Epidemiology generates interest by providing plausible associations, and biochemistry and molecular biology attempt to pin down cause–effect relationships in concrete molecular terms. In this Viewpoint, we posit that coronary heart disease (CHD) and its relationship to work stress may qualify as prime example of an entity that profits from recent advances in these 2 areas of research. Relationships to hydrogen peroxide (H$_2$O$_2$) and ion channels provide clues for elucidating molecular pathophysiology related to psychosocial stress.

The cardiovascular system is a target of psychosocial stress. The pathophysiological chain of events linking chronic psychosocial stress with cardiovascular disease (CVD) includes dysregulation in the hypothalamic–pituitary–adrenal axis and in the autonomic nervous system. Among the physiological changes are increased heart rate, increased blood pressure, energy mobilization, decreased insulin sensitivity, and endothelial dysfunction. These processes may ultimately result in manifest CVD. In terms of population health, the largest part of the burden of CVD is attributed to CHD. Epidemiological associations of chronic psychosocial stress at work, a core social stressor in modern life, with CHD have been repeatedly confirmed (see below). For instance, in a recent multicohort study of 90,164 individuals, the simultaneous exposure to 2 major forms of chronic psychosocial stress at work, job strain and effort–reward imbalance, revealed a 1.4-fold increase in risk for incident CHD. Much needs to be learned on the molecular signals involved.

Role of Oxidative Distress in CHD Development

There is evidence linking psychosocial stress to mononuclear cell activation via nuclear factor κB. Fine tuning of major molecular redox switches, such as nuclear factor κB and nuclear factor E2–related factor 2/Kelch-like ECH-associated protein 1, is a central focus in current research on oxidative stress. H$_2$O$_2$ emerged as a central redox signaling molecule, occurring as normal metabolite at nanomolar concentration under physiological conditions (1–10 nmol/L H$_2$O$_2$), which is denoted as oxidative eustress, whereas higher concentrations (>100 nmol/L H$_2$O$_2$) are denoted as oxidative distress (Figure A). H$_2$O$_2$ is now established as an endothelial-derived hyperpolarizing factor that plays an important role in coronary autoregulation. Recently, Kv1.5 channels were found to contribute to H$_2$O$_2$-induced dilation in human arteries and to be modulated in CHD. Major sources of H$_2$O$_2$ are the NADPH oxidases and the mitochondrial sites of H$_2$O$_2$ generation. How the pathophysiological link is implemented is a major task for current research.

Exposure to intrinsic or extrinsic stressors compromises the cellular redox homeostasis of the organism, resulting in a preponderance of oxidants. Acute psychological stress responses in neuroendocrine, metabolic, inflammatory, and transcriptional processes are modulated by mitochondrial functions. Repeated, chronic exposure to an extrinsic stressor may contribute to impaired mitochondrial function, oxidative distress, and subsequent physiological dysregulation resulting in allostatic overload and susceptibility to CHD. Recent results from animal studies demonstrate that exposure to chronic low-level noise as an extrinsic stressor leads to elevated release of stress hormones, increased levels of surrogate markers of oxidative stress in vascular tissue and plasma, blood pressure increase, proinflammatory activity in vascular tissue, and enhanced endothelial dysfunction. Such experimental evidence supports the hypothesis of stress-related mechanisms underlying the epidemiologically established association between exposure to chronic noise and elevated relative risks of developing hypertension and incident CHD.

Chronic Psychosocial Stress at Work and CHD

Here, we propose to use available evidence on associations of chronically stressful work, a prominent and widely prevalent socioenvironmental stressor, with CHD as a blueprint of interdisciplinary inquiry, integrating pathways that may mediate this association. In Figure B, a graphical representation of these pathways is displayed. The chain of events is represented here by arrows, with only a few indicators given to reduce complexity. To illustrate this conceptual approach, the arrows A to C are briefly discussed:

A: Epidemiological Association Between Work Stress and CHD

A series of prospective epidemiological studies has identified distinct deleterious components within the complexity and diversity of potentially stressful psychosocial work
environments by applying a stress-theoretical model, with 2 stressors, job strain and effort–reward imbalance. Job strain considers threat to control as a crucial element, maintaining that individuals working in jobs defined by high demand (eg, heavy work pressure) and low control over their task are at elevated cardiovascular risk. In effort–reward imbalance, threat to reward at work is considered a core stressor, where individuals spending high efforts at work without receiving adequate rewards (salary, promotion, job security, and recognition) are at elevated cardiovascular risk. Results from >20 cohort studies demonstrate a 1.4-fold increased risk of CHD in work stress exposed versus nonexposed individuals, as mentioned above.1,2 In these estimates, the influence of established cardiovascular risk factors has been adjusted for in multivariate statistical analysis.

B: Work Stress and Molecular Biomarkers: Autonomic Nervous System and Oxidative Stress

Epidemiological cohort studies need to be substantiated by experimental and quasiexperimental investigations to elucidate underlying pathways. Such studies included measurement of job strain or effort–reward imbalance and reported associations with indicators of elevated autonomic nervous system activity (eg, secretion of cortisol and noradrenaline, increased blood pressure and heart rate, and diminished heart rate variability).8 In addition, a relationship of enhanced activity in the autonomic nervous system with markers of oxidative stress in blood or vascular tissue or with a concomitant increase of nuclear factor κB and proinflammatory activity was documented.3 Oxidative biomarkers, such as urinary 8-hydroxy-2’-deoxyguanosine and H2O2, showed associations in human job stress settings,15 as well as anticipatory cortisol reactivity.9 As shown in a rat model of psychosocial stress, there is an early elevation of NADPH oxidase-2–derived oxidative stress in the hypothalamus.10

C: From Oxidative Stress to CVD

This link has been well established in animal studies (eg, Ref. 14), and there is preliminary evidence in studies on human subjects. As mentioned above, H2O2-induced vasodilation in CHD was impaired because of switching of potassium channels.7 Clinical cardiovascular risk factors are well established and correlate in

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**Table. Potential Targets of Interest in the Work Stress–Oxidative Stress–Coronary Heart Disease Chain of Events**

<table>
<thead>
<tr>
<th>Central/Autonomic Nervous System</th>
<th>Messenger Molecules/Assay Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPA axis</td>
<td>Cortisol</td>
</tr>
<tr>
<td>SAM axis</td>
<td>Noradrenaline</td>
</tr>
<tr>
<td>NOX enzymes (NOX 1, 2, 4)</td>
<td>H2O2</td>
</tr>
<tr>
<td>Circulatory/cardiac cell sites</td>
<td></td>
</tr>
<tr>
<td>NOX enzymes</td>
<td>H2O2</td>
</tr>
<tr>
<td>NOS enzymes</td>
<td>NO</td>
</tr>
<tr>
<td>Redox signaling</td>
<td>Thioredoxins, peroxiredoxins</td>
</tr>
<tr>
<td>Molecular redox switches</td>
<td>NF-κB, Nr2f2/Keap1</td>
</tr>
<tr>
<td>Ion channels</td>
<td>K+ channels (Kv1.5)</td>
</tr>
<tr>
<td>Chromatin</td>
<td>Telomere shortening; sirtuins</td>
</tr>
<tr>
<td>DNA damage</td>
<td>8-oxodG; comet assay</td>
</tr>
<tr>
<td>RNA damage</td>
<td>8-oxoG</td>
</tr>
<tr>
<td>Micro-RNAs</td>
<td>miR-200c</td>
</tr>
<tr>
<td>Protein modification/damage</td>
<td>Nitrotyrosine; eg, MICAL</td>
</tr>
<tr>
<td>Lipid peroxidation/damage</td>
<td>F2-Isoprostanes</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Cytokines; inflammasome, NLRP3</td>
</tr>
<tr>
<td>Macrophage</td>
<td>MKP1</td>
</tr>
</tbody>
</table>

Some targets and the involved molecular species are mentioned as examples of a much more rich panoply. Because of restrictions in the number of references, the major current sources of information on these cannot be spelled out; some of the topics are treated in Sies et al.4 H2O2 indicates hydrogen peroxide; HPA axis, hypothalamic–pituitary–adrenal axis; Keap1, Kelch-like ECH-associated protein 1; MICAL, molecule interacting with CasL; MKP1, mitogen-activated protein phosphatase-1; NF-κB, nuclear factor κB; NLRP3, NACHT, LRR, and PYD domains-containing protein 3; NOS, nitric oxide synthase; NOX, NADPH oxidase; Nr2, nuclear factor E2–related factor 2; and SAM axis, sympatho–adrenomedullary axis.
numerous studies in CVD epidemiology. The current state of knowledge on CVD and oxidative stress has been compiled, focusing on the major enzymatic sources of oxidants, NADPH oxidases, mitochondria, xanthine oxidase, lipoxygenase, and myeloperoxidase. The challenge is to closely monitor the state of oxidative distress in molecular terms in controlled human studies on work stress and other forms of psychosocial stress. Table provides a list of target systems and target molecules that deserve further scrutiny in the identification of molecular links of work stress to the final outcome, CHD.

**Outlook and Focus for Future Research**

To summarize, the case of exposure to chronically stressful work and its association with elevated CVD risk, CHD in particular, has been chosen to illustrate progress in knowledge on a chain of molecular events leading from exposure to a psychosocial stressor to the development of a stress-related chronic disease, mediated by distinct psychobiological and biochemical mechanisms. This calls for enhanced interdisciplinary investigations among human populations applying advanced methods of molecular, biomedical, and epidemiological researches. Elucidating a key role of oxidative stress in the development of this cascade of events is considered crucial. Furthermore, it is hoped that the efficacy of distinct preventive measures can be enhanced, based on improved knowledge on pivotal metabolites such as H$_2$O$_2$. Such measures are urgently needed in view of a growing burden of chronic diseases in aging societies.

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**Disclosures**

None.

**References**


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