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## **Pathophysiological Changes Occuring in Cardiovascular and Immune Systems In Response to Stress**

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### **Abstract**

Cardiovascular and immune system pathophysiological changes and diseases may be attributed to stress. Sometimes stress may be beneficial when it is not 'overwhelming' as it may improve performance in certain cases. Modern medicine is focusing on the close relationship between stress and cardiovascular and immune system morbidity and mortality. New therapeutic strategies have to be set in place. Brief naturalistic stressors (such as exams) were associated with potentially adaptive upregulation of some parameters of natural immunity and downregulation of some functions of specific immunity; tended to suppress cellular immunity while preserved humoral immunity. On the other hand chronic stressors were associated with suppression of both cellular and humoral immunity. In some cases, physical vulnerability as a function of age or disease also increased vulnerability to immune change during stressors. In mammals, physiological responses such as "fight or flight." to chronic stressors, include changes that increase the delivery of oxygen and glucose to the heart and the large skeletal muscles. The changes in Immune responses to stressful situations may be part of these adaptive responses. Psychological challenges are capable of modifying various features of the immune response.

**Keywords:** Stress; Pathophysiology of Cardiovascular diseases; Pathophysiology of Immune system.

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## **1. Introduction**

### **1.1. Stress**

Relationship between stress and pathophysiological disease is still scientifically questioned and only in the past decades, the stress concept and its association with health restrictions and diseases has become a major focus in medicine [1].

The modern stress concept is based on the fundamental work of Hans Selye who has studied the effects of stress on health and the physiological integrity of biological organisms [1–3]. Thereby, stress is now used as an umbrella term that summarizes the effects of psychosocial and environmental factors on physical or mental well-being [1,4,5].

Stressors elicit a stress response, which eventually leads to physiological, behavioral, and psychological adjustments in order to enhance the organism's chances to ultimately survive [3,5–7]. The body uses and loses metabolic energy in order to repeatedly adapt to physical challenges and psychosocial threats. Keeping a dynamic physiological balance throughout ongoing (environmental) perturbations is a crucial step to maintain survival, biological integrity, and health [1,7].

The disturbing stimulus can be defined as a state of disharmony, or threatened homeostasis/balance. Biochemical (neurotransmitter, peptides, steroids), physiological (heart rate, blood pressure), and behavioral (anxiety, depression, tension) concomitants of this response may co-mediate it [8]. Over time, we have referred to this normally protective response as stress, and the process of documenting the disturbance as the stress response [9].

Two major components of the autoregulatory stress response in vertebrates are known thus far, and they are both connected with the nervous system and its associated glands: the hypothalamic-pituitary-adrenal (HPA) axis and the sympathoadrenal medullary (SAM) system [10–13]. These two systems – HPA and SAM – are normally operating to maintain homeostasis.

Stress response is susceptible to pathophysiological factors or processes and further has an impact upon many biological functions [1,4,10,11]. The mediators of stress response can have both protective and harmful effects in organs like the heart, the brain and the immune system [7].

## **2. Structure**

### **2.1. Stress related cardiovascular diseases**

Despite clinical 'intuition', an 'easy and clear' relationship between stress and cardiovascular diseases had not been delineated, and this may have been due to the complexity of the stress phenomenon [3,4,6,7].

People who often get 'stressed out' and irritated or are always 'on the run' are classified as As type A pattern, tend to have a higher susceptibility to diseases of the circulatory system [14], hostility and anger have become a major focus in the context of 'stressful' factors with a greater cardiovascular risk [15]. (Figure 1).

<b>Type A</b>
ambition
aggression
rivalry
impatience
(muscular) tension
heightened attention ('taut attention')
fast speech
acceleration of activities ('on the run')
irritability
hostility
anger

**Figure 1:** Type A behavioral pattern.

This pattern describes a characteristic behavioral coping strategy in challenging ('stressful') situations. It has been suspected to be related to a higher susceptibility to diseases of the circulatory system [14,16]. In a number of recent studies, however, researchers report no specific effect of Type A behavior on risk of coronary heart disease or other cardiovascular diseases [83]. Instead, latest evaluations of the epidemiological literature indicate definite connections between hostility and risk for cardiovascular disease [15,17,18]. This heightened risk is associated with an increased sympathetic activity [16,18], enhanced catecholamine/cortisol responses (stress responses) to behavioral stress, and elevated total serum cholesterol levels [16,18]. Research on the effects of behavioral phenomena on myocardial ischemia in coronary artery disease patients has provided a pathophysiological model for understanding the mechanisms by which mental stress can trigger clinical cardiovascular events [20]. Here, the activation of stress response-related pathways seems to be crucial and is capable of facilitating deleterious processes in the long-term: Via its actions on the central and autonomic nervous systems, stress can produce a cascade of regulatory responses that may actually lead, in vulnerable individuals, to myocardial ischemia, ventricular fibrillation, plaque rupture, or coronary thrombosis [19]

Further, social support can buffer against the effects of stress while a disrupted, unstable social environment increases the stress related risk for cardiovascular incidents [20]

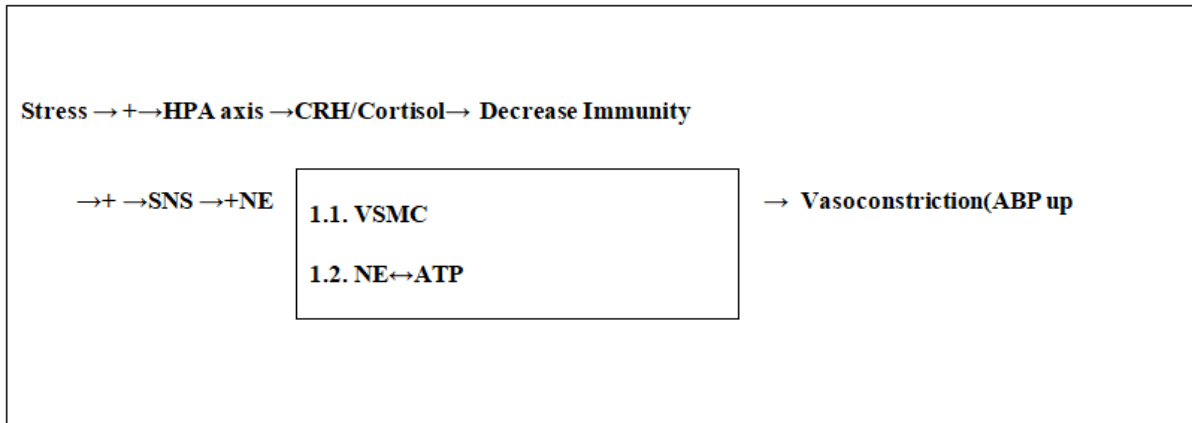
In a study examining cynomolgus monkeys that had been put under social pressure (introduction of a stranger to

a stable four-member social group), the social manipulation produced persistent sympathetic arousal and decreased the endothelial integrity of various vascular segments, leading to endothelial dysfunction – a precursor of atherosclerosis [20].

Interestingly, the detrimental effects of this experimentally applied psychosocial stress can be prevented by the use of beta-adrenergic (sympathetic) blocking agents [20].

## 2.2. Stress and Hypertension

The etiology and pathophysiology of hypertension are complex. Besides primary, essential, or idiopathic forms, symptomatic (secondary) forms exist. Aging, atherosclerosis, risk factors, and sympathetic nervous system activity (stress) may play a critical role in secondary hypertension [21]. Stress has been shown to be important in vascular hypertension. It may either serve as a risk factor [22], induce blood pressure spikes, or increase an already elevated blood pressure [13,23,24]. Stress may even, in part, cause or contribute to the clinical onset of arterial hypertension in certain cases [22–24].



**Figure 2:** Stress stimulates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). Corticotropin releasing hormone (CRH), cortisol, and catecholamines like norepinephrine (NE) are released. In the vascular smooth muscle cell (VSMC), NE and adenosine triphosphate (ATP) interact, leading to vasoconstriction. Thus, the blood pressure (BP) increases, eventually facilitating arterial hypertension (references see text; [25])

Animal models have illustrated the critical role of sympathetic arousal, associated with stress, in the development of hypertension [16]. In particular, acute stress is capable of immediately increasing the arterial blood pressure [23]. This is probably due to vasoconstriction, triggered by enhanced SNS activity [13] (Figure 2).

Additionally, chronic stress may lead to hypertension and prolonged/ /lasting side effects, eventually fixating vascular lesions and facilitating cardiovascular complications [20,21].

Taken together, stress contributes to the onset, development, and progression of a variety of cardiovascular

diseases. In particular, mental and psychosocial stressors apparently have a profound impact upon the circulatory system. Individual differences may further play a role, since susceptibility and reactivity in relation to stress show a subjective component. However, the SNS activity obviously represents a critical link, a crucial effector of the stress response and its potentially deteriorating influences on the cardiovascular system.

### ***2.3. Mechanisms of Stress Effects on the Immune System***

Virtually nothing is known about the psychological pathways linking stressors with the immune system. Many theorists have argued that affect is a final common pathway for stressors, (26), yet studies have enjoyed limited success in attempting to explain people's immune responses to life experiences on the basis of their emotional states alone (27,28)

A series of studies in the mid-1990s was able to show via beta-adrenergic blockade that activation of the sympathetic nervous system was responsible for the immune system effects of acute stressors

Apart from these findings, however, little is known about biological mechanisms, especially with regard to more enduring stressors that occur in the real world. (29,30)

Future studies could also benefit from a greater emphasis on behavior as a potential mechanism. This strategy has proven useful in studies of clinically depressed patients, in which decreased physical activity and psychomotor retardation (33), increased body mass (32), disturbed sleep (33), have been shown to explain some of the immune dysregulation evident in this population. There is already preliminary evidence, for instance, that sleep loss might be responsible for some of the immune system changes that accompany stressors ( 34)

**Stress, the Immune System, and Disease** The most pressing question that future research needs to address is the extent to which stressor induced changes in the immune system have meaningful implications for disease susceptibility in otherwise healthy humans.

In the 30 years since work in the field of psychoneuroimmunology began, studies have convincingly established that stressful experiences alter features of the immune response as well as confer vulnerability to adverse medical outcomes that are either mediated by or resisted by the immune system. However, with the exception of recent work on upper respiratory infection (35), studies have not yet tied these disparate strands of work together nor determined whether immune system changes are the mechanism through which stressors increase susceptibility to disease onset. In contrast, studies of vulnerable populations such as people with HIV have shown changes in immunity to predict disease progression (36).

Cytokine expression represents a relatively new and promising example of an avenue for research linking stress, immune change, and disease. For example, chronic stress may elicit prolonged secretion of cortisol, to which white blood cells mount a counterregulatory response by downregulating their cortisol receptors. This downregulation, in turn, reduces the cells' capacity to respond to anti-inflammatory signals and allows cytokine-mediated inflammatory processes to flourish (37).

Stress therefore might contribute to the course of diseases involving excessive nonspecific inflammation (e.g., multiple sclerosis, rheumatoid arthritis, coronary heart disease) and thereby increase risk for excess morbidity and mortality (38). Another example of the importance of cytokines to clinical pathology is in asthma and allergy, in which emerging evidence implicates excess Th2 cytokine secretion in the exacerbation of these diseases (39).

### **3. Discussion**

Stress implies a challenge (stimulus) that requires behavioral, psychological, and physiological changes (adaptations) to be successfully met, therefore using a state of hyperarousal for the initiation of necessary counteracting reactions [69]. The state of hyperarousal involves physiological mechanisms that are known as the stress/emergency response or fight-or-flight response, a set of physiological changes that occur in stressful situations and that prepare the 'stressed' organism either to fight – or flight. This evolutionarily old state of alertness had first been described by Walter Cannon in the first half of the 20th century [10,11].

Thereby, the profound physiological alterations observable in stress – involving the HPA axis and the SNS – exert effects upon the whole organism. Even though set in place to be helpful, stress may yet lead to onset, development, or progression of pathophysiological disease processes [1,4,7].

This may be particularly true in chronic stress (or when an overwhelming acute stressor occurs), where the organism's resources to withstand the 'challenge of stress' may prove to be insufficient in the long-term or may expire prematurely [1,3–5]. Hence, the stress response itself has the capacity to do harm [7].

Further, when stress response mechanisms are not sufficient to meet the primary goal (adjustment to challenge or counteract the stressors, survival), the original stimulus/stressor may take over in a sense – the organism may 'capitulate' [5]. It now may suffer deteriorating biological alterations, sickness, severe disease, or even death [5,7]. This state has been referred to as conservation-withdrawal or the giving up/given up state [1].

In particular, mental, behavioral, and psychosocial stressors are of importance. These findings correspond to similar outcomes obtained in immunological diseases [7].

However, with regard to cardiovascular diseases, stress most often happens to be deleterious: Since sympathetic nervous system activity is increased in stress [39] and the circulatory system obviously/by nature is sensitive to alterations in autonomic activity levels [21,40–42], stress – chronic stress in particular – is capable of thoroughly elevating the overall and specific cardiovascular risk [21,39].

In this way, some of the negative effects that stress triggers in the circulatory system resemble inflammatory processes: As stress affects the immune system, pathophysiological pathways activated here may also be stimulated and become important in certain cardiovascular diseases (e.g., myocardial infarction, atherosclerosis/endothelial dysfunction) [7,39].

This is especially key since the cellular immune response initiated by the macrophage is important for the

initiation and progression of atherosclerosis [64]. In addition to SNS and HPA pathways (involving norepinephrine and cortisol) and the cellular immune response, NO signaling also seems to be relevant in stress-related cardiovascular diseases [7,10,15, 16,43,44,46]. However, the concrete pathophysiological mechanisms, molecular autoregulatory signaling pathways, and interrelationships involved are not totally understood yet, and further research is necessary to get a more complete picture [50].

Stress levels apparently are high and still growing in the 'western world' [1,21,50]. This fact may explain the rising – subjective – perception of stress in industrialized countries (enhanced perception of acute and chronic stress) [1,4], and the elevated risk for the development of diseases of the circulatory system . 'Life style' has become a central focus of prevention [1]. This 'epidemic of stress' [1] that has occurred in the west in the last decades runs the risk of becoming a critical medical issue: New strategies need to be put in place to stop the detrimental results that stress can have in cardiovascular patients [4,21,39]. Thus, stress management, cognitive behavioral strategies, and the use of relaxation response techniques are of growing future importance [1,50].

Immunity, its cytokine profile, and its regulation by anti-inflammatory agents such as cortisol, may determine the disparate effects of different kinds of stressors.

#### **4. Conclusion**

Stress-related disease emerges, predominantly, out of the fact that we so often activate a physiological system that has evolved for responding to acute physical emergencies, but we turn it on for months on end, worrying about mortgages, relationships, and promotions.

A strong evidence for an importance of stress in disease processes related to the circulatory system and immune system Stress plays a significant role in susceptibility, progress, and outcome of cardiovascular diseases. In particular, stress may cause or exacerbate disease processes depending on the type of stressor involved (e.g, physical, chemical, biological, mental, psychosocial etc.) and/or the duration of its influence on an organism.

Stress contributes to the onset, development, and progression of a variety of cardiovascular diseases. Here, mental and psychosocial stressors have a profound impact, and in this regard, the sympathetic nervous system represents a generally important effector of the stress response with potentially deleterious influences on the cardiovascular system. Subjective or individual differences have to be taken into account too. This fact can make it difficult to predict an expected result following the experience of challenging stimuli (stressors) that are able to evoke the stress response and lead to physiological, psychological, and behavioral adjustments.

Worry is more likely to result in stress-related immune change than objective experience and the idea that stress-related immune change results in stress related disease. Though the results of the meta-analysis were not encouraging on the first point, many of these studies suffered from methodological limitations.

We hope that these results will inform investigations that go beyond the relationship between a stressful event and an immune parameter to investigate the psychological phenomena that mediate that relationship. Finally, these results can also inform investigations into stress, immunity, and disease process. Whether the disease is

characterized by natural or specific

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