary events.

Conclusion

For the past several decades attention to the psychosocial and behavioral factors in cardiovascular disease has increased significantly. As evidence has clarified how psychological factors affect the cardiovascular system, it is time now to focus on treatment interventions. It is to be hoped that the efforts of clinicians and researchers to prevent and to treat cardiovascular disorders related to psychological factors will be successful.

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