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Psychological Stress, Inflammation, and Coronary Heart Disease

Petra H. Wirtz[1] **· Roland von Känel**[2]

Abstract
Purpose of Review In this review, we summarize evidence on the risk factor psychological stress in the context of coronary heart disease (CHD) in humans and explore the role of inflammation as a potential underlying mechanism.
Recent Findings While chronic stress increases the risk of incident CHD and poor cardiovascular prognosis, acute emotional stress can trigger acute CHD events in vulnerable patients. Evidence supporting a potential role for inflammation as a promising biological mechanism comes from population-based studies showing associations between chronic stress and increased inflammation. Similarly, experimental studies demonstrate acute stress-induced increases in inflammatory markers and suggest modulatory potential for pharmacological and biobehavioral interventions. So far, studies investigating patients with cardiovascular disease are few and the full sequence of events from stress to inflammation to CHD remains to be established.
Summary Psychological stress is an independent CHD risk factor associated with increased inflammation. Although promising, causality needs to be further explored.

Keywords Psychosocial stress · Inflammation · Coronary heart disease · Cytokines · C-reactive protein · Interleukin · Inflammatory stress response · Intervention · Job burnout · Exhaustion

Introduction

Coronary heart disease (CHD) with atherosclerosis as the underlying predominantly inflammatory process remains to be a major cause of morbidity and mortality worldwide [1–3]. In this review, we focus on the risk factors psychological stress and inflammation in the context of CHD in humans. In terms of psychological stress, we distinguish between acute stress and major chronic stressors such as work stress, dementia caregiving, or social isolation and resulting exhaustion or burnout. To address pathophysiological mechanisms linking psychological stress with CHD in humans, the accumulated research reviewed here summarizes findings on acute stress reactivity of inflammatory measures in healthy participants and CHD patients, as well as on chronic stress and chronic low-grade inflammation. We selectively review pharmacological and psycho-behavioral intervention studies aimed at reducing inflammatory stress reactivity or basal inflammation and identify important gaps of knowledge for future research.

CHD and Inflammation

Coronary heart disease (CHD) is the most common form of disease affecting the heart and considered a leading public health burden in industrialized countries [1–3]. According to 2016 epidemiological update, it accounts for 20% of deaths in Europe [2]. CHD is a slowly developing chronic disease that mainly results from a progressive narrowing of blood vessels

✉ Petra H. Wirtz
petra.wirtz@uni-konstanz.de

[1] Biological Work and Health Psychology, Department of Psychology, University of Konstanz, Universitaetsstrasse 10, 78457 Constance Baden-Wuerttemberg, Germany

[2] Department of Neurology, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland

that supply the myocardium with oxygenated blood, giving rise to ischemia at times of increased oxygen demands. Clinical endpoints include an inadequate ejection of blood from the heart (heart failure), irregular cardiac rhythms (arrhythmias), or acute coronary syndromes (ACSs) such as myocardial infarctions and unstable angina, which are often followed by sudden cardiac death [4]. The main cause of CHD is atherosclerosis, a progressive chronic inflammatory process of arterial wall thickening. Atherosclerosis promotes retention of cholesterol transported by low-density lipoproteins (LDLs) in the artery wall. The subsequent primarily oxidative modification of vascular LDL particles is considered the key process that promotes an inflammatory response to this endothelial injury. Recruited macrophages ingest modified LDL particles, develop into lipid-laden foam cells, and further stimulate local inflammation, e.g., by secreting inflammatory mediators such as pro-inflammatory cytokines [5, 6, 7•]. Early atherosclerotic lesions termed "fatty streaks" consist of subendothelial lipid depositions, cholesterol-loaded macrophage foam cells, and T cells. With disease progression, interactions between immune and resident vessel wall cells eventually result in the formation of an atherosclerotic plaque. Atherosclerotic plaques are key features of more complex atherosclerotic lesions and have a necrotic core that consists of apoptotic and necrotic cells, cell debris, and cholesterol crystals. The necrotic core is covered by a fibrous cap, with "shoulder" regions infiltrated by activated T cells, macrophages, and mast cells producing pro-inflammatory mediators and enzymes. Plaque growth can narrow the lumen of an artery and thus induce stenosis that can contribute to ischemia in the surrounding tissue. Plaque rupture leads to exposure of its thrombogenic content to the blood triggering a thrombotic response that can either obliterate the lumen immediately or detach to become an embolus that can induce ischemia distal to its point of origin. Life-threatening consequences of these processes are ACS and stroke [7•].

Risk Factors for CHD: Inflammation as an Intermediate Biological Risk Factor

Different categories of risk factors have been identified to independently increase the risk of developing CHD. *Classical* or *conventional risk factors* are older age, male gender, smoking, hypertension, hyperlipidemia, insulin resistance and diabetes, physical inactivity, and obesity [8]. Comparably more novel CHD risk factors comprise *intermediate biological risk factors* such as markers of inflammation and the coagulation-related parameters fibrinogen and D-dimer [8]. While the inflammatory nature of atherosclerosis predisposes local inflammation to relate to the stage of atherosclerotic lesion progression, elevated circulating levels of inflammatory markers are indicative of low-grade systemic inflammation; meanwhile, the latter have reliably been identified as independent CHD risk factors in large-scale prospective cohort studies (for review (9)). Primary or upstream pro-inflammatory cytokines such as Interleukin (IL)-1β or tumor necrosis factor (TNF)-α are secreted in all phases of atherosclerotic lesion progression and induce expression of "messenger" or secondary signaling cytokines such as IL-6 [8]. Indeed, circulating levels of the inflammatory cytokines TNF-α and IL-6 independently predict the risk of CHD and/or coronary events [9, 10]. Although abundant experimental and pathologic data also implicate IL-1β in atherogenesis, there is a lack of epidemiologic studies relating circulating IL-1β to cardiovascular risk supposedly because IL-1β levels are not reliably measurable in plasma samples [9]. IL-6 can travel from local sites of inflammation to the liver where it stimulates protein synthesis characteristic of the acute phase response. The primarily in the liver secreted acute phase protein C-reactive protein (CRP) is a downstream marker of inflammation that has emerged as a major risk factor for CHD [9, 11]. Finally, *psychological factors* such as psychological stress represent a further category of independent CHD risk factors that based on their duration can be classified as acute, episodic, or chronic psychological risk factors [8, 12]. Major categories of psychological risk factors refer to acute emotional/psychological triggers of ACS and stroke (e.g., outbursts of anger), chronic psychosocial stressors (e.g., job strain and family stress), personality traits (e.g., anger-proneness/hostility), and negative effect like anxiety and depression [13]. There is increasing evidence linking psychological risk factors and CHD through inflammatory processes, including major depression and acute and chronic psychological stressors [14]. In the following, we will focus on psychological stress and inflammation in the context of CHD in humans (see Fig. 1).

Psychological Stress as an Independent Psychological Risk Factor for CHD

What Is Stress?

The concept of stress, as first termed and described in the medical literature by Hans Selye, was characterized by nonspecifity of the (neuroendocrine) stress response of the body to any noxious agent, or stimulus, respectively [15]. Later conceptualizations of stress distinguished between "stressors" as stress reactivity evoking external and internal stimuli and a person's response to a stressor referred to as "stress reaction" or "stress response." Stress reactivity comprises different levels in terms of cognitive, emotional, behavioral, and physiological responses. According to the widely accepted transactional model of stress, an individual's cognitive appraisal of a situation determines whether the situation is perceived as a stressor that consequently evokes a stress response [16]. More precisely, the "primary appraisal" of a situation as irrelevant, challenging, or threatening together with the "secondary appraisal" assessing the

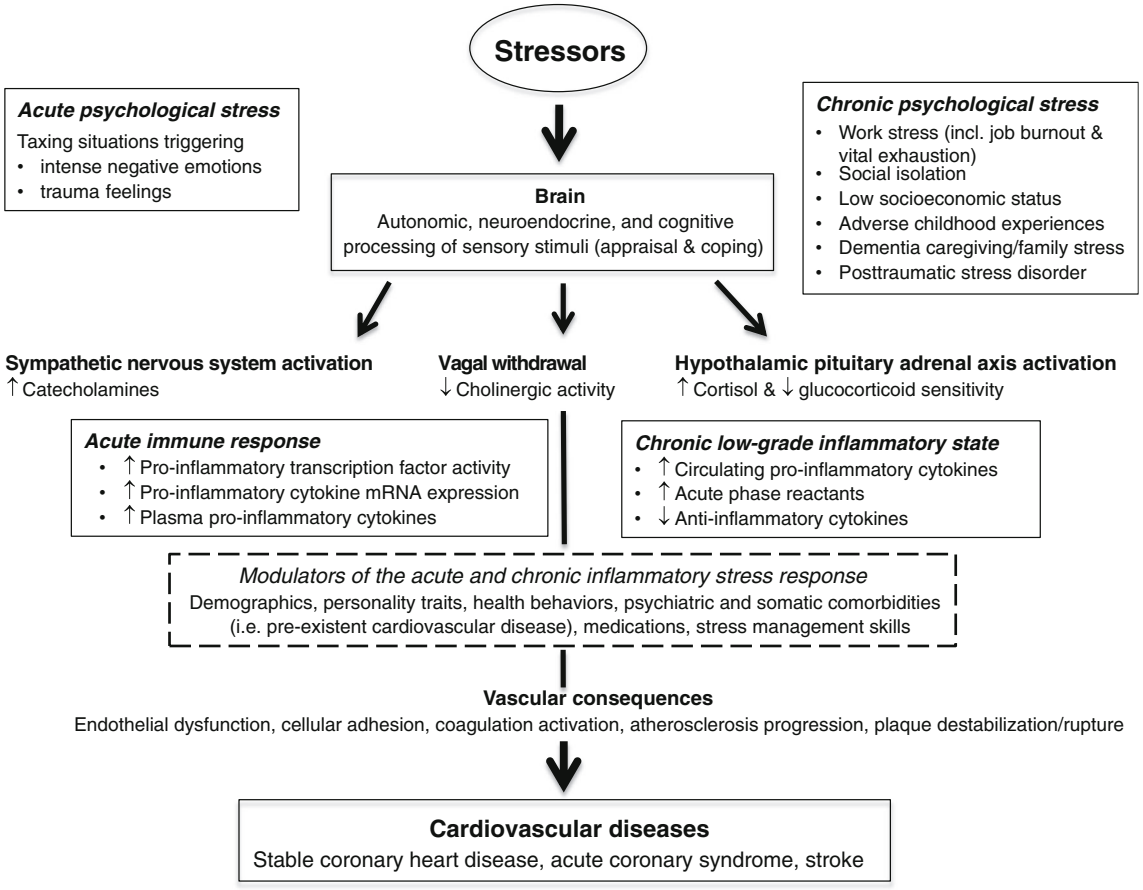

Fig. 1 Schematic overview of the most prominent inflammatory effects of the stress response thought to play a role in cardiovascular disease. Depending on cortical information processing and appraised coping resources, taxing situations become "psychological stressors," which initiate autonomic- and neuroendocrine-driven inflammatory changes. A multitude of demographic and health-related factors may modulate both the acute and chronic inflammatory response to stress with its vascular consequences and the ultimate clinical manifestation of cardiovascular diseases. ↑ increased, ↓ decreased

individual's perceived coping options, i.e., competences to control and manage the situation, result in the individual's interpretation of the situation as stressful or not. A situation is perceived as stressful if interpreted as challenging or threatening and at the same time exceeding the individual's perceived coping resources [16]. It is important to note that stress perception and induced stress responses can largely differ between individuals depending on a variety of modulating trait and state influences.

Stress research generally differentiates between acute and chronic stress, although there is no clear time point or interval to separate acute from chronic [17]. While acute stress refers to short-term stress, chronic stress is considered a cumulative result of repeated or prolonged stress exposure. Work stress, social isolation/loneliness, caregiving to a demented spouse, and low economic status, but also daily hassles, represent manifestations of chronic psychosocial stressors [17, 18], whereas exhaustion or burnout are conceptualized as consequences of exposure to chronic stressors [19–21].

Chronic Stress and CHD Incidence

Data from epidemiologic prospective studies show that chronic stress is associated with an excess risk of CHD incidence supporting the status of stress as a causal CHD risk factor [22•]. *Stress at work* is among the most commonly studied chronic adulthood stressors. A meta-analysis with totally 197,473 participants from 13 European cohort studies showed job strain resulting from high job demands and low job control (versus no job strain) to be associated with a significantly increased risk of incident CHD after a mean follow-up of 7.5 years independently of age and sex (HR 1.23, 95% CI 1.10–1.37) [23•]. The population attributable risk for job strain in that study was 3.4% [23•]. Also, working long hours (≥ 55 h per week) compared with standard hours (35–40 h per week) were independent of age, sex, and socioeconomic status associated with a significantly increased risk of incident CRH in a meta-analysis comprising data from more than 600,000 participants over a mean follow-up of 8.5 years (RR 1.13,

95% CI 1.02–1.26) [24]. Finally, the age-adjusted relative risk of high versus low perceived job insecurity for incident CHD was 1.32 (95% CI 1.09–1.59) in a meta-analysis comprising almost 175,000 participants after a mean follow-up of 9.7 years [25]. Another important chronic stressor in adulthood is *social isolation*. The pooled relative risk for social isolation, loneliness, and first CHD event identified in a meta-analysis of 11 prospective cohort studies was 1.29 (95% CI 1.04–1.59) [26]. Similarly, *low socioeconomic status* (SES) during childhood was associated with a 1.4 times higher mortality from CHD compared with high childhood SES after adjustment for confounders such as smoking and adulthood SES [27]. Low socioeconomic position in adulthood has also been associated with incidence of CHD or myocardial infarction, respectively [28, 29].

A consequence of chronic stress exposure is *vital exhaustion*, a state characterized by a combination of unusual fatigue, loss of energy, increased irritability, and feelings of demoralization [19, 30]. In the Copenhagen City Heart Study, a prospective population-based study with a median follow-up of 21.5 years, vital exhaustion was in men (HR = 2.36, 95% CI 1.70–3.26, PAR = 33.1%, 95% CI 17.2–45.9%) and women (HR = 2.07, 95% CI 1.61–2.68, PAR = 27.7%, 95% CI 18.6–36.7) among the highest ranking risk factors by importance for both fatal and non-fatal CHD risk [31].

Stress as a Triggering Factor for Acute Coronary Syndromes

ACS such as myocardial infarctions and unstable angina typically occur in persons with advanced coronary atherosclerosis. It has been suggested that particularly in persons with vulnerable atherosclerotic plaques, ACS can be triggered by acute stimuli in the hours preceding the coronary event for (review (22•)). Investigations in survivors of ACS suggest that acute emotional stress can act as a trigger for ACS. Meta-analytic data using the comparable time period 24 h before the hazard period as control period revealed a pooled relative risk of ACS symptom onset being preceded by a period of acute anger, stress, or depressed mood of almost 2.5 (95% CI 1.75–3.51) [22•]. Emotional stress in terms of negative emotions was estimated to play a role in 3.9% (95% CI 0.99–10.34) of ACS in a study analyzing the population attributable risk [32]. In the context of assumed interactions with disease severity, the effects on ACS onset seem to vary with nature and intensity of the emotional stressors. For example, in the 2 h following outbursts of anger, meta-analytic data revealed a 4.7 times (95% CI 2.50–8.99) higher ACS risk compared with other times. The absolute risk was found to be higher for individuals with a higher baseline cardiovascular disease (CVD) risk and for individuals who have frequent outbursts of anger [33••]. Moreover, the incidence of MI increased more than 20-fold in the 24 h after the death of a significant person [34] and a diagnosis of cancer was associated with a 5.6 times (95% CI 5.2–5.9) higher relative risk of CVD death within 1 week [35]. In addition to inflammatory responses destabilizing the vulnerable plaque, the underlying psychobiological processes may also include stress-induced hemodynamic and prothrombotic responses, as well as sympathetic and neuroendocrine activation [36].

Potential Mechanisms Underlying the CHD Risk with Psychological Stress

In order to understand the mechanisms underlying the CHD and maybe also ACS risk with psychological stress, the testing of physiological reactivity to mental stress as a controlled challenge is considered to allow for mechanistic insights as a window into the complex psychological and physiological processes involved in the development and progression of CHD [37, 38]. The most potent acute psychosocial stressors in terms of inducing strongest physiological stress responses (e.g., the standardized and well-established Trier Social Stress Test (TSST) [39]) combine public speaking with cognitive tasks (e.g., mental arithmetic) [40•]. Thereby, they comprise stress-inducing situation characteristics such as social-evaluative threat, in which others could negatively judge performance, uncontrollability, ambiguity, or novelty. In addition to allow for mechanistic insights, the responses to acute psychosocial laboratory stress testing may also reflect an individual's response pattern to real-life stressors [41]; moreover, accumulation of disturbed stress responses in daily life may have pathophysiological significance [42].

An individual's tendency to show large-magnitude or exaggerated physiological reactions to acute stressors often combined with delayed recovery of these reactions has been implicated in CHD risk. More precisely, several lines of evidence suggest that particularly exaggerated cardiovascular reactivity and delayed recovery to acute laboratory challenge predict adverse cardiovascular outcomes including CHD severity, CHD events, or mortality [43, 44]. In addition to cardiovascular hyperreactivity, stress-induced hyperactivation (and/or delayed recovery) of the hypothalamus-pituitary adrenal (HPA) axis and the sympathetic nervous system (SNS) supposedly increase CHD or ACS risk, either directly and/or by inducing adverse changes in intermediate biological risk factors such as lipids, hemostatic factors, or inflammatory activity [22•, 36, 45, 46, 47••]. In the following, we will focus on inflammatory activity in the context of stress.

Acute Stress and Inflammation

Healthy Participants An increasing amount of research investigated reactivity of inflammatory markers in reaction to acute psychosocial stress exposure in healthy participants. Regarding circulating inflammatory mediators, a recent

systematic review and meta-analysis [47••] confirmed previous meta-analytic findings [48] of robust moderate to large delayed stress-related increases in the cytokines IL-6 and IL-1β and extended them to small to medium increases in TNF-α, although there were no increases in CRP. While highest IL-6 increases were observed 90–120 min following stress, further research extending the recovery period beyond a 2-h window is needed to determine when peak and recovery occur, particularly so for circulating IL-6 [47••], but also for other cytokines.

The mechanisms underlying the well-documented effects of acute psychosocial stress on pro-inflammatory cytokines are beginning to be understood. We investigated in healthy male participants the effect of acute psychosocial stress induction by the TSST as compared to a non-stress control condition on inflammatory measures on both the transcriptional and protein level to test for stress kinetics and intercorrelations [49•]. We showed that acute stress induced significant and rapid increases in DNA binding activity of the pro-inflammatory transcription factor NF-κB (NF-κB-BA) with highest levels immediately after and 10 min after stress compared with a non-stress control condition [49•]; this concurs with previous literature [50•, 51], although not unequivocally so [52]. Moreover, in terms of gene expression, stress-exposure induced delayed increases in whole-blood mRNA levels of IL-1β and IL-6, but not of anti-inflammatory IL-10, with highest levels observed at the end of the observation period, i.e., 120 min after stress cessation [49•]. Similarly, mRNA levels of NF-κB and its inhibitor IκBα were highest at the same time point, i.e., 120 min after stress. While the finding of highest IL-1β mRNA levels at 120 min after stress supported a previous study by Steptoe and coworkers [53], another study notably without a non-stress control group found earlier increases in gene expression for IL-1β, IL-6, NF-κB, and IκBα mRNA, with highest IL-6 mRNA levels 30 min after stress exposure [54]. In our study, greater stress-induced increases in NF-κB-BA, i.e., active NF-κB, related to higher subsequent delayed stress-induced increases in mRNA levels of the NF-κB-regulated cytokines IL-1β and IL-6 as well as of NF-κB and IκBα. Interestingly, plasma cytokine levels of IL-1β and IL-6 did not relate to either NF-κB-BA or mRNA levels [49•]. We concluded from our and other findings that acute psychosocial stress immediately induces activation of NF-κB, which after translocation from cytoplasm to the nucleus up-regulates mRNA expression of pro-inflammatory cytokines with the aim of later cytokine production. Moreover, activated NF-κB also induces an auto-regulatory feedback mechanism by inducing expression of IκBα and NF-κB subunits in order to limit its own activation and to restore its basal cytoplasmic state [49•]. This proposed cascade of events may represent a well-orchestrated mechanism to cope with stressful situations. However, chronic, e.g., sustained or repeated stress exposure, may accumulate in terms of dysfunctional pro-inflammatory reactivity and thus contribute to negative health outcomes such as CHD.

CHD Patients The literature on stress reactivity of inflammatory markers in CHD patients is scarce but overall supports a potentially elevated inflammatory stress reactivity. The first study investigating acute stress responses of inflammatory markers in CHD patients compared male and female CAD patients (2–4 weeks after successful elective percutaneous coronary intervention) with healthy controls in reaction to a 4-min anger recall interview followed by 4 min of mental arithmetic [55]. Inflammatory markers including IL-6 and CRP were assessed before, during, and about 30 min after the mental challenge. Comparisons between CHD patients and controls revealed larger CRP increases with mental arithmetic in the patients. Moreover, patients with high norepinephrine responsiveness to mental arithmetic had larger increases both, in CRP and IL-6 [55]. Further studies in CHD patients, although without a healthy control group, tested for modulating influences. One study tested whether age and sex would relate to alterations in IL-6 reactivity to 5-min mental stress testing in male and female patients with a recent MI (< 6 months) [56]. The stress testing comprised a 2-min preparation phase followed by a 3-min speech about a made-up real-life stressful situation in front of a video camera and an audience wearing white coats, and plasma IL-6 was assessed at baseline, as well as 60 and 90 min after stress. Compared with age-matched men, women 50 years or younger showed markedly higher IL-6 concentrations both at baseline and 60 and 90 min after recovery from stress. All patient groups displayed functional IL-6 stress reactivity, and no differences were found between men and women older than 50 years of age [56]. In male ACS survivors (> 6 months), IL-6 plasma levels were assessed before and up to 120 min after a stress testing procedure involving a 5-min color-word interference task followed by 5-min simulated public speaking [57]. Hostility was assessed in the patients, and higher hostility scores predicted elevated IL-6 concentrations 75 and 120 min post task suggesting that hostile individuals with advanced CVD may be particularly susceptible to stress-induced increases in inflammation. The authors concluded that these findings may have implications for emotionally triggered cardiac event risk. However, while the pathophysiological processes underlying emotional triggering of ACS likely involve heightened platelet activation following acute mental stress [58•, 59], the potential role of inflammatory measures still remains to be investigated. Notably, the assessment of platelet activation in these studies involved immune cells such as monocytes [58•, 59], neutrophils [58•], and leukocytes in general [58•], all of which are capable of cytokine production.

Chronic Stress and Inflammation

Several forms of chronic stress have been demonstrated to be associated with chronic systemic low-grade inflammation, characterized by increased levels of inflammatory cytokines and acute-phase reactants on the one hand and/or decreased anti-inflammatory cytokines such as IL-4 on the other, both in cross-sectional and longitudinal studies. Specifically, an increasing body of literature supports the notion of increased markers of systemic inflammation among individuals experiencing chronic psychological or social stress related to early life stress; caregiving burden; stress at work, including job burnout and other states of vital exhaustion consequent to chronic stress exposure; low socioeconomic status, and social isolation [18, 21, 60]. The same has been observed for posttraumatic stress disorder, a mental disorder that develops in the aftermath of a life-threatening event such as natural disasters, war-related activities, and serious physical diseases [61]. Most of these research findings come from population-based studies, whereas few such studies have been performed in patients with CVD.

Data from the Dunedin birth cohort revealed early life stress in the form of childhood maltreatment, including maternal rejection at age 3, exposure to harsh discipline at ages 7 and 9, and multiple episodes of severe physical punishment through age 11, to be a predictor of higher CRP, fibrinogen, and white blood cell count at age 32 [62•]. Specifically, childhood maltreatment contributed to more than 10% of cases with clinically relevantly increased CRP levels in the adult population, independently of co-occurring early life risks, stress in adulthood, and health behavior.

The chronic stress of providing informal care to a spouse with Alzheimer's disease has been associated with increased levels of TNF-α and CRP over an observation period of 3 years; in turn, 3 months after death of the spouse, CRP and soluble intercellular adhesion molecule-1 (sICAM-1) were both decreased, suggesting that cessation of caregiver stress had a favorable effect on caregivers' pro-inflammatory state [63]. Increases in inflammation-related biomarkers were associated with problems such as disturbed sleep, burden or pain, and caregiving characteristics, including daily stressors and the duration of caregiving [64].

In Chinese workers, high job stress operationalized as a mismatch between high effort spent and low reward received at work, as well as overcommitment to work, were associated with increased levels of CRP, both in men and women [65]. After a follow-up of 12 years, the increased risk of sudden cardiac death or fatal/non-fatal myocardial infarction in employees from Germany with high job strain was attenuated with adjustment for CRP and sICAM-1, suggesting the stress-associated inflammatory burden associated with job stress may contribute to stress-related CHD [66]. In teachers, we found a correlation between high symptom levels of job burnout (exhaustion, depersonalization, and lack of accomplishment) with TNF-α and the TNF-α/IL-4 ratio, controlling for sociodemographic factors, medication, health behavior, metabolic factors, and symptoms of anxiety and depression [67]. Also, in a middle-aged general population from Sweden, vital exhaustion showed an inverse relationship with circulating IL-6 levels, controlling for age, sex, medical conditions, and cardiovascular risk factors [68]. Apparently healthy middle-aged men high in vital exhaustion had significantly higher CRP levels, although similar TNF-α levels, than non-exhausted men [69]. In addition, glucocorticoids were less able to inhibit lipopolysaccharide-stimulated IL-6 release in vitro, suggesting reduced glucocorticoid sensitivity compatible with altered regulation of monocyte cytokine production as one possible pathway linking vital exhaustion with atherosclerosis [69]. To concur, in men with severe stable angina, those with vital exhaustion had significantly higher plasma levels of IL-1β and TNF-α, but similar IL-6 levels, compared to those without exhaustion [70].

A systematic review revealed higher CRP levels in individuals with chronic stress related to low socioeconomic status, including low income and education, in the majority of reviewed studies [71]. Although non-white race/ethnicity explained some of this association, the prospective Coronary Artery Risk Development in Young Adults study found lower income and education to be associated with higher increases in CRP over a 13-year period, independently of many confounding variables, including ethnicity [72]. In the latter cohort, feelings of social isolation also were a significant moderator of the association between sleep disturbances and heightened CRP levels over a 5-year follow-up [73]. Similarly, greater loneliness was associated with larger responses in IL-6 and IL-1Ra to acute mental stress in female but not male employees of the Whitehall II cohort, independently of age, grade of employment, body mass index, and smoking status [74].

Regarding posttraumatic stress disorder, meta-analytic evidence shows heightened IL-1β, TNF-α, and IL-6 levels compared with non-PTSD controls, even after controlling for comorbid major depression [75]. Similarly, in a study on patients with PTSD attributable to the traumatic experience of myocardial infarction, IL-6 was significantly higher than in patients without PTSD after controlling for depressive symptoms [76].

Involved Mechanisms

The most often discussed mechanisms that may link chronic stress with inflammation relate to dysfunction in the autonomic nervous system and hypothalamic-pituitary adrenal axis [18]. Particularly, chronically elevated secretion of stress hormones such as catecholamines and cortisol may relate to production of pro-inflammatory cytokines and CRP [69, 77]. In turn, vagal withdrawal and decreased parasympathetic

activity, respectively, gives rise to increased production of pro-inflammatory cytokines like IL-1β and TNF-α by immunocompetent cells expressing acetylcholine receptors, including tissue macrophages. The mechanism behind is disinhibition of the cholinergic anti-inflammatory pathway that is mediated by vagally induced release of acetylcholine that blocks cytokine production via the nicotinic alpha 7 receptor subunit, a regulator of cytokine transcription and translation [78]. In addition to production of inflammatory cytokines by cells of the immune system, the adipose tissue seems a major source of stress-induced increases in plasma levels of pro-inflammatory markers [60].

Experimental Modulation of Inflammatory Stress Reactivity

Data from cross-sectional studies suggest that circulating inflammatory stress responses are moderated by biological and psychological factors. In addition to the above-mentioned moderating influences derived from CHD patient studies (norepinephrine stress response, anger, age and gender effects) [55–57], further moderators identified from studies in non-CHD populations have been summarized [47••]. Biobehavioral (smoking, lower physical fitness, obesity, poor sleep), demographic (African American race, lower socioeconomic status), and psychosocial (loneliness, high work stress in terms of high effort-reward imbalance, negative affective response to the task) health risk factors were reported to be associated with larger stress-induced increases in circulating inflammatory markers [47••]. To extend cross-sectional assessment, we describe selected pharmacological and biobehavioral intervention studies in the following.

Pharmacological Interventions

We previously tested whether selected pharmacological interventions with beneficial effects on cardiovascular health would attenuate the reactivity of circulating inflammatory measures to acute stress induction. In a placebo-controlled randomized trial, 5-day treatment with aspirin (100 mg), but not propranolol (80 mg), significantly attenuated the acute stress-induced increase in IL-6 120 min after stress in healthy men [79•]. Moreover, a single intake of 50 g of flavanol-rich dark chocolate as compared to a flavanol-free placebo chocolate attenuated intracellular pro-inflammatory reactivity to TSST-stress 120 min later in healthy men [80]. The dark chocolate group revealed a blunted stress reactivity of NFκB-BA, IL-1β mRNA, and IL-6 mRNA with higher plasma levels of the flavanol epicatechin relating to lower pro-inflammatory stress reactivity.

Psychobehavioral Interventions

Randomized controlled trials testing as to whether biobehavioral interventions targeting chronic stress may reduce inflammation are still few in number, have mainly been performed in individuals without CVD, and did not explore whether reduction in inflammation translated into favorable cardiovascular outcomes. Previous interventions have aimed at reducing stress reactivity of inflammatory markers or chronic low-grade inflammation.

In healthy adults, 6 weeks of training in compassion meditation did not result in lower IL-6 responses to acute psychosocial stress (TSST) than a health discussion control intervention; however, subjects with greater meditation practice times had smaller IL-6 stress responses than did those with less practice times [81]. In adolescents with early life stress, cognitively-based compassion training did not affect CRP levels differently from a wait-list control intervention; however, greater engagement in training sessions was associated with a reduction in CRP from baseline to the 6-week assessment [82]. In dementia caregivers, the Pleasant Event Program, which comprises of identification/scheduling and participation in leisure activities by the caregiver, significantly lowered IL-6 levels compared with an information support control intervention after 6 weeks of treatment, but not at 1-year follow-up [83]. In contrast, in another study with dementia caregivers, mindfulness meditation and education class did not achieve lower CRP and IL-6 levels when compared with a respite only condition after 8 weeks [84]. In stressed job-seeking unemployed community adults, 3-day intensive mindfulness meditation training lowered IL-6 levels compared with relaxation training at 4-month follow-up, whereby the effect was mediated by activity in brain regions important in top-down executive control [85]. Compared to an education control group, 2 months of low-dose workplace-based mindfulness intervention did not significantly lower CRP and IL-6 levels in employees with CRP > 3.0 mg/ml and at risk of CVD or with CVD [86]. Also, in lonely older adults, an 8-week mindfulness-based stress reduction program downregulated the NF-κB-associated pro-inflammatory gene expression profile along with reduction in feelings of loneliness compared to a wait-list control group [87].

Open Questions and Future Directions

Despite promising research, no studies to date have established the full sequence from stress to inflammation to CHD. While the mechanisms underlying inflammation activation with acute and chronic stress are increasingly unraveled, this knowledge bases mainly on study findings in samples of healthy or at least apparently healthy subjects participating in laboratory experiments and population-based studies, respectively. Intriguingly, the stress-associated inflammation might partially contribute to coronary pathogenesis. However, few such studies have been performed

in patients with established atherosclerotic CVD. Ultimately, whether stress-associated inflammation worsens the prognosis in cardiac patients may seem a fruitful question to study. This is even more so, as biobehavioral interventions, such as mindfulness-based training programs, were shown to alleviate the inflammatory burden, so they might have the potential to lower risk for recurrent cardiac events when added to standard multimodal interventions, for instance as part of cardiac rehabilitation [88]. Therefore, future controlled studies with sufficiently long observation periods are needed to clarify whether reactivity of extracellular and intracellular inflammatory measures to repetitive and/or prolonged stress exposure results in chronic low-grade inflammation, whether both these processes are indeed excessive in CHD patients compared to non-CHD controls; and also, whether they contribute to CHD incidence, progression, and ACS triggering, respectively. Moreover, further potential modulating factors and targets for successful interventions ought to be identified.

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Compliance with Ethical Standards

Conflict of Interest Petra H. Wirtz declares no conflict of interest. Roland von Känel reports personal fees from Vifor AG Switzerland.

Human and Animal Rights and Informed Consent This article reviews published studies and does not present original data with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major Importance

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