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Stress in cardiovascular diseases

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Summary

Objective: Evidence for a connection between stress and selected cardiovascular diseases is analyzed. Does stress cause or exacerbate cardiovascular diseases?

Method: The stress phenomenon is illustrated and the impact of stress on the circulatory system is examined. In particular, the pathophysiological significance of stress in hypertension, atherosclerosis, coronary artery disease, myocardial infarction (and others) is described.

Results: Stress plays a major role in various (patho)physiological processes associated with the circulatory system. Thereby, it potentially has ameliorating or detrimental capacities. However, with regard to cardiovascular diseases, stress most often is related to deleterious results. The specific outcome depends on multiple variables (amount of stress, duration of its influence, patient's history/predisposition, genetic components – as they all may alter functions of the basic stress response components: the hypothalamic-pituitary-adrenal axis and the sympathoadrenal medullary system).

Conclusion: Stress has a major impact upon the circulatory system. It plays a significant role in susceptibility, progress, and outcome of cardiovascular diseases. Subjective or individual differences have also to be taken into account. Stress, especially 'adequate' acute stress – stress that is not 'overwhelming' – may improve performance and thus be beneficial in certain cases. The close relationship between stress and cardiovascular diseases may represent an important aspect of modern medicine. New therapeutic strategies have to be set in place.

key words: **stress • diseases • cardiovascular system**

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1. BACKGROUND: STRESS

In our modern world, science has begun to evaluate and re-examine traditional concepts and beliefs about 'stress' [1]. In particular, the suggested relationship between stress and pathophysiological disease processes has come under detailed investigation [1]. Albeit common opinion, this relationship 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]. In particular, stressors and stress reactions are distinguished [1,5].

The interest of various medical fields and disciplines in the area of stress-related diseases and research is rapidly growing [1]: The idea that challenging stimuli (stressors) elicit a stress response, which eventually leads to physiological, behavioral, and psychological adjustments in order to enhance the organism's chances to cope (and – ultimately – to survive), is now widely accepted [3,5–7].

Balance is 'key' in stress: Through an extremely complicated equilibrium called 'homeostasis', all living organisms maintain their survival in the face of both externally and internally generated stimuli (stressors). This apparent harmony – or balance – is constantly challenged [8,9]. Thus, all life forms have developed mechanisms to overcome immediate perturbations, i.e, protective perturbation response [10]. It can also be said that the ability to overcome perturbations is essential to survival and longevity, as it insures that the 'molecular message' is passed on. Thus, keeping a dynamic physiological balance throughout ongoing (environmental) perturbations is a crucial step to maintain survival, biological integrity, and health [1,7].

A new schema has been proposed to help us better understand the interrelationships among external environmental and internal behavioral stressors, the physiological responses to these challenges (stress responses), and disease/illness. Terms used such as 'homeostasis' and 'allostasis' are both now considered important in stress. Thereby, allostasis refers to the maintenance of overall stability (homeostasis) through the constant adjustment and balancing of various components in the process of adapting to challenge (aiming at a state of dynamic balance) [5,7]. McEwen has stated that allostasis is the process that keeps us alive and functioning by promoting adaptation and coping – at least in the short run [6].

The body uses and looses metabolic energy in order to repeatedly adapt to physical challenges and psychosocial threats. 'Allostatic load' refers to this wear and tear on the organism forced to use allostatic mechanisms over and over in response to stressors [7]. As a result, an overuse of allostasis phenomena on one hand or an inefficiency in allostatic response functioning on the other may occur – related to the need to turn response pathways on and off in a succession of stress responses.

The broad spectrum of stimuli capable of engaging an intentionally protective (allostatic) response is remarkable and reflects upon how well integrated our perceptions of the physical and psychological worlds are [11]. In this context, the challenging (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 [12]. Over time, we have referred to this normally protective response as stress, and the process of documenting the disturbance as the stress response [10].

We also find stress response pathways in invertebrates [10]. Indeed, the highly regulated vertebrate stress response mechanism has its origins in the invertebrate nervous system, if not earlier in evolution. This view is based on recent evidence that, in both animal groups, the immune and nervous systems appear to utilize similar intercellular signal molecules. These signal processes appear to be involved in similar activities [10].

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 [13–16]. Frequently, the SAM is equated with the sympathetic nervous system (SNS). These two systems – HPA and SAM – are normally operating to maintain a delicate state of balance (homeostasis), in order to continue the organism's integrity even under highly challenging conditions (allostatic load, perturbations). However, while the allostatic stress response represents a complex and sensible instrument, it is susceptible to pathophysiological factors or processes and further has an impact upon many biological functions [1,4,13,14]. Thus, depending on circumstances, it may likewise exert ameliorating or detrimental effects. In other words, the mediators of allostasis can have both protective and harmful effects in organs like the heart, the brain and the immune system [7].

Stress has an impact upon the immune system [7]. It plays a significant role in susceptibility, progress, and outcome of immunological diseases. In particular, stress may cause or exacerbate disease processes depending on the type of stressor involved (e.g, physical, chemical, biological, mental, social etc.) and/or the duration of its influence on an organism [5,7]. Thus, the objective of this work is to examine the relationship between stress and cardiovascular diseases: Do we find similar evidence for an importance of stress in disease processes related to the circulatory system? Does stress exacerbate or even cause cardiovascular diseases?

2. STRESS-RELATED CARDIOVASCULAR DISEASES

For many years, the proposed clinical effects of stress on the cardiovascular system have been discussed [17]. However, until recently, only a few studies investigating stress and its impact upon the circulatory system have been conducted and evidence has been relatively weak for a long time. 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]. The situation changed somewhat when the concept of different behavioral patterns involved in cardiovascular diseases occurred [18].

The introduction of various types – or patterns – of behavior (particularly 'Type A') into the analysis of environment/stressors and its effects upon cardiovascular diseases helped to better explain the nature of stress and stress-related pathophysiological mechanisms - and to find interdependencies or measure a correlation between stress and cardiovascular diseases [18]. Type A behavior, for example, describes people who often get 'stressed out' and irritated or are always 'on the run'. Theses individuals tend to have a higher susceptibility to diseases of the circulatory system [18]. However, the nature of this relationship is not as obvious as it seems *prima facie*, and recent research has demonstrated that the 'hostility' component - out of the suggested Type A pattern – is especially associated with a greater cardiovascular risk [19]. Therefore, hostility and anger have become a major focus in the context of 'stressful' factors that facilitate cardiovascular problems [19] (Figure 1).

Although many different types of potential stressors exist (see above), mental and psychosocial stressors are

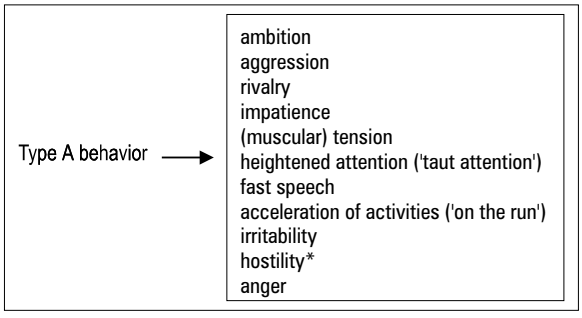

Figure 1. Type A behavioral pattern. This pattern describes a characteristic behavioral coping strategy in challenging ('stressful') situations. It has been suspected to be related to a higher susceptibility to diseases of the circulatory system [18,82]. In a number of recent studies, however, researchers 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 [19,83,84]. This heightened risk is associated with an increased sympathetic activity [82,84], enhanced catecholamine/cortisol responses (stress responses) to behavioral stress, and elevated total serum cholesterol levels [82,84].

apparently powerful and exert profound effects on the circulatory system. 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 [20]. Further, social support can buffer against the effects of stress while a disrupted, unstable social environment increases the stress related risk for cardiovascular incidents [21]. 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 [21]. Interestingly, the detrimental effects of this experimentally applied psychosocial stress can be prevented by the use of beta-adrenergic (sympathetic) blocking agents [21]. Thus, psychosocial factors, such as environmental stress and responsiveness to stress, are representing newer, 'nontraditional' [22] cardiovascular risk factors with an evident relation to cardiovascular disease [22]. In the following, this relationship will be examined in detail with respect to its significance in specific cardiovascular diseases.

2.1. 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 [23].

Stress has been shown to be important in vascular hypertension. It may either serve as a risk factor [24], induce blood pressure spikes, or increase an already elevated blood pressure [16,25,26]. Stress may even, in part, cause or contribute to the clinical onset of arterial hypertension in certain cases [27–29]. Here, animal

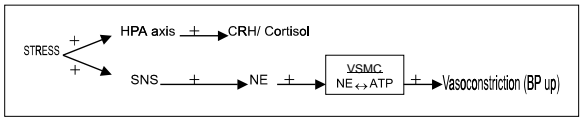

Figure 2. Stress stimulates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). Corticotropin releasing hormone (CRH), cortisol, and catecholamines like norepinephrine (NE) are released. In the vascular smooth muscle cell (VSMC), NE and adenosine triphosphate (ATP) interact, leading to vasoconstriction. Thus, the blood pressure (BP) increases, eventually facilitating arterial hypertension (references see text; [85]).

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 [25]. This is probably due to vasoconstriction, triggered by enhanced SNS activity [16] (Figure 2). Additionally, chronic stress may lead to hypertension and prolonged/ /lasting side effects, eventually fixating vascular lesions and facilitating cardiovascular complications [21–23]. Both detrimental sympathetic activity (and the SNS effector norepinephrine) and also ameliorating nitric oxide (NO) pathways are involved: Since NO inhibits norepinephrine-dependent vascular contraction and is capable of lowering arterial blood pressure, vascular responsiveness to contractile substances like norepinephrine may be significantly attenuated by release or exposure to NO [30,31]. Furthermore, an impaired NO synthesis (in mice) has been demonstrated to result in increased sensitivity the pressor effect of mineralocorticoids in the presence or absence of an increased saline intake [32]. Therefore, NO may actually decrease the blood pressure in mineralocorticoid-sensitive cases [32]. This possible contribution of NO pathways to the adaptive response to mineralocorticoid excess may point out an impact of NO on natriuresis and blood pressure levels [32]. Hence, the stress physiology involved in hypertension includes different systems, e.g, the SNS and coupled NO pathways.

In a recent study investigating the connection between psychosocial work stress and cardiovascular diseases, it has been demonstrated that stress affects the appearance of complications in arterial hypertension [33]. Moreover, people under stressful work conditions (such as high demand, low control, many emotional and psychosocial stressors, e.g, seen in health workers) who had developed hypertension earlier, have been shown to be more vulnerable to angina pectoris, myocardial infarction, and cerebrovascular insults compared to controls [4,33,34]. Thus, stress not only affects the onset, development, and progression of hypertension, but also the number of associated cardiovascular complications.

2.2. Atherosclerosis

The pathophysiology of atherosclerosis seems to be multifaceted and many etiological factors may be of importance. For example, high-fat diets (e.g, high-cholesterol, saturated fats) can induce atherosclerosis [35,21], and atherosclerosis caused by moderate hyperlipoproteinemia is highly susceptible to the influence of psychosocial stress [36]. Since oxidative stress may induce endothelial dysfunction and injury, and since endothelial injury (destruction of the endothelial integrity) has been considered an initiating event in atherogenesis [35], oxidative stress/free radical activity may also contribute to the pathophysiology of atherosclerosis [37].

Mental or psychosocial stress is associated with endothelial dysfunction and atherosclerosis in many ways. The atherosclerosis-associated endothelial dysfunction has been shown to 'cause' abnormal vascular responses to stress, leading to a paradoxical constriction, especially at points of a preexisting stenosis [38]. In fact, this paradoxical pattern of response (constriction instead of the normal, reasonable vasodilation) actually represents the substantial and hazardous nature of endothelial dysfunction.

Behavioral or psychosocial stress induces or influences the development and progression of atherosclerosis [36,39–41]. Thereby, psychosocial stress has been demonstrated to increase oxidative stress [37] and induce endothelial injury [35] - processes mediated via sympathoadrenal activation (beta 1-adrenoceptor activation) that lead to atherosclerosis, particularly around branching points of the descending aorta (monkey model) [35,36]. This development may be stopped by therapeutic beta-blockade, e.g, by application of metoprolol [21]. Thus, psychosocial stress, also described as 'asymmetries in the psychosocial environment' [35,36], may lead to a (hyper)arousal of the sympathetic nervous system and consequently to endothelial dysfunction [21,41].

Behavioral or psychosocial stressors have an effect on estrogen activity (as they are able to induce a decrease) which may be of importance for the development of premenopausal atherosclerosis [41]. Hence, low estrogen concentrations – together with an associated hypercortisolemia (found in stress) - may be related to the accelerated onset of otherwise rare premenopausal atherosclerosis, since estrogen seems to be a strong protective factor against atherosclerosis in premenopausal female monkeys [41].

Mental stress (such as challenging mental arithmetic) and even physical stress may also cause endothelial dysfunction [21,38,42], and the connection between mental stress and atherosclerosis has already been examined [21,43]. Thereby, the tendency to show exaggerated cardiovascular responses/enhanced reactivity to mental stressors (e.g, observable in exaggerated blood pressure responses) increases the atherosclerotic risk significantly [43]. Taken together, substantial evidence exists to state that mental or psychosocial stressors play a significant role in processes involved in atherosclerosis.

2.3. Coronary Artery Disease

In general, coronary artery disease (CAD) describes a special form of atherosclerosis that manifests itself in the coronary arteries. Thus, both fields overlap and what has been demonstrated for atherosclerosis may almost be transferred and adopted here. Yet, these common aspects will not be particularly focused on in the following. Instead, some specific facts will be examined.

Stress is strongly associated with CAD [15,44,45]. In particular, mental stress often is a severe cause for angina and may specifically worsen CAD [38,46–48]. Further, mental stress may induce substantial myocardial ischemia, since it is capable of activating the 'ischemic response' (i.e, decrease in left ventricular ejection fraction > or = 5%, for > or = 60 seconds) by provoking a dynamic decrease in coronary supply [36,42,

46,49–51]. The actual induction of an ischemic response via mental stress represents a risk factor for future cardiac events: mental stress-related myocardial ischemia adversely affects prognosis in CAD patients and predicts a greater severity of CAD in its course [42,49]. Additionally, hostility and anger have also been shown to negatively influence ejection fraction and myocardial blood circulation, pointing out the importance of these phenomena for the etiology of CAD [19,52]. However, other forms of stress have an impact too: Behavioral/psychosocial stress has been demonstrated to participate in the development of CAD [36,39], and this effect may be linked to neuroendocrine mediation (e.g, sympathoadrenal activation) [36]. In general, the sympathetic nervous system seems to be important: Angina/chest pain, in connection with normal coronary angiograms, may frequently be associated with chronic sympathetic (hyper)arousal [53]. Therefore, angina may be related to sympathetic pathways in certain cases [53]. Finally, social stress also alters endothelial function and integrity, and it may even cause substantial endothel injury (presumably via beta-adrenoceptor pathways), consequently leading to coronary dysfunction [54].

2.4. Myocardial Infarction

Myocardial infarction (MI) describes an ischemic event that follows an acute interruption of a sufficient coronary blood supply, usually going along with CAD, coronary spasm, thromboembolism, arrhythmia, trauma etc. [55,56]. Stress clearly has the potential to actively trigger this threatening cardiac event [38,42,57], and here, mental stress appears to be exceptionally potent [51,57–59]. Mental stress obviously has a profound impact on long-term cardiac events and outcome too [50]. In particular, mental stress may cause paradoxical constrictions in patients with CAD/atherosclerosis, especially at points of stenosis – a response that correlates with the extent of atherosclerosis (plaque) and with the endothelium-dependent response to an infusion of acetylcholine (verification of endothelial dysfunction): Local failure of dilation causes unopposed constriction [38]. Additionally, mental stress not only increases the myocardial oxygen demand (via sympathoadrenal activation) but also involves a reduction in the myocardial oxygen supply, an eventually fatal consequence [42,59]. Thus, stress may be critical in MI.

2.5. Others

In non-insulin-dependent diabetes mellitus (NIDDM), a causal association with stress (i.e, with an 'excessive stress response', corticotropin releasing hormone-hyperactivity) has been discussed recently [60]. In addition, stroke has been shown to be connected with psychosocial stress [39]. Further, cardiomyopathy (CM) has been demonstrated to be related to stress in particular cases [61]. Nonetheless, the concrete association remains unclear and underlying mechanisms are not yet well understood.

In the aging cardiovascular system, an increased overflow of norepinephrine to the plasma frequently occurs, presumably due to a reduced norepinephrine reuptake following sympathetic stimulation [62]. This effect is particularly observable after administering or experiencing mental stress [62]. Thus, an 'excess' of norepinephrine may regularly appear in older people [28,62]. Further, aging increases human sympathetic nervous system activity at rest [62], thereby potentially enhancing frequency and intensity of possible stress responses [62]. However, this fact may be modified by a parallel decreased SNS reactivity (as discussed in elderly people) – which may, in turn, reduce an elevated risk related to sympathetic (hyper) arousal [62,63]. Nevertheless, oxidative stress is increased in older organisms (stress responses, nitric oxide pathways may be involved; see [64]), and this fact may contribute to the pathophysiology of atherosclerosis and other chronic diseases prevalently associated with aging [37]. Therefore, (prolonged) stress, as it potentially enhances sympathetic activity and norepinephrine levels (see above), may exert deleterious long-term/chronic effects on the aging cardiovascular system. The kind of mental stress that eventuates in major depressive disorder is associated with a reduction in what is called heart rate variability (HRV) [65]. This means that there is too much beat-to-beat regularity usually driven by hyper-sympathetic tone at the expense of parasympathetic influence. Some researchers believe this is why depression conveys an increased relative risk of cardiac disease [65].

Arrhythmia is often related to stress/stressful stimuli. For example, stress immediately increases the heart rate and induces alterations in heart rate reactivity [25,44]. Hence, SNS activity may represent a crucial underlying mechanism. Stress has further been identified as a contributor to chronic heart failure (CHF). Here, sympathetic (hyper)arousal may also be involved [66]. Thereby, neuropeptide Y coexists with norepinephrine in sympathetic nerves and is co-released on sympathetic activation: Cardiac failure is associated with an increased release of norepinephrine and neuropeptide Y from the resting – and the stimulated/'stressed' – heart [66]. Further, endothelial dysfunction is a key feature of CHF, contributing to enhanced peripheral vasoconstriction and impaired exercise capacity (exercise intolerance) [67,68]. As illustrated above, endothelial dysfunction may be associated with stress.

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.

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 [13,14]. 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].

Does stress affect the circulatory system and trigger cardiovascular diseases? This question has been controversy in the past [4]. However, as we have reviewed, stress has a major impact upon the cardiovascular system, and a variety of cardiovascular diseases are influenced by stressors and challenging stimuli (see above). In particular, mental, behavioral, and psychosocial stressors are of importance. These findings correspond to similar outcomes obtained in immunological diseases [7]. Thereby, the effects exerted by stress may either be beneficial or detrimental, depending on a multitude of factors (including specific types of stressors, duration or timing of stress, and individual differences in susceptibility) [1,7]. In principal, stress may have both properties [1,4,7]. However, with regard to cardiovascular diseases, stress most often happens to be deleterious: Since sympathetic nervous system activity is increased in stress [70] and the circulatory system obviously/by nature is sensitive to alterations in autonomic activity levels [23,71–73], stress – chronic stress in particular – is capable of thoroughly elevating the overall and specific cardiovascular risk [23,70]. This statement applies for healthy subjects at risk of developing cardiovascular diseases as well as for patients already suffering from pathological cardiovascular conditions [4,70,72]. 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) [7,70]. 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, 16,30–32,74]. However, the concrete (patho)physiological mechanisms, molecular autoregulatory signaling pathways, and interrelationships involved are not totally understood yet, and further research is necessary to get a more complete picture [64].

The concept of balance/homeostasis – and corresponding to this: allostasis – has become crucial in stress research. Following a challenge (stressful stimulus, stressor), survival and balance are usually maintained within a steady, well-tuned range by activating various adaptive autoregulatory cascades [1,7]. These mechanisms, eventually leading to the desired ('re-balanced' or 'adapted') conditions, involve biological, psychological, and sociological corrective measures [75]. However – as mentioned before – in the case of chronic or prolonged stress, the 'original' state of balance may not be achievable anymore (i.e, a new balance needs to be found →dynamic balance), or a price in health conditions may have to be paid for the keeping of a 'given' balance. Allostasis refers to this dynamic 'wear and tear' that the organism experiences – especially within the circulatory system (see above).

Stress levels apparently are high and still growing in the 'western world' [1,23,76–78]. 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 (see above). '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 [4,23,70]. Thus, stress management, cognitive behavioral strategies, and the use of relaxation response techniques are of growing future importance [1,75].

Studying stress is not any easy undertaking. One problem has always been to uniformly define stress – a problem whose significance decreased over the last years [1]. Another problem is that the measurement of stress is difficult and complex [4]. Here, the recent creation of standardized measuring instruments and methods has turned out to be very helpful. Today, more and more accepted scales, scores, and experimental procedures are in use [1,4,79,80]. Still, stress is more or less regarded as an umbrella term or rubric, which encompasses a wide range of meanings into the effects of various psychosocial and environmental factors on physical and mental well-being [1,3–5,7]. Thus, describing the effects of stress upon health and/or disease processes makes it necessary to look at the details. For example, various forms of stress and stressors may be involved: There are physical, chemical, biological, psychological, and other stimuli existing that may all be capable of causing stress [5,7]. In the majority of cases described in the scientific

medical literature, mental/psychological, psychosocial, and physiological/physical stressors are distinguished and they are all of great clinical significance with regard to the relationship between stress and diseases. Moreover, each type of stressor obviously possesses slightly different capacities and may lead to a specific (patho)physiological outcome. Also, the amount of 'stress', the duration of its influence, and the perception or cognition of it (by an affected organism) are important considerations as well. In addition, subjective components further have to be taken into account [81]. Taken together, stress remains a highly significant constituent of cardiovascular disease processes. Thereby, as mentioned above, mental, behavioral, and psychosocial stressors need to be focused upon in (future) medical approaches dealing with stress and its association with cardiovascular diseases.

4. Conclusions

Stress has a major impact upon the circulatory system. Moreover, we find strong evidence for an importance of stress in disease processes related to the circulatory 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. Thereby, 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 allostatic stress response and lead to physiological, psychological, and behavioral adjustments. Nonetheless, 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.

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