

# Current Status Of Cardiovascular Risk Due To Stress

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## Abstract

Modern life is full of stress because of many factors cardiovascular system is more prone to be affected by stress. Hypothalamus–pituitary–adrenal axis is activated by stress and stress elicits changes in sympathetic – parasympathetic balance, which might negatively affect the cardiovascular system acutely- by precipitating myocardial infarction, acute thrombotic events, left ventricular dysfunctions or arrhythmias, and chronically – by accelerating the atherosclerotic process too. It provides an overview of the concept of Stress, association with cardiovascular events and risk, its mechanism and with therapeutic implications.

## INTRODUCTION

Modern life is full of stress and stress is often used as a ubiquitous descriptor of people's feeling of being uncomfortable or dissatisfied. Formal definitions of stress are frequently as varied and vague as that implicitly articulated in the media and by the man on the street. Webster's Third New International Dictionary defines stress (leaving out definitions not appropriate to emotions) as “distress” or “a physical, chemical, or emotional factor (as trauma, histamine, or fear) to which an individual fails to make a satisfactory adaptation, and which causes physiologic tensions that may be a contributory cause of disease”<sup>1</sup>. Likewise, Dorland's Illustrated Medical Dictionary (28<sup>th</sup> ed.) has defined stress (again using only emotionally related uses) as the “the sum of biological reactions to any adverse stimulus, physical, mental or emotional, internal or external, that tends to disturb the organism's homeostasis; should these compensating reactions be inadequate or inappropriate, they may lead to disorders” or as “the stimuli that elicit stress reactions”<sup>2</sup>.

Hans Selye, one of the original pioneers in modern stress research, initially described stress as “essentially the rate of all wear and tear caused by life. Later he defined stress as “the nonspecific (that is common) result of any demand upon the body, be the effect mental or somatic”. His, and others, elucidation of the somatic effects of stress helped to bring the field of stress into the arenas of science and medicine<sup>3</sup>. Putting all of these definitions together, the term stress has been used in at least three major ways<sup>1,2,3</sup>.

Stress as a “stressor” – Stress is often used to refer to one or more stressors. That is, an influence which causes tension, anxiety or disruption of homeostasis. The stressor(s) may originate from external sources such as danger during war time or even difficult people. It can also arise from internal thoughts and feelings, such as guilt, daily worries, and unfulfilled expectations. Stressors can be single or multifaceted as discussed below.

Stress as “distress” – Stress may refer to internal feelings of distress, tension or anxiety caused by a stressor(s). Positive or pleasurable events could also cause stress<sup>3</sup>. Selye coined the word “eustress” to described situations where stressors did not cause harm, or were even beneficial. In such circumstances, the term ‘anti-stressor’ has been used<sup>4</sup>.

Stress as a “biological response” – Some scientists and physicians have defined stress in a more objective manner, by defining it by the existence of measurable and predictable physiological effects that distress or stressors produce. These biological effects are reproducible, stereotyped, and defined by the specific genetic characteristics of a given organism.

## THE GENERAL ADAPTATION SYNDROME

Selye, as a young contemporary of Cannon, developed the concept of the “General Adaptation Syndrome (GAS)” or the “Biologic Stress Syndrome”<sup>3</sup>. The GAS articulates stress as an event, which elicits three stages of reaction. Selye compared these stages with developmental stages of life that are characterized by low resistance and exaggerated responses to stressors as a child, enhanced coping and

adaptation to stressors as an adult, and eventual diminished ability to adapt to stressors in old age leading to death. The three stages of the GAS include <sup>3,5</sup> .

**Alarm Stage** – In the initial ALARM stage, the classic fight or flight reaction ensues. A stressor (physical or emotional) disrupts homeostasis of the subjects. Adrenal catecholamine secretion and other biologic responses occur and the individual experiences heightened arousal, increased heart rate and blood pressure, and the psychological urge to attack or flee from the stressor event. As the Alarm stage continues, and assuming that the individual survives, the body's natural inclination toward homeostasis yields the Stage of Resistance.

**Stage of Resistance** – In this stage, the body attempts to calm and better control the changes started in the alarm reaction. The individual settles into a psychological mode of coping and possibly co-existing with the stressor, if the stressor cannot be eliminated. The individual then enters what Selye termed the Stage of Exhaustion.

**Stage of Exhaustion** – In this stage, a stressor persists despite attempts to either remove exposure to it, or to peacefully coexist with it. The individual basically “gives in” due to resource /energy depletion. Diminished functional capacity, sleep, rest, or even death, are forced upon the person.

**Hypothalamus–Pituitary–Adrenal Axis and Other Hormonal Changes vis-à-vis stress:**

The hypothalamic-pituitary-adrenal axis is activated by corticotropin-releasing hormone from the paraventricular nucleus of the hypothalamus, which prompts the release of corticotropin from the pituitary, stimulating the production of glucocorticoids (especially cortisol) from the adrenal cortex and to a lesser extent, mineralocorticoids and adrenal androgens <sup>6</sup> . Cortisol has central energy-conserving effects, including inhibition of the release of gonadotropins, growth hormone, and thyroid stimulating hormone, but is better known for its somatic effects, including inhibition of inflammatory and immune responses, central redistribution of adiposity, reduced insulin sensitivity, and pressor effects <sup>7</sup> .

The peripheral sympathetic nervous system, the other effector limb of the stress response, innervates tissues throughout the body, especially the heart, vasculature, and adrenal medulla. It is the means by which the brain effects body organs in response to acute stress. The adrenal medulla responds with systemic catecholamine release

(predominantly epinephrine), whereas the sympathetic nerve terminals that line the vasculature release norepinephrine, which accounts for most circulating norepinephrine. The sympathetic nervous system has not only direct cardiostimulatory effects (chronotropy and inotropy via 1-adrenergic receptors) and pressor effects (via 1-adrenergic receptors), but also metabolic effects (insulin resistance and lipolysis) and varied immunological effects <sup>8</sup> , including inhibition of mast-cell degranulation but stimulation of interleukin 6 release.

## STRESS AND CARDIOVASCULAR RESPONSE

Evidence is compelling that acute mental stress triggers major autonomic cardiovascular responses and acute cardiac events. Evidence that chronic mental stress leads to or promotes chronic cardiovascular disease is highly controversial. Most mental-health professionals believe that healthy subjects can experience short-term, mild-to-moderate mental stress without developing mental illness, particularly if subjects have the coping skills to find relief. Injuries unavoidable, and uncontrollable mental stresses have the capacity to induce adverse cardiovascular responses <sup>9</sup> .

At times we distinguish between fear and anxiety, and at other times we use the terms interchangeably because the body responds immediately in similar ways to these stimuli. Fear is the body's physical and mental response to external (known) danger. Anxiety is the body's physical and mental response to internal (unknown) danger (conflict). Also, we may conceptualize anxiety as the body's response to expected (future) loss and depression as a response to past loss. This model has anxiety and depression on a continuum. Finally, using “kindling” models, stimulus driven (“exogenous”) stress can become autonomous (“endogenous”) or stress (or mental illness) <sup>10</sup> .

The exercise is different from stress. The body's response to isotonic (aerobic) exercise and to isometric (anaerobic) exercise is different clinically. During isotonic exercise, the large muscle groups move the body through space. Examples include jogging, bicycle riding, and swimming. In healthy subjects, reduced peripheral vascular resistance and a sharply increased cardiac output accompany isotonic exercise. During low levels of isotonic exercise, the body principally increases heart rate to increase cardiac output. During very high isotonic exercise levels, increased stroke volume also contributes to increased cardiac output.

The body moves large muscle groups against one another

during isometric (sustained muscle contraction) exercise. Examples include weight lifting and snow shoveling. In healthy subjects during weight lifting the body withdraws vagal tone and within seconds, heart rate increase and blood pressure elevation follow. This reflex is so potent that it can override normally set baroreceptors. Increased myocardial wall tension, increased peripheral vascular resistance, and increased myocardial oxygen demands accompany the modest cardiac output increase associated with isometric exercise.

### **CARDIOVASCULAR RESPONSE TO ACUTE MENTAL STRESS IN NORMAL SUBJECTS**

#### **BLOOD PRESSURE**

Central neural mechanisms govern mental stress-included blood pressure changes<sup>11</sup>. Central nervous system components involved in this control include the medulla oblongata, medial geniculate body, amygdala, hypothalamus, and brainstem. Mental stress induced changes in blood pressure are usually reproducible and vary by mental stress activity. Blood pressure change from baseline depends on many variables including duration of stress, time of measurement, expectations, psychological preparedness, and background of subjects.

Many studies reported significant (about 10-20%) blood pressure increase in healthy subjects when facing mental stress. For example, in a study of 50 normal subjects, a color-word conflict test increased blood pressure mean values from 125/82 to 134/87 mm Hg<sup>12</sup>. Greater blood pressure reactivity may occur with an active stressor (color-word conflict test) than a passive stressor (watching a film of industrial accidents<sup>12</sup>).

#### **HEART RATE**

Mental stress commonly increases heart rate<sup>13</sup>. In normal subjects, a color-card conflict test increased mean heart rate by 28 beats per minute compared with baseline measurements<sup>14</sup>. In 10 healthy subjects, a word identification test increased heart rate by 4 beats per minute (BPM) within 5 minutes, and a color-card conflict test increased heart rate from 60 to 70 BPM after 3 minutes. Progressively difficult mathematical problems led to progressive heart rate increase even video game stressors can increase heart rate by about 10 BPM<sup>15</sup>.

### **DOUBLE PRODUCT: BLOOD PRESSURE AND HEART RATE**

The product of blood pressure X heart rate is called the

“double product” and is used as an index of myocardial oxygen consumption. Lacy et al<sup>16</sup> used this parameter to study 11 patients referred to a cardiac catheterization laboratory for evaluation of chest pain. Simulated public speaking stress produced increased double product and vasoconstriction of normal coronary artery segments in subjects with and without coronary artery disease. Mental stress influences cardiac output, stroke volume, forearm blood flow, left ventricular ejection fraction, peripheral vascular resistance, and cardiac microcirculation<sup>17,18</sup>.

### **EFFECT OF ACUTE MENTAL STRESS ON CARDIOVASCULAR DISEASE**

#### **BLOOD PRESSURE**

Many studies reported significant (about 10-20%) blood pressure increase in subjects with cardiovascular disease when facing mental stress<sup>19</sup>. Mental stress via limbic-hypothalamic activity may contribute to the multifactorial etiology of essential hypertension<sup>20</sup>.

The report on post-myocardial infarction patients studies using Swan-Ganz catheterization, mental arithmetic stress increased blood pressure from 138/89 to 160/101 mm Hg and increased peripheral vascular resistance by 81 121 dynes X seconds X cm<sup>21</sup>. In this same group<sup>21</sup>, bicycle exercise caused a decrease in peripheral vascular resistance. Similarly, mental arithmetic stress increased systolic blood pressure 21-24 mm Hg and diastolic blood pressure 12 – 13 mm Hg, public speaking increased systolic blood pressure 28 mm Hg and diastolic blood pressure 19 mm Hg in post-myocardial infarction patients<sup>19</sup>.

Comparing different stressors showed that color-word conflict testing, arithmetic testing, and public speaking and reading increased systolic blood pressure in patients with cardiac wall motion abnormalities comparable to exercise-induced systolic blood pressure changes (bicycle to point of chest pain or exhaustion)<sup>22</sup>. In the same studies, changes in diastolic blood pressure during mental stress testing were greater than physical exercise-induced changes.

#### **HEART RATE**

Among post-myocardial infarction patients, public speaking induced an increase in heart rate of 25 BPM<sup>19</sup>. In adolescents, heart rate reactivity to mental stress was greater in subjects with hypertension than control<sup>23</sup>. The multicenter Cardiac Arrhythmia Pilot Study (CAPS) reported increased cardiac arrest and mortality associated with decreased heart rate reactivity, major depression, and

type B behavior in a study population with recent myocardial infarction and substantive ventricular ectopy <sup>24</sup> .

In heart-transplant recipients, Shapiro et al <sup>25</sup> compared native and heart-transplant tissue to determine mental stress influence on heart rate. Arithmetic testing increased heart rate in native (innervated) tissue from 89.4  $\pm$  3.4 to 93.8  $\pm$  3.8 BPM and increased heart rate in grafted tissue 84.7  $\pm$  3.5 to 86.7  $\pm$  3.9 BPM.

### LEFT VENTRICULAR PERFORMANCE

Mental stress may induce left ventricular wall motion and ejection fraction abnormalities among subjects with coronary artery disease who experience exercise-induced ischemia <sup>22</sup> . In a study of 39 patients with coronary artery disease, new wall motion abnormalities appeared in 59% of patients exposed to mental stress. Mental stress may alter left ventricular performance with or without inducing pain or electrocardiographic changes <sup>26</sup> . Among subjects with dilated cardiomyopathy and congestive heart failure, mental arithmetic stress may increase left ventricular wall stiffness and increase left ventricular filling pressure, such changes leave patients vulnerable to further complications of cardiovascular disease including arrhythmias and sudden death. Bairey et al <sup>27</sup> reported that beta-blockers reduced exercise-induced left ventricular wall motion abnormalities but did not alter mental stress-induced wall motion abnormalities.

### CARDIAC ARRHYTHMIAS

Mental stress in humans and other animals will decrease cardiac electrical stability even in subjects with normal hearts <sup>28</sup> . Premature ventricular contractions appear among subjects driving in heavy traffic and other stressful situations, ectopic ventricular beats may increase during public speaking and decrease with beta-blocker administration <sup>29</sup> .

### LONG QT SYNDROME

Arrhythmias associated with the long QT syndrome are particularly susceptible to the influences of the autonomic nervous system <sup>30</sup> , and therefore to mental stress. Mental stress such as fear in long QT syndrome patients has led to ventricular fibrillation and may explain how stress can induce syncope or sudden death, about 58% of long QT syndrome patients reported that syncope related to severe emotional stress <sup>31</sup> .

Acute physical stressor such as surgery, trauma, and intense

physical exertion are well-known triggers of cardiovascular events. Emotional stressors are increasingly recognized as precipitants of such events. On the day of the Northridge earthquake in Los Angeles, CA, USA in 1994, the number of cardiac deaths within the city and surrounding county in individuals who did not undergo direct physical trauma or increased physical exertions was two to five times higher than the usual rate <sup>32</sup> .

In patients with coronary disease the risk of acute myocardial infarction in the short period after an anger outburst seems to be twice that for other periods <sup>33</sup> , emotional stress was a more common precipitant of acute infarction than was physical exertion.

In patients with pre-existing coronary disease, acute cardiovascular events after emotional stress might result from increased shear stress at the site of a weak atherosclerotic plaque (with subsequent plaque rupture) of from regional myocardial ischaemia distal to a stenotic vessel leading to ventricular dysrhythmias <sup>34</sup> . In 42 elderly hypertensive patients who underwent routine phlebotomy before and after a major earthquake in Japan, there were statistically significant increases in blood pressure, packed-cell volume, and haemostatic factors, which were especially pronounced in patients reporting the highest stress <sup>35</sup> .

Emotional stress might also produce proarrhythmic effects. In 12 patients who were wearing Holter monitors during an earthquake in Taiwan in 1999, symptoms logs showed palpitations in all 12 patients at the time of the earthquake with associated tachycardia and transient impairment in heart-rate variability <sup>34</sup> . Similarly, with widespread use of implantable pacemakers and defibrillators, we now have finer temporal resolution of the arrhythmic sequelae of everyday stressor. In one study, 15% of defibrillator firings took place after acute episodes of anger (by contrast with 3% of control periods) <sup>36</sup> .

Even in the absence of underlying coronary disease, severe acute emotional stress can precipitate a specific type myocardial dysfunction associated with apical ballooning of the left ventricular systolic function <sup>38</sup> .

Electrocardiography (ECG) shows prolonged QT intervals and diffuse T wave inversion, probably the results of increased myocardial sympathetic nerve activity. "Cardiac enzyme concentrations are raised only slightly in most cases. This syndrome, referred to as stress cardiomyopathy or takotsubo cardiomyopathy (named after the Japanese fishing

pot use to trap octopuses that resembles the shape of the stunned left ventricle) is associated with circulating catecholamine concentrations more than three times those seen in Killip class III myocardial infarction <sup>37</sup> .

### EFFECT OF CHRONIC MENTAL STRESS ON CARDIOVASCULAR DISEASE

Subacute and chronic stressors associated with psychological and emotional adjustment are associated with an increased risk of cardiac events, similar to traditional cardiovascular risk factors. Parkern et al <sup>39</sup> reported that mortality from all causes, particularly cardiovascular ones, is increased in the months after the death of a spouse. Similarly, the fear in the USA subsequent to the terrorist attacks on the World Trade Center in New York in 2001 resulted in a rate of defibrillator firings of two to three times normal during the month after the event <sup>40</sup> . These defibrillator firings occurred in patients living far from the catastrophe and in those with both ischaemic and non-ischaemic cardiomyopathies. The distribution of arrhythmic events (not all occurring on the day of the attacks) suggests that psychological fallout of the event lasted for weeks <sup>41</sup> .

Stress of daily living can also increase risk of cardiovascular events. In one study of work-related stressors <sup>42</sup> , upcoming deadlines were associated with a six folds increase in myocardial infarction. Kivimaki M et al <sup>43</sup> reported that chronic work-related stress could carry a two to three times higher risk of cardiac events, especially when employees perceive little control over their work environment. Likewise, in women with established coronary disease, marital stress was associated with a risk of recurrent events three times higher than in women with no marital stress <sup>44</sup> .

Frequent anger and hostility also predict incident coronary events <sup>45</sup> . In the Atherosclerosis Risk in Communities Study <sup>46</sup> , normotensive patients with high anger temperament scores (characterized by frequent or long-lasting anger reactions with little or no provocation) had a hazard ratio of 2.3 for fatal or non-fatal cardiac events after adjustment for traditional cardiovascular risk factors. Chronic anxiety also is a predictor of cardiovascular events, both ischaemic heart disease events and sudden death. Severe phobic anxiety, in particular, has been associated with increases in cardiac events of 1.3 to 3.0 times, perhaps via frequent paroxysms of fear <sup>47</sup> .

Personality types – both type A and type D – lead to unhealthy responses to daily psychological stressors. The

type D (distressed) personality is characterized by a combination of pessimistic emotions and introversion, which prevents sharing emotions with others. Type D individuals are gloomy, anxious and socially inept worriers <sup>48</sup> . By contrast, in the type A personality, anxiety and hypervigilance are directed outward as competitive, aggressive, irritable, and sometimes hostile behaviours. Type A personality has received attention as a potential cardiovascular risk factor for two decades, but results have been mixed as to whether this personality type is truly associated with cardiovascular events <sup>49</sup> .

### MECHANISMS OF CARDIOVASCULAR DISEASE IN CHRONIC EMOTIONAL STRESS

Acute stress, can trigger acute thrombotic, arrhythmic, or mechanical cardiovascular events, chronic stress seems to affect cardiovascular risk mainly by acceleration of the atherosclerotic process. Although physiological pathways exist through which chronic stress could potentiate cardiovascular disease (such as increased blood pressure), behavioural changes (such as medical non-compliance, smoking, or sedentary lifestyle) might also accompany chronic psychological stressors <sup>50</sup> . There is a consistent relation between chronic emotional or psychosocial stress and coronary atherosclerosis (and atherosclerotic risk factors), and these relations persist after adjustment for confounding variables, including lifestyle variables. This association suggests, that stress itself contributes to cardiovascular morbidity in the general population. Acute stress elicits rapid increases in circulating catecholamine and cortisol concentrations, different forms of chronic stress might lead to different neuroendocrine response. Some forms of chronic stress, such as post-traumatic stress disorder, can be associated with a blunted amplitude of cortisol secretion and diminished responsiveness to acute stressors, perhaps due to a repetitive over stimulation of the hypothalamic-pituitary-adrenal stress response (analogous to  $\beta$ -cell failure in patients with insulin resistance) with compensatory activation of the sympathetic nervous system

<sup>51</sup> .

The likelihood of developing myocardial arrhythmia is also subject to genetic variation. The ryanodine receptor affects the clinical manifestations of circulating catecholamines. Mutations in the gene for this receptor render individuals susceptible to ventricular tachycardia during catecholamine challenges, whether induced by exercise or by emotional triggers <sup>52</sup> . Similarly patients with congenital long QT syndromes due to mutations in genes for sodium or

potassium channels are also at risk of sudden death after catecholamine surges<sup>53</sup>.

### DIURNAL VARIATIONS

Activity of (hypothalamic-pituitary-adrenal) axis, and the sympathetic nervous system, show striking diurnal variation. Peak corticotropin and cortisol concentrations occur in the early morning, and peak cortisol concentrations can be ten times higher than at trough<sup>54</sup>. Circulating norepinephrine and epinephrine concentrations shows large diurnal variation with increases throughout the day and decreases at night.

Proposed mechanisms to explain why ischaemic heart events and cerebrovascular events are more common in the early morning than at other times include increasing morning catecholamine concentrations, highest cortisol concentrations, hypercoagulability, and endothelial dysfunction<sup>55,56</sup>. Not surprisingly, in view of the association between the stress systems and the sleep-wake cycle, disruption of sleep pattern interferes with autonomic balance and function of the hypothalamic-pituitary-adrenal axis. Sleep deprivation blunts the normal trough in circadian cortisol concentrations and also increases sympathetic nervous system activity at the expense of parasympathetic tone<sup>57</sup>. Via stress system activation and perhaps via other hormone and immune mechanisms as well, sleep disruption is associated with several metabolic disorders, including obesity and insulin resistance<sup>58</sup>.

### THERAPEUTIC IMPLICATION

There are evidences that relaxation techniques or methods such as meditation, yoga, and prayer can modify indices of autonomic activation at beneficial in relieving stress<sup>59,60</sup>.

Drug therapies have been studied to a limited extent. Bernardi L et al<sup>60</sup> In the SADHART study reported that the treatment with sertaline was not powered to detect differences in clinical end point. (In this study 369 depressed patients who had recently had myocardial infarction were randomly assigned sertaline or placebo for 24 weeks).

In the ENRICHD study that enrolled nearly 2500 myocardial infarction patients with depression or low social support, or both, to cognitive behaviours therapy versus usual care and recorded no effect on event – free survival with modest improvement in depression and social isolation score<sup>61</sup>. Taylor CB et al<sup>62</sup> reported a relative reduction in death or recurrent myocardial infarction of about 40% in patients with major depression who were prescribed selective

serotonin reuptake inhibitor.

JoAnn Difede et al<sup>63</sup> reported that Virtual Reality (VR) is an effective treatment tool for enhancing exposure therapy for both civilians and disaster workers with Post Traumatic Stress Disorder and may be especially useful for those patients who cannot engage in imaginal exposure therapy.

### SUMMARY

In normal subjects acute mental stress may alter heart rate, double product, cardiac output stroke volume and cardiac microcirculation. Acute mental stress increases blood pressure and heart rate in patients with cardiovascular disease. Angina pectoris and other evidence of ischaemic heart disease may accompany this increase in heart rate. Evidence exists for a strong and consistent association of acute and chronic psychological stress with cardiovascular risk factors and with outcomes such as ischaemia, arrhythmias and pump failure. Stress is modifiable-risk factor for acute and chronic cardiovascular disorders. Stress may be managed by healthy lifestyle, anger management, meditation, yoga, prayer and treatment of mental illness.

Some of the most promising studies about stress and cardiovascular system have been made possible by the genomic revolution with identification of genes could prove to be important therapeutic targets and emergence of targeted evidence-based interventions.

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