Impact of Acute and Chronic Psychosocial Stress on Vascular Inflammation

Julia Hinterdobler,1,2 Heribert Schunkert,1,2 Thorsten Kessler,1,2 and Hendrik B. Sager1,2,i

Abstract

Significance: Atherosclerosis and its complications, such as acute coronary syndromes, are the leading causes of death worldwide. A wide range of inflammatory processes substantially contribute to the initiation and progression of cardiovascular disease (CVD). In addition, epidemiological studies strongly associate both chronic stress and acute psychosocial stress with the occurrence of CVDs.

Recent Advances: Extensive research during recent decades has not only identified major pathways in cardiovascular inflammation but also revealed a link between psychosocial factors and the immune system in the context of atherosclerosis. Both chronic and acute psychosocial stress drive systemic inflammation via neuroimmune interactions and promote atherosclerosis progression.

Critical Issues: The associations human epidemiological studies found between psychosocial stress and cardiovascular inflammation have been substantiated by additional experimental studies in mice and humans. However, we do not yet fully understand the mechanisms through which psychosocial stress drives cardiovascular inflammation; consequently, specific treatment, although urgently needed, is lacking.

Future Directions: Psychosocial factors are increasingly acknowledged as risk factors for CVD and are currently treated via behavioral interventions. Additional mechanistic insights might provide novel pharmacological treatment options to reduce stress-related morbidity and mortality. Antioxid. Redox Signal. 35, 1531–1550.

Keywords: psychosocial stress, vascular inflammation, risk factors for atherosclerosis, neuroimmune interactions

Introduction

Atherosclerosis and its complications, such as acute myocardial infarction (MI) and stroke, are the leading causes of death worldwide (136). A chronic disease of the vessel wall, atherosclerosis may ultimately lead to lumen narrowing, partial or complete obstruction, and reduced blood flow to downstream organs (91). Despite considerable progress in treating atherosclerosis, the prevalence of its complications almost doubled in the past three decades (132, 136).

Extensive research into the underlying mechanisms has identified that inflammatory—along with metabolic—components significantly contribute to the etiology of atherosclerosis (90). In this context, various studies have demonstrated that classical and nonclassical cardiovascular risk factors are involved in the pathology of atherosclerosis via the modulation of inflammatory processes (146). Psychosocial stress in particular is a cardiovascular risk factor that is strongly linked to cardiovascular disease (CVD) (75). The complex interplay of the nervous, hormonal, metabolic, and immune systems during stress responses harbors great potential for interventions in the ways psychosocial stress impacts cardiovascular inflammation. In this review, we discuss recent scientific discoveries and developments that investigate the effects of acute and chronic psychosocial stress on cardiovascular inflammation.
The Role of Inflammation in the Pathogenesis of Atherosclerosis

Atherosclerosis is the underlying pathology for a variety of cardiovascular complications and has long been considered a largely metabolic disease, caused by high plasma cholesterol levels and passive lipid accumulation inside the vessel wall (141). However, in recent decades, a great number of experimental, epidemiological, and lately also clinical studies have convincingly shown that inflammation plays an important role in the etiology of atherosclerosis (1, 133, 163, 176). This is reinforced by the fact that the incidence of CVD remains high, even after efficient lipid-lowering treatment became widely used (77, 134).

Various experimental studies have dissected the mechanisms that underlie atherosclerosis initiation and progression. As a first step, in a setting with high plasma low-density lipoprotein (LDL) levels and additional proinflammatory stimuli, endothelial dysfunction in atherosclerosis-prone regions with disturbed flow favors the uptake of cholesterol-loaded LDL. This promotes the upregulation of adhesion molecules on endothelial cells and the subsequent recruitment of inflammatory leukocytes (93). Among these recruited cells, specifically dedicated blood monocyte-derived macrophages clear both nonmodified and oxidized cholesterol particles and then become foam cells (89).

If initial clearance fails, inflammation persists and is further promoted by a wide range of leukocytes that release proinflammatory mediators such as interleukin (IL) 1β, tumor necrosis factor alpha (TNFα), and various other cytokines and chemokines (1, 190). To separate the plaque content from the lumen, smooth muscle cells (SMCs) are recruited from the tunica media to the tunica intima and produce an extracellular matrix that forms a fibrous cap and stabilizes the atheromatous plaque (161).

In general, lesions with a thick fibrous cap, low inflammatory cell activity, and small necrotic cores (accumulation of lipids and apoptotic macrophages inside the atheroma) are considered stable plaques (152). However, these plaques can transition into unstable/vulnerable plaques. Plaque inflammatory leukocytes can promote extracellular matrix degradation and SMC death, which can ultimately lead to plaque rupture or erosion with atherothrombosis that causes cardiovascular complications such as MI or stroke (92). Figure 1 illustrates the cellular processes that lead to the initiation and progression of atherosclerotic lesions.

The role of neutrophils in vascular inflammation

The innate immune system has long been considered the first line of defense against infections, as innate immune system effector cells, such as neutrophils, are rapidly recruited to sites of acute inflammation (150). However, innate immune cells are now widely understood as contributors to chronic sterile inflammation that occurs in atherosclerosis (27, 53). Neutrophils contribute to all stages of the disease: initiation, progression, and atherosclerotic lesion rupture (158).

As described above, lipid accumulation in the vessel wall causes endothelial dysfunction and immune cell recruitment. A growing body of evidence indicates that neutrophils are among the first cells recruited to early atherosclerotic lesions and contribute significantly to the subsequent recruitment of, for example, inflammatory monocytes (141, 158). High cholesterol levels affect not only the recruitment of neutrophils to atherosclerotic lesions but also their production in the bone marrow (150). Experimental studies could prove that hypercholesterolemia induces the proliferation of hematopoietic stem cells with a specific bias toward the myeloid (neutrophils, monocytes, and macrophages) lineage, resulting in blood neutrophilia and monocytosis (21, 29, 189).

Upon activation, neutrophils promote lesion progression through various mechanisms, including macrophage activation and the release of neutrophil extracellular traps, proinflammatory web-like structures consisting of DNA and proteins (45, 151). Ultimately, neutrophils contribute to plaque destabilization by releasing a wide spectrum of proinflammatory mediators and matrix-degrading enzymes (41, 101).

In line with their mechanistic function in the pathology of atherosclerosis, high levels of neutrophils in plasma and inside atherosclerotic lesions have been associated with an increased risk for cardiovascular events (63, 94). Indeed, a recent analysis of five large randomized clinical trials showed...

![FIG. 1. Cellular processes involved in atherosclerosis development.](Image)
that the neutrophil–lymphocyte ratio is a readily available inflammatory biomarker that predicts cardiovascular outcomes (2). Moreover, the neutrophil–lymphocyte ratio is modulated by canakinumab—a monoclonal antibody against proinflammatory IL-1β—and may therefore help guide anti-inflammatory treatment (2).

**The role of monocytes and macrophages in vascular inflammation**

Similar to neutrophils, inflammatory monocytes are recruited from blood to sites of inflammation (141). In early atherosclerosis, the inflamed endothelium expresses adhesion molecules and chemokines that promote monocyte recruitment (129). Activated endothelial cells raise the expression of intercellular adhesion molecule 1 (ICAM-1), vascular adhesion molecule 1 (VCAM-1) and selectins, among others, and secrete proinflammatory and leukocyte-attracting chemokines such as CC-chemokine ligand (CCL) 2 (60). As mentioned above, prior neutrophil recruitment is thought to further enhance inflammation and consequently promote monocyte recruitment.

Once inside the atherosclerotic lesion, most inflammatory monocytes differentiate into macrophages dedicated to ingesting cholesterol particles (107). The resulting lipid-loaded macrophages, termed foam cells, further fuel inflammation by, for example, secreting IL-1β (30). Of note, recent studies have demonstrated that macrophage accumulation in atherosclerosis is also driven by local proliferation and SMC transdifferentiation into macrophage-like cells (54, 92, 135).

In advanced atherosclerotic lesions, macrophages contribute to the development of unstable plaques as prolonged inflammation and disturbed efferocytosis (phagocytic clearance of apoptotic cells) promote macrophage death and necrotic core expansion (141). In addition, activated macrophages produce different kinds of proteinases, such as matrix metalloproteinases, that lead to fibrous cap breakdown (90, 107). Although macrophages are generally considered the main drivers of inflammation in atherosclerosis, accumulating evidence has demonstrated the heterogeneity of lesional macrophages, highlighted the importance of macrophages in atherosclerosis regression, and thus propagated a more nuanced view of the role of macrophages in atherosclerosis (7, 38, 170, 183).

As mentioned above, both hyperlipidemia and hyperglycemia contribute to high blood monocyte levels in atherosclerosis by increasing their production in the bone marrow. In addition, release from the bone marrow is promoted by circulating chemokines such as CCL2, CCL7, and CXC-chemokine ligand 1 (CXCL1) (28, 166). Similar to neutrophils, high numbers of inflammatory blood monocytes are strongly associated with CVD risk (8, 49).

**The role of lymphocytes in vascular inflammation**

While the role of innate immune cells in atherosclerosis is widely acknowledged, adaptive immune responses also contribute to all stages of atherosclerosis (56). Lymphocytes, namely T and B cells, are the cellular key players of the adaptive immune system with their reactions being highly specific and long-lasting (72). In atherosclerosis initiation, myeloid infiltration, as a response to LDL accumulation, is accompanied by the recruitment of both T and B cells (44). Some of these cells harbor a specific receptor to recognize the core component of LDL, apolipoprotein B, which has led to the notion that atherosclerosis is an inflammatory disease that involves autoimmune processes (184).

Although both T and B cells can be found in atherosclerotic plaques, T cells are more prominent throughout all stages of the disease and constitute approximately one-fourth of all plaque leukocytes (72, 184). T lymphocytes have been found to play controversial roles in atherosclerosis progression. Both the predominant cluster of differentiation (CD) 4+ effector T cells and the cytotoxic CD8+ T cells have been shown to be proatherogenic, while some CD4+ regulatory T cells exert highly atheroprotective functions (56, 194). T cell polarization inside the plaque occurs as a result of the interaction with antigen-presenting cells (184). Here, costimulatory molecules on the interacting cells and cytokines released by the antigen-presenting cell decide on the fate of the naive T cell, which results in the activation into either a pro- or antiatherogenic phenotype. Based on their polarization, mature T cells exert their pro- or anti-inflammatory functions by effecting other T cells, B cells, and tissue-resident cells (184).

Classically, B cells can be distinguished into B1 cells that are part of the innate immune system, and B2 cells that can differentiate into plasma cells and secrete immunoglobulin G (IgG) antibodies (184). Both types are found in atherosclerotic plaques although less frequent than T cells. While B1 cells are attributed to be exclusively atheroprotective, B2 cells seem to exert both pro- and antiatherogenic responses inside plaques (3, 17, 82).

Taken together, the adaptive immune system is involved in pro- and anti-inflammatory processes in atherosclerosis. Current models suggest a general transition from antiatherogenic to proatherogenic mechanisms during disease progression although it is still unclear if this switch is a cause or a consequence (184). Although research has discovered multiple roles of the adaptive immune system in CVD, experimental studies on the risk factors of atherosclerosis have predominantly focused on the roles of the innate system until now.

**Risk Factors of Atherosclerosis**

**Classical risk factors**

Certain risk factors and cardiovascular inflammation are connected throughout the pathophysiological processes leading to the development of atherosclerosis. Some classical risk factors are largely nonmodifiable. Being male, for example, is one such classical risk factor for CVD risk, and recent studies link at least part of its association with increased vascular inflammation in both animals and humans (97).

Aging is yet another independent risk factor for CVD; biological aging is associated with various inflammatory processes such as increased oxidative stress or more circulating inflammatory cytokines (167, 177). Clonal hematopoiesis, the process in which increasing numbers of white blood cells derive from one single clone due to specific somatic mutations in hematopoietic stem cells (64), has recently been identified as a pathophysiological mechanism that links aging with atherosclerosis (65). In atherosclerotic mice, clonal hematopoiesis resulted in a stronger activation of inflammatory pathways and thus accelerated atherosclerosis progression (43).
Hereditary components also contribute to CVD risk, and a multitude of genetic loci have been associated with CVD in large-cohort, genome-wide association studies (17a, 55). Interestingly, many of these loci are associated with genes that are part of inflammatory pathways (100). Additional to an inherent genetic component in atherosclerosis itself, certain classical risk factors such as high cholesterol levels, arterial hypertension, and diabetes also harbor some degree of genetic predisposition (15, 46a, 95).

As outlined above, high cholesterol levels contribute to the initiation and progression of atherosclerosis by acting as an important proinflammatory stimulus. Of note, obesity and unhealthy diet, which are also considered classical risk factors for atherosclerosis (35, 121, 178), strongly promote high cholesterol levels (19). Arterial hypertension is another classical risk factor and acts on the integrity of the endothelial cell layer (98). Ongoing research is intensively investigating the link between atherosclerosis and diabetes, with the general proinflammatory milieu in diabetic patients mostly likely being a major player in the development of atherosclerosis (70, 123).

Smoking is yet another classical risk factor for cardiovascular inflammation and promotes atherosclerosis via both local and systemic proinflammatory effects, for example, by circulating toxic compounds and increasing hematopoietic stem cell proliferation (111, 149, 154). Elevated hematopoiesis contributes to atherosclerosis progression by enhancing inflammatory leukocyte supply (117, 146).

Nonclassical risk factors

It has become increasingly clear that apart from classical risk factors, additional lifestyle factors and other coexisting pathologies influence CVD (Fig. 2). Many of these risk factors have only recently been identified and are thus referred to as nonclassical or nontraditional risk factors. Both viral and bacterial respiratory infections create a higher risk for MI not only during the acute infection but also in the postinfection phase (81, 114). Mechanistically, the acute increase in CVD events may be caused by elevated procoagulant activity, while long-term effects may exacerbate vascular inflammation and hence promote progression of atherosclerosis (140). Moreover, sterile inflammatory pathologies such as prior MI, stroke, or rheumatoid arthritis are linked to increased cardiovascular risk (31, 153). Mechanistically, both nonsterile and sterile inflammations partly exert their effects on cardiovascular inflammation by raising the proinflammatory leukocyte supply through increased production in the bone marrow (31, 32, 140), a mechanism shared by other nonclassical risk factors such as sedentary lifestyle and sleep deprivation (42, 102, 146).

Regular exercise reduces cardiovascular risk through metabolic and antihypertensive effects (86), and a recent study in mice demonstrated that physical activity (simulated by voluntary wheel running) also mitigates cardiovascular inflammation (42). The researchers showed that regular exercise reduces leptin levels and blood leukocyte numbers in mice and humans. In mice, low leptin levels induce bone marrow niche quiescence and retention factors, which limit proinflammatory leukocyte supply. As a consequence, cardiovascular inflammation and atherosclerotic plaque size are curtailed in exercising mice.

A similar picture is emerging with regard to poor sleep quality or sleep deprivation. While epidemiological studies had already linked insufficient sleep to higher cardiovascular risk (13, 162, 165), a recent study in mice uncovered a direct link between sleep and cardiovascular inflammation (102). Here again, the effect on atherosclerosis is mediated via increased proinflammatory leukocyte production in the bone marrow: sleep fragmentation causes the hypothalamus to generate less hypocretin, a circulating hormone that normally restricts myeloid cell production in the bone marrow.

Furthermore, the impact of air, light, and noise pollution on CVD health has long been underestimated (87, 112). While air pollution can directly act on inflammatory pathways, noise pollution likely increases CVD risk by modulating other lifestyle risk factors such as sleep and psychosocial stress (112). In detail, air pollution has been shown to influence a wide range of inflammatory processes, including blood leukocyte levels, leukocyte activation, circulating cytokine levels, and endothelial dysfunction (110, 113), which can all act on cardiovascular inflammation. Indeed, air pollution promoted cardiovascular inflammation in mouse models of atherosclerosis (105). Still, it is not yet clear if the effects of air pollution occur primarily through direct action of circulating fine particulate matter (2.5 μm in diameter and less), systemic neuroendocrine activation, and/or systemic inflammation caused by lung injury. In contrast, noise pollution presumably exerts indirect effects by activating physiological stress responses, which are further outlined below. Stress perception in this context may be both conscious (during daytime) and subconscious (during sleep) (112). Data from animal experiments indicate that noise pollution may act on cardiovascular inflammation via various mechanisms, including circulating cytokines, endothelial dysfunction, and neutrophil infiltration into atherosclerotic plaques (79, 109).

Over the past years, the term “exposome” has been established to summarize the cumulative effect of lifelong, conscious or unconscious, environmental risk factor exposure (23, 171).
International projects/consortia such as “ENNAH” (European Network on Noise and Health), “ELAPSE” (Effects of Low Level Air Pollution: A Study in Europe), and EXPOsOMICS seek to reveal how a combination of different environmental risk factors influence each other and how they affect human health including CVD (20, 39, 85, 173). The exposome concept includes air pollution and noise pollution, and also other factors such as chemical pollution, diet, sleep disruption, social isolation, and work stress (23).

Psychosocial stress, both chronic and acute, is yet another independent risk factor for atherosclerosis that in the past few years has been closely investigated in the context of cardiovascular inflammation. This review aims to summarize the latest advances in this specific research area.

Psychosocial stress in vascular inflammation and CVD. Stress has been defined as a constellation of events comprising a stimulus (stressor) that precipitates a reaction in the brain (stress perception) and activates physiologic fight-or-flight systems in the body (175). Psychosocial stressors can be classified as chronic or acute, based on exposure severity and duration (26). Determining strict discrimination criteria, however, is hardly possible, and parameters vary widely between scientific publications. In general, chronic stress is considered exposure to low or moderate and consistent or repetitive stressors such as caring responsibilities, job strain, job insecurity, social isolation, lack of social support, financial stress, marital unhappiness, long-term depression, hopelessness, loneliness, and type A or D personality (75). In contrast, acute stress refers to short-term (minutes up to days) and severe stressors such as anger outburst, emotional upset, anxiety, sadness, grief, bereavement, natural disasters, acts of war and terrorism, major sporting events, and work stress (high-pressure deadline at work) (106).

Naturally, acute stress can also transition into chronic stress, and perceived severity strongly depends on individual stress susceptibility (33). The distinction between distress (negative stress) and eustress (positive stress) is yet another way to classify psychosocial stressors (12), and individual perception plays an even bigger role in this differentiation. For simplicity, this review only summarizes current literature on the effects of distress on cardiovascular inflammation.

Exposure to an external stressor promotes the activation of a physiological stress response. From an evolutionary perspective, this reaction is essential to ensure survival in so-called fight-or-flight situations (116). To trigger a fight-or-flight response, the respective stimulus needs to be perceived by the brain, where subsequent neuronal networks activate three major pathways in the body (Fig. 3) (83).

One pathway is the hypothalamic/pituitary/adrenal (HPA) axis. Here, the hypothalamus releases the corticotropin releasing hormone (CRH), which leads the pituitary gland to secrete the adrenocorticotropic hormone (ACTH) into the bloodstream. In the adrenal cortex, ACTH leads to systemic release of glucocorticoid hormones such as cortisol. The other two pathways exert their functions via the sympathetic nervous system (SNS). The sympatho-adrenomedullary (SAM) axis involves sympathetic innervation of the adrenal medulla, which releases systemic catecholamines (epinephrine and norepinephrine) in response to stimulation. SNS activation through stress perception can also directly activate dedicated end organs via sympathetic nerve endings locally releasing norepinephrine.

The purpose of this physiological response is to prepare the body to react to threats and endure potential injuries (116). Body functions necessary for bolstering survival, such as

**FIG. 3. Stress perception activates distinct physiological stress responses.** Once the brain perceives an external stressor, the body attempts to restore homeostasis by activating systemic stress responses. The HPA axis results in the release of glucocorticoids from the adrenal cortex, while sympathetic nervous system activation causes systemic (via the adrenal medulla) and local (via sympathetic nerve endings) release of catecholamines. Altogether, these act on respective end organs to prepare the body for a fight-or-flight situation. ACTH, adrenocorticotropic hormone; HPA, hypothalamus/ pituitary/adrenal.
blood perfusion of skeletal muscles, energy mobilization, ventilation of the lungs and heart rate, are increased while supply to, for example, the digestive and reproductive systems, is curtailed (125).

Neuroimmunology is a rapidly developing research area studying interactions between the nervous and immune systems. Both systems are responsible for maintaining homeostasis despite adverse environmental stimuli, and it is widely acknowledged that they operate together to exert appropriate adaptations to potential threats (142). Stress situations promote neuroimmune interactions, but they also occur constantly under steady-state conditions during which they control, for example, circadian leukocyte trafficking (62, 145). In this context, the SNS seems to play a specific pivotal role in rhythmic leukocyte recruitment (66).

Interactions between the nervous and immune systems are bidirectional, but signaling from the nervous to the immune system seems to be especially critical with regard to the negative effects of stress on human health (47). Despite contributing to a low-grade inflammatory milieu in the body, psychosocial stress is thought to compromise the body’s ability to mount a proper immune reaction in response to infections. Accordingly, stimulating adrenergic signaling over 7 days resulted in reduced host resistance to viral infections in a study investigating how adrenergic signaling affects the innate immune response in a mouse model (180). Furthermore, a recent publication showed that acute stress leads the adipose tissue to release more IL-6, which is needed to ensure glucose supply in a fight-or-flight situation but would have detrimental effects regarding concomitant bacterial infection (128).

Other studies, by contrast, suggest that acute psychosocial stress has a short-term immune-enhancing effect, for example, by mobilizing immune cells from the bone marrow or redistributing leukocytes to sites of inflammation (25, 175). Overall, the effect of psychosocial stress on the immune system may depend on the combination of the stress duration and the specific type of environmental challenge in which it occurs (62).

In the context of vascular inflammation and atherosclerosis, we have just begun to explore neuroimmune interactions. Nervous system activity is critical to the regulation of stem cell proliferation in hematopoietic organs and the release of mature leukocytes (18, 71, 124). Of note, sympathetic neuronal activation promotes the proliferation of splenic hematopoietic progenitor cells with a concomitant myeloid cell bias (169). Recent publications have also demonstrated that the nervous system directly affects immune processes in the vessel wall (18). Depleting the SNS, for instance, reversed adhesion molecule upregulation by aortic endothelial cells in a mouse model of MI (139).

It is only logical that neuroimmune interactions are also involved in linking psychosocial stress and cardiovascular inflammation. Experimental studies on psychosocial stress have identified three major areas with potential influence on CVD. First, the physiological stress response strongly influences hemodynamic parameters such as cardiac output, blood pressure, and heart rate (138). Second, activation of the different stress axes can also affect hemostatic parameters such as platelet activation (67, 78). In the following sections, this review seeks to summarize experimental evidence for the third area: the inflammatory contribution of psychosocial stress to CVD risk (Fig. 4).

**Chronic psychosocial stress.** Results from the INTERHEART study provide a large body of evidence for the association between psychosocial stress and CVD (188). This large case/control study in 52 countries quantified the relationships between major cardiovascular risk factors, including long-term psychosocial factors, and the occurrence of MI. In this study, the prevalence of psychosocial stress is associated with an odds ratio of 2.67 for MI. In contrast to the INTERHEART study, which analyzed psychosocial stressors in a summarized category, other large-scale studies investigated the links between CVD and isolated long-term psychosocial stressors, such as job strain, childhood abuse, and social isolation. Meta-analyses of corresponding studies reported odds ratios of up to 1.5 for associations between psychosocial stressors and cardiovascular endpoints (75, 174). Results from the Whitehall II study highlighted that perceiving stress as negative stress is important for the adverse effects of psychosocial stress on cardiovascular health (115).

In epidemiological studies, effect sizes for the relationship between psychosocial stress and CVD have been statistically corrected for other variables. However, chronic stress may exacerbate the risk for CVD even further by promoting lifestyle factors that are themselves risk factors for CVD such as smoking, sedentary lifestyle, unhealthy diet, or disturbed sleep (75, 122).

Observational studies not only link chronic psychosocial stress to CVD in general but also suggest a contribution by inflammatory processes. In this regard, higher levels of clinical proinflammatory risk markers such as TNFα, IL-6, C-reactive protein (CRP), and soluble adhesion molecules were found in plasma samples from individuals with a high burden of chronic stress (68, 73, 83). Similarly, a study in medical residents on an intensive care unit found increased levels of blood inflammatory leukocytes when residents were on duty compared with when they were off duty (57). Using state-of-the-art imaging techniques, researchers also showed an association between resting amygdala activity—the amygdala is part of the brain’s limbic system and processes emotional responses—reflecting the degree of perceived stress and the risk for cardiovascular events (164). On top of that, amygdala activity was directly connected with bone marrow activity, reflecting hematopoiesis, and arterial inflammation (69, 164). Further evidence for the influence of chronic psychosocial stress on cardiovascular inflammation in humans is available from intervention trials, which consistently show reduced inflammatory activation in response to immune challenges following stress-reducing interventions (144).

Findings in animal studies may reveal the mechanistic processes underlying the adverse effect of chronic psychosocial stress on vascular inflammation; hence, data from animal studies are inevitable. Attaining useful accurate results requires proper experimental models for both atherosclerosis and the simulation of chronic psychosocial stress. Classically, atherosclerosis experiments are done in animals with specific genetic knockouts that lead to hypercholesteremia and consequently result in the development of lesions similar to human atherosclerosis. Due to the need for genetic modification and their advantageously short generation times, mouse models are predominantly used (46). Most such mouse models harbor a knockout in either the apolipoprotein E
FIG. 4. The role of psychosocial stress in cardiovascular inflammation. Both chronic and acute psychosocial stress act as major players in the inflammatory cascades that lead to the initiation and progression of atherosclerosis. This figure summarizes current evidence regarding how chronic and acute psychosocial stress affect leukocyte distribution, systemic proinflammatory signaling, leukocyte and endothelial cell activation, and inflammatory processes inside the vessel wall. Oxidative stress and inflammation are key drivers of atherosclerotic plaque development. Evidence from human experimental data, = evidence from animal experimental data. PBMC, peripheral blood mononuclear cell; SMC, smooth muscle cell.
(ApoE) gene or the LDL gene, and both varieties develop hyperlipidemia and vascular inflammation when fed a cholesterol-enriched diet. Models for simulating chronic psychosocial stress in animals are numerous and were mostly established by behavioral neuroscience studies (120, 147). In chronic stress models, animals are exposed to a single mild stressor or a combination of mild stressors repetitively over a longer time period (83). Social isolation and defeat, disrupted circadian rhythm, and environmental noise are just a few examples of the wide range of unpleasant situations that are used as stressors in animal studies (Fig. 5).

As described above, chronic psychosocial stress is associated with higher levels of inflammatory markers in humans. This has been confirmed by animal studies that demonstrated the presence of systemic low-grade inflammation as a result of chronic psychosocial stress (6, 104). Likewise, chronic psychosocial stress increased circulating inflammatory leukocyte levels in an animal model of chronic stress (57). This increase is reportedly caused by the SNS overactivity in the bone marrow, subsequently leading to increased hematopoietic stem cell proliferation and release of neutrophils and inflammatory monocytes into the blood stream. Leukocytes not only undergo quantitative changes but also alter their phenotypes qualitatively in response to chronic stress. A study using repeated social defeat demonstrated that circulating leukocytes acquire a proinflammatory gene signature in response to chronic stress, hand in hand with a bias toward myelopoiesis in bone marrow hematopoiesis (126).

Another phenomenon that applies in chronic psychosocial stress is the concept of trained immunity. It describes the observation that not only the adaptive immune system but also the innate immune system develops immunological memory to previous challenges (119). Immunological memory is conveyed by both epigenetic and metabolic reprogramming in innate immune cells (37). In first studies, trained immunity was shown to play a role in the response to immune challenges after initial priming with stress hormones. Monocytes that were exposed to high levels of norepinephrine and subsequently differentiated to macrophages in vitro mounted a heightened proinflammatory response after restimulation with lipopolysaccharide (LPS) (58). Accordingly, a murine macrophage-like cell line secreted higher amounts of IL-6 and TNFα when primed with glucocorticoids before LPS stimulation (156).

Inflammation in chronic stress situations affects not only leukocytes but also their counterparts in the process of leukocyte recruitment: endothelial cells. It is well known that circulating cytokines activate endothelial cells (11, 96) and, as outlined above, chronic psychosocial stress strongly contributes to systemic low-grade inflammation. Mechanistically, most cytokines upregulate adhesion molecule expression on endothelial cells, a change that subsequently leads to more leukocyte recruitment in the underlying tissue (24, 127). Furthermore, systemic activation of the renin/angiotensin/aldosterone system during chronic psychosocial stress may contribute to endothelial dysfunction and cardiovascular inflammation (148). The renin/angiotensin/aldosterone system involves a multitude of players, such as angiotensin II, that act jointly to regulate fluid balance and blood pressure. Angiotensin II, similar to systemic proinflammatory cytokines, induces increased expression of adhesion molecules, chemokines, and cytokines by endothelial cells (50, 99). Beyond that, endothelial cells express receptors for all major stress hormones (139, 193) and may thus be activated directly by elevated circulating hormone levels.

Taken together, the abovementioned experimental studies demonstrate the proinflammatory potential of psychosocial stress. Indeed, various experimental evidences demonstrate accelerated atherosclerosis development in chronic stress models (83). Reports about changes in lesion size are

| Chronic stress | Experimental procedure |
|----------------|-----------------------|
| Stressors      |                       |
| social defeat  |                       |
| cage tilt      |                       |
| isolation/crowding |               |
| damp bedding   |                       |
| removal of bedding |                   |
| overnight illumination |         |
| rapid light-dark changes |       |
| cold exposure  |                       |
| environmental noise |                |
| ...            |                       |
| Duration: weeks to months |       |

| Acute stress   | Experimental procedure |
|----------------|-----------------------|
| Stressors      |                       |
| restraint stress|                      |
| pain stress models |                |
| predator-prey stress |            |
| social defeat   |                       |
| water immersion stress |          |
| ...            |                       |
| Duration: hours to days |       |

FIG. 5. Experimental mouse models to induce psychosocial stress. In experimental models for chronic stress, animals are exposed to a single mild stressor or a combination of mild stressors repetitively for weeks up to months. By contrast, experimental models for acute stress use severe stressors over a short period of time (hours to days). s, Stress exposure.
inconsistent (9, 10), however, researchers agree that chronic psychosocial stress changes the plaque phenotype toward a more unstable lesion, which includes more plaque inflammatory leukocytes (57, 191, 192), fewer plaque SMCs (191, 192), higher expression levels of matrix metalloproteinases (57, 192) and, consequently, reduced plaque collagen content (192) and a thinner fibrous cap (118, 191). Of note, standard murine models of atherosclerosis acquire features of unstable plaques but lack plaque rupture or erosion, which frequently occur as the ultimate consequences of atherosclerosis in humans. Using additional gene knockouts or surgical techniques, researchers were recently able to mimic these conditions in mice (152). In an ApoE(−/−)Fbn1(C1039G+/−) mouse model that develops exacerbated atherosclerosis and spontaneous plaque ruptures, chronic psychosocial stress indeed increased plaque instability and the incidence of MI (137).

Overall, evidence for the proinflammatory effect of chronic psychosocial stress has expanded greatly in recent years, with general consensus regarding its capacity to promote vascular inflammation and atherosclerosis progression. Mechanistically, this is one aspect of the links between chronic stress and higher CVD risk in affected patients.

Acute psychosocial stress. In contrast to chronic stress, which increases the risk for CVD gradually over time, acute stress is a major trigger for acute cardiovascular events in people with manifest atherosclerosis (106, 159). In recent decades, natural catastrophes, such as earthquakes, or other population-level disasters, such as war and terror attacks, have been associated with higher incidences of acute cardiovascular events (4, 103). Following an earthquake in the Los Angeles area in 1994, for example, the occurrence of sudden deaths from cardiac causes rose around fivefold compared with control periods before the earthquake and in the preceding years (88). However, even more moderate stressors such as major sporting events have been linked to cardiovascular complications (181).

The notion that acute stress can trigger acute cardiac events is further supported by a great number of individual-level studies (34). A recent meta-analysis calculated a 4.74 higher risk for MI or acute coronary syndrome within 2 h following anger, for example (108). This was confirmed in a sub-analysis of the INTERHEART study that reported a 2.44 higher odds ratio for acute MI associated with emotional upset (155).

Observational studies show that, similar to chronic psychosocial stress, acute stress is linked to inflammation (83). In a study investigating the effect of a stressful sporting event, classical inflammatory mediators such as soluble vascular adhesion molecule 1 (sVCAM-1), monocyte chemoattractant protein 1 (MCP-1), and TNFα were up to 65% higher in subjects experiencing a stress-associated ACS event compared with control patients (182). Likewise, patients suffering from Takotsubo cardiomyopathy, an acute stress-associated type of nonischemic cardiomyopathy, displayed higher plasma levels of inflammatory cytokines (143).

Experimental human data provided further evidence that acute stress produces proinflammatory responses in the body. Psychological research experiments involving public speaking tests, arithmetic tasks, or a combination of different stressors were the first simulations of acute psychosocial stress in humans. In a study using oral presentations as a stress model in physicians, participants had increased plasma levels of IL-1β and ICAM-1 (59). A classical adhesion molecule on endothelial cells, ICAM-1 mediates leukocyte recruitment and is upregulated under inflammatory conditions. Its soluble form is also found in plasma and serves as a biomarker for atherosclerotic plaque burden (5). In another study using a standardized public speaking stressor, greater peripheral vasoconstriction with mental stress was associated with a higher risk of adverse cardiovascular outcomes in participants with preexisting CVD (74). Of note, the researchers observed an association between greater peripheral vasoconstriction and circulating norepinephrine and IL-6 plasma levels. An interesting recent study showed that increased mental stress-induced myocardial ischemia in young women post-MI is accompanied by more microvascular dysfunction than in their male counterparts (168). Importantly, microvascular dysfunction has been linked to systemic inflammation by several studies (36, 130, 131). In a randomized-controlled trial using a sequential series of psychosocial stressors, acute stress raised the plasma levels of IL-6 and IL-1β (80). In addition, this rise in inflammatory cytokines was accompanied by a proinflammatory gene expression profile in blood leukocytes, an effect likely mediated by the transcription factor nuclear factor kappa B (NF-κB). Another recent randomized-controlled trial study reported increased IL-6 levels in a CO2 stress test that simulated acute stress in humans (76). This test was previously established as a more severe experimental model for panic disorders (172).

While chronic psychosocial stress consistently elevated circulating leukocytes and inflammatory subtypes in human and animal studies (57), things are less clear in acute psychosocial stress. On the one hand, for example, performing a speech task resulted in general leukocytosis and higher levels of all major leukocyte subtypes (48). On the other hand, a study that used skydiving as a model for acute psychosocial stress reported increased neutrophils and natural killer cells, while lymphocyte and monocyte levels decreased immediately before and after the jump compared with baseline (14). These differences may be explained by the different kinetics of leukocyte populations and varied stress stimuli used in studies. The picture becomes even more complex as the acute stress response redistributes leukocyte subsets between hematopoietic organs, blood, and various tissues (62).

As with chronic psychosocial stress, detailed mechanistic data on how acute stress exacerbates disease come from animal and cell culture experiments. To simulate acute stress, studies use severe stressors including restraint stress (128, 175, 187), in which animals are immobilized for minutes up to several hours, pain stress models such as eye bleeding (128) or social defeat (Fig. 5) (128, 187).

Similar to human experimental data, animal studies demonstrate that an acute stress procedure impacts circulating blood leukocyte levels. However, in contrast to human data, individual studies using animal models have more aligned outcomes, mostly likely due to better standardization in animal experiments. Such studies consistently report a decline in circulating monocyte and lymphocyte levels after at least 30 min of acute stress, while neutrophil levels are unchanged or even increase (61, 175, 186, 187). Initially, leukocytes are massively mobilized from reservoirs, but blood numbers rapidly decline as leukocytes traffic to sites of inflammation and immune activation (25).
This redistribution also requires endothelial cell compartment activation in the respective tissue. However, although researchers show that psychosocial stress robustly affects the endothelium in the context of hemodynamic processes (40, 125, 168), very little is known about the inflammatory consequences. Our group recently proved that locally released norepinephrine activates endothelial cells under acute stress exposure (61). As a consequence, activated endothelial cells increasingly express cell adhesion molecules and release chemokines, which result in enhanced blood inflammatory leukocyte recruitment to susceptible tissues, especially atherosclerotic plaques. In addition, similar to chronic stress situations, the increased circulating chemokines likely further activate the endothelium in an already proinflammatory setting due to preexisting atherosclerosis. Cardiovascular events such as MI can themselves be regarded as acute psychosocial stress. Accordingly, prior MI accelerated atherosclerosis in an animal model (31).

As plaque rupture does not often occur in classical, atherosclerotic animal models, research previously focused primarily on how acute psychosocial stress impacted plaque phenotypes, cardiac function, and hemostatic processes (83). Researchers showed that acute psychosocial stress leads to plaque destabilization (84) and ultimately MI in hypercholesterolemic ApoE−/− mice (16). Indeed, our group recently showed that acute mental stress affects plaque stability in a mouse plaque rupture model. Mechanistically, increased plaque rupture incidence was accompanied by higher intimal myeloid cell numbers and decreased SMC and collagen content (61).

As mentioned above, human data suggest an association between acute stress and systemic inflammation, and significantly accumulating recent evidence also links acute psychosocial stress to increased vascular inflammation.

**Clinical Outlook and Future Perspectives**

In summary, society faces a high burden of psychosocial stress-related CVD cases. Although lipid-lowering therapy has greatly reduced CVD risk in recent decades, the residual risk remains substantial, and psychosocial factors strongly contribute to this condition (188). Indeed, both chronic stress and acute stress are associated with CVD risk, even in patients receiving state-of-the-art treatment (181).

Successful intervention in this area first requires the identification of people at risk (75). These individuals have both preexisting atherosclerosis and either a high burden of chronic stress or a behavior type that is especially susceptible

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**FIG. 6. Therapeutic options of psychosocial stress.** People at high risk of stress-induced CVD can potentially be treated at three different levels alongside the physiological stress response cascade. Especially in chronic stress, the stimulus itself can be removed/reduced. On the stress perception level, behavioral intervention strategies may increase resilience to stressful events or strengthen coping strategies. In addition, external support strategies by the individual environment can be established. Pharmacological interventions to modify the stress response itself can target inflammatory processes (as outlined in this review), and also hemodynamics and hemostasis. However, up to now, pharmacological interventions in the context of psychosocial stress and CVD are not routinely used in clinical practice. CVD, cardiovascular disease.
to acute stress. Biomarkers such as hormone levels and platelet aggregates at baseline or after stress challenges might help identify people carrying this type of risk (160).

Behavioral interventions might be best suited to reducing chronic stress. Such interventions include both population-based and targeted approaches; the latter is mostly used in secondary prevention (75). It is worth noting that the occurrence of acute stress strongly depends on external factors and cannot necessarily be reduced by behavioral interventions. Still, possible behavioral intervention strategies may target coping mechanisms in particularly stress-susceptible individuals (52, 185) or provide external support strategies in both chronic stress and acute stress. Potential resilience and coping mechanisms that might be entwined include mindfulness, meditation, cognitive behavioral therapy, and physical activity (157, 179). Up to now, however, systematic analysis of such interventions in controlled trials is lacking (75).

Along with behavioral interventions, susceptible individuals may need pharmacological treatment (Fig. 6). However, there are currently no drugs that reduce chronic or acute stress-associated inflammation, partly due to a paucity of mechanistic understanding. In chronic stress, the specific effects of stress hormones on endothelial cells and intraplaque processes particularly need to be addressed. For the acute stress response, different questions remain unanswered. It is still largely unknown whether acute mental stress influences other vascular cell types apart from endothelial cells. Furthermore, the effects of acute mental stress on circulating leukocytes warrant further investigation. Most of all, tailoring pharmacological interventions requires a deeper knowledge of stress-specific mechanistic effects on inflammation. The majority of circulating cytokines are upregulated during psychosocial stress, for example, IL-1β and IL-6, are also crucial players in the immune response to nonsterile infections. Thus, targeting these cytokines in stress therapy may lead to off-target effects and increase, for instance, the incidence of fatal infections.

All in all, psychosocial factors are increasingly acknowledged as key to the primary and secondary prevention of CVD. Going forward, additional mechanistic studies are needed to provide better tools for behavioral and pharmacological treatment options.

Authors' Contributions

J.H. and H.B.S. conceptualized the content, reviewed the literature, wrote the article, and generated figures. H.S. and T.K. discussed and edited the review.

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Address correspondence to:
Prof. Hendrik B. Sager
Department of Cardiology
German Heart Centre Munich
Technical University Munich
Lazaretstr. 36
Munich, 80636
Germany

E-mail: hendrik.sager@tum.de

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Abbreviations Used

- ACTH = adrenocorticotropic hormone
- ApoE = apolipoprotein E
- CCL = CC-chemokine ligand
- CD = cluster of differentiation
- CVD = cardiovascular disease
- DFG = Deutsche Forschungsgemeinschaft
- HPA = hypothalamus/pituitary/adrenal
- ICAM-1 = intercellular adhesion molecule 1
- IL = interleukin
- LDL = low-density lipoprotein
- LPS = lipopolysaccharide
- MI = myocardial infarction
- PBMC = peripheral blood mononuclear cell
- RA = rheumatoid arthritis
- SMC = smooth muscle cell
- SNS = sympathetic nervous system
- TNFα = tumor necrosis factor alpha