Review

Stress and Atherosclerotic Cardiovascular Disease

Nobutaka Inoue

Department of Cardiovascular Medicine, Kobe Rosai Hospital, Kobe, Japan

Recent major advances in medical science have introduced a wide variety of treatments against atherosclerosis-based cardiovascular diseases, which has led to a significant reduction in mortality associated with these diseases. However, atherosclerosis-based cardiovascular disease remains a leading cause of death. Furthermore, progress in medical science has demonstrated the pathogenesis of cardiovascular disease to be complicated, with a wide variety of underlying factors. Among these factors, stress is thought to be pivotal. Several types of stress are involved in the development of cardiovascular disease, including oxidative stress, mental stress, hemodynamic stress and social stress. Accumulating evidence indicates that traditional risk factors for atherosclerosis, including diabetes, hyperlipidemia, hypertension and smoking, induce oxidative stress in the vasculature. Oxidative stress is implicated in the pathogenesis of endothelial dysfunction, atherogenesis, hypertension and remodeling of blood vessels. Meanwhile, mental stress is a well-known major contributor to the development of cardiovascular disease. The cardiovascular system is constantly exposed to hemodynamic stress by the blood flow and/or pulsation, and hemodynamic stress exerts profound effects on the biology of vascular cells and cardiomyocytes. In addition, social stress, such as that due to a lack of social support, poverty or living alone, has a negative impact on the incidence of cardiovascular disease. Furthermore, there are interactions between mental, oxidative and hemodynamic stress. The production of reactive oxygen species is increased under high levels of mental stress in close association with oxidative stress. These stress responses and their interactions play central roles in the pathogenesis of atherosclerosis-based cardiovascular disease. Accordingly, the pathophysiological and clinical implications of stress are discussed in this article.

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Stress and Cardiovascular Disease

The word "stress" was previously used only in physics to refer to the force exerted on an object; however, in the mid-20th century, Dr. Hans Selye changed this concept by using the term to describe a noxious stimulus, such as the threat of a physical attack, chronic discomfort or excessive physical activity. Living creatures have dexterous systems that respond to stimuli (stressors) and help them to adapt to the alterations induced by stressors. Therefore, homeostasis in the body is maintained via the stress response. The relationship between stressors and the stress response is similar to that observed following the distortion of a ball under loading (**Fig. 1A**). Maladaptation due to an imbalance between stressors and the stress response can be an initiator or promoter of various diseases, including cardiovascular disease (**Fig. 1B**).

Selye demonstrated that a wide variety of stressors can induce similar processes, regardless of the type of stimuli; he referred to this phenomenon as general adaptation syndrome[1, 2]. There are three phases of general adaptation syndrome. The first is the alarm or "fight or flight" response, which prepares the organism for the challenge of the stressful stimuli. The second phase involves the chronic adaptation to a stressful stimulus, while the final phase constitutes a state of fatigue, in which the adaptive system begins to fail.

Address for correspondence: Nobutaka Inoue, Department of Cardiovascular Medicine, Kobe Rosai Hospital, 4-1-23, Kagoike Touri, Chuo-Ku, Kobe 651-0053, Japan
E-mail: nobutaka@kobeh.rofuku.go.jp
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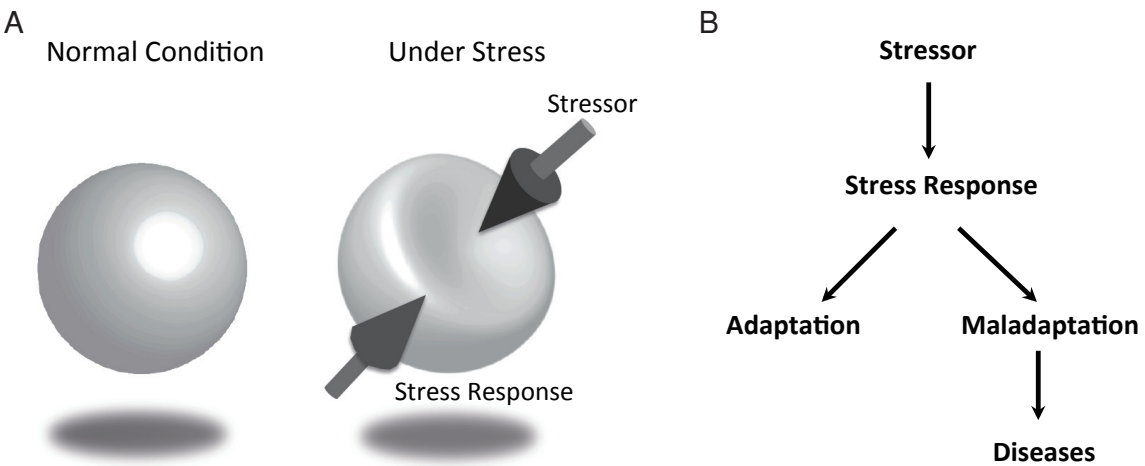

Fig. 1. A. Relationship between stressors and the stress response. B. An imbalance between stressors and the stress response as an initiator or promoter of various diseases, including cardiovascular disease.

Selye demonstrated the importance of the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis in these processes. More importantly, he reported that the final stage of general adaptation syndrome, wherein the adaptive system is exhausted, results in nonspecific illness.

Since Selye's pioneering work, many scientists and physicians have conducted investigations aimed at understanding the physiological and pathophysiological responses to biological stress. Selye's original hypothesis, that excessive mental stress leads to systemic stress, the symptoms of which manifest in peripheral tissues, is now well accepted. It is clear that prolonged or excessive emotional or mental stress can lead to depression, chronic anxiety, post-traumatic stress syndrome and/or chronic panic disorder. It is also evident that these psychological modulations are closely associated with the pathogenesis of cardiovascular disease. In fact, psychosocial stress and/or depression are stronger risk factors for myocardial infarction than traditional cardiovascular risk factors, such as hypertension and obesity[3].

In addition to mental stress, other types of stress are related to cardiovascular disease. For example, oxidative and hemodynamic stress are both profoundly involved in the pathogenesis of cardiovascular disease. A large number of *in vitro* and *in vivo* investigations have provided evidence that major atherosclerotic risk factors, such as diabetes, smoking, hypertension and dyslipidemia, induce oxidative stress in the vasculature. In fact, the generation of superoxide is enhanced in atherosclerotic vessels in patients with unstable angina pectoris and atherosclerotic aortic aneurysms[4, 5]. On the other hand, the cardiovascular system is constantly exposed to hemodynamic forces due to either the blood flow or pulsation. In the vasculature, endothelial cells are constantly exposed to three kinds of hemodynamic stress; shear stress, stretch forces and pressure. Endothelial cells differentially recognize these hemodynamic stressors as mechanical stimuli and transmit signals into the interior of the cells via mechanotransduction. These intracellular events induce a variety of cellular responses that involve alterations in cell morphology as well as the cell function and gene expression; however, the precise molecular mechanisms underlying these processes have not yet been fully identified. It is known that stress responses resulting from hemodynamic forces exert profound effects on the biology of vascular cells. For example, areas exposed to low levels of shear stress in the vascular bed are vulnerable to atherosclerotic changes, whereas high levels of shear stress exert protective effects against atherogenesis[6, 7]. The exposure of atherosclerotic plaque in coronary arteries to intense stretch forces or shear stress can trigger rupture or destruction of the plaque, inducing acute coronary syndrome.

Considering the importance of various types of stress in the pathogenesis of cardiovascular disease, obtaining a better understanding of stress responses may be helpful for treating cardiovascular diseases.

Mental Stress as a Risk Factor for Cardiovascular Disease

Previous clinical and epidemiological investigations have provided evidence that various psychological factors play important roles in the pathogenesis of

Table 1. Psychological and social factors related to cardiovascular disease

Depression
Anxiety syndrome
Personality and character traits
Type A behavior pattern
Hostility
Competition
Social Isolation and lack of social support
Chronic and subacute life stress
Posttraumatic stress disorder

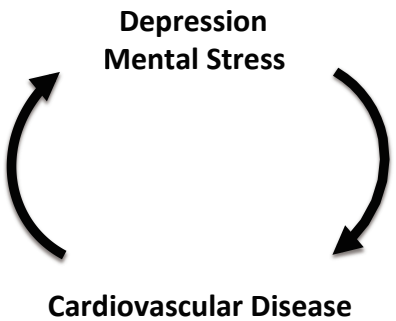

Fig. 2. A vicious cycle consisting of depression and cardiovascular disease.

atherosclerotic cardiovascular disease. The major psychological factors related to cardiovascular diseases are listed in **Table 1**.

Abundant evidence suggests that there is a close association between mental stress and cardiovascular disease. For example, the INTERHEART trial is an international case-control study conducted to evaluate the relationship between psychological stress and acute myocardial infarction[8]. In that study, the relationship between mental stress and/or social factors and the incidence of myocardial infarction was evaluated among 11,119 patients with a history of acute myocardial infarction compared to 13,648 control subjects. The results showed that the patients with a history of myocardial infarction had a higher prevalence of all types of mental and social stress, regardless of ethnicity and gender. The odds ratio for depression was 1.38 (99% CI 1.19-1.61), adjusted for age, gender, geographic region and the smoking status.

There have been numerous investigations indicating an etiological association between depression and the development of cardiovascular disease in initially healthy subjects. Iso *et al*. analyzed the results of the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) Sponsored by the Ministry of Education, a large-scale cohort investigation, and clearly demonstrated that perceived mental stress is associated with increased mortality due to stroke and coronary heart disease[9]. In the JACC study, a total of 73,424 Japanese subjects (30,180 men and 43,244 women) 40 to 79 years of age without a history of stroke, coronary heart disease or cancer completed a lifestyle questionnaire including questions about their perception of mental stress. The results demonstrated that women with high levels of stress have a two-fold higher age-adjusted risk of mortality due to stroke and/or coronary heart disease than those who report low stress levels. The multivariate relative risk for women who perceived a high versus low level of stress was 2.24 (95% CI 1.52 to 3.31, $p<0.001$) for total stroke and 2.28 (95% CI 1.17 to 4.43, $p<0.02$) for coronary heart disease. Among men, these relationships were generally weaker, although still suggestive of an increased risk of myocardial infarction.

Rugulies R. performed a meta-analysis of 11 studies to investigate the impact of depression on the development of coronary heart disease in initially healthy subjects and reported that the overall relative risk for the development of coronary heart disease in depressed subjects was 1.64 (95% CI=1.29-2.08, $p<0.001$)[10]. Furthermore, Wulsin *et al*. performed a meta-analysis to examine the relative risk of depression for the onset of coronary artery disease and reported that the combined overall relative risk of depression for the onset of coronary disease was 1.64 (95% CI =1.41-1.90)[11]. The NIPPON DATA80, a prospective epidemiological study conducted in Japan, demonstrated that the relative risk of coronary artery disease-related death among individuals with a total cholesterol level of 240-259 mg/dL was 1.8 compared with individuals with a total cholesterol level of 160-179 mg/dL[12]. These findings indicate that the association between mental stress and the risk of cardiovascular disease is similar to that observed for high total cholesterol.

Furthermore, depression has a significantly negative impact on the prognosis of patients with coronary artery disease. There is evidence that post-myocardial infarction depression is independently associated with cardiac mortality. According to the results of a meta-analysis, post-myocardial infarction depression is associated with a 2- to 2.5-fold increased risk of a poor cardiovascular outcome[13].

Depression is more prevalent among the patients with coronary artery disease than in the general population[14]. Moreover, we previously found that 45% of patients with acute myocardial infarction suffered from depression[15], and the prevalence of depression among

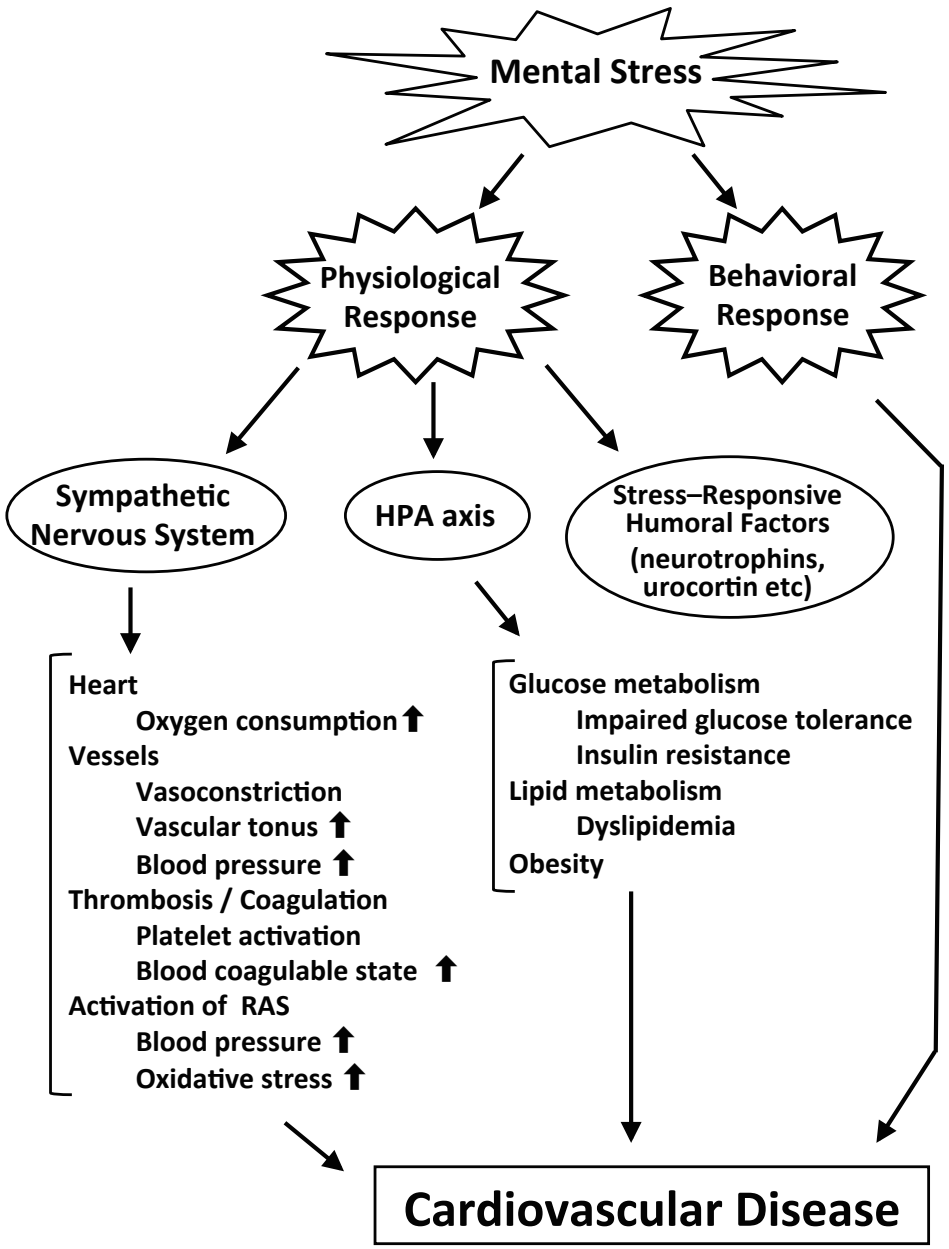

Fig. 3. Mechanism(s) underlying the exacerbation of cardiovascular disease due to mental stress. Mental stress induces two kinds of responses: physiological and behavioral responses. In terms of physiological responses, the sympathetic nervous system and HPA axis are activated. Under the activation of these two major systems, a wide variety of cellular events are involved in the pathogenesis of cardiovascular disease.

In addition, various stress-responsive humoral factors are regulated, including neurotrophins and urocortin.

subjects with a history of acute myocardial infarction was equal to that observed in patients with lung cancer treated at our hospital[15]. It is difficult to elucidate the cause-effect relationship between depression and coronary artery disease; however, depression may predispose patients to developing cardiovascular disease, while the disease itself may depress the mental state. Furthermore, mental stress results in the deterioration and progression of cardiovascular disease. In other words, there is possibility of a vicious cycle consisting

of depression and coronary artery disease (**Fig. 2**).

Natural Disasters, Mental Stress and Cardiovascular Disease

Japan experiences frequent earthquakes. In particular, the two most disastrous earthquakes in recent memory are the East Japan Great Earthquake of 2011 and the Great Hanshin-Awaji Earthquake of 1995. Many lives were lost in these great earthquakes, and many people subsequently died from cardiovascular disease after the disasters. Ogawa *et al*. reported that the number of deaths from acute myocardial infarction dramatically increased in the year of the Great Hanshin-Awaji Earthquake compared with the average number of deaths from acute myocardial infarction observed during the preceding decade[16]. Furthermore, it has been reported that the number of patients with acute myocardial infarction, pneumonia, stroke, cardiopulmonary arrest or heart failure significantly increased after the East Japan Great Earthquake[17]. In addition to natural disasters, human-caused disasters, such as terrorism and wars, are thought to be associated with the development of cardiac disease[18, 19]. Based on this background, there is a close relationship between disasters and the incidence of cardiovascular disease.

During natural disasters, the lack of medical support and/or the breakdown of essential utilities results in the aggravation of cardiovascular disease. In addition, the sufferers of natural disasters may feel a sense of deprivation or anxiety. Such psychological burdens may induce mental stress, which can exert negative effects on the occurrence of cardiovascular disease.

Mechanisms Underlying the Exacerbation of Cardiovascular Disease by Mental Stress

The mechanisms by which mental stress and/or depression induce or exacerbate cardiovascular disease remain to be clarified. However, it is necessary to consider such mechanisms from two different viewpoints, that is, physiological and behavioral responses (**Fig. 3**).

In terms of physiological responses, two major systems are activated: the sympathetic nervous system and the HPA axis. In addition to these two systems, a wide variety of stress-responsive humoral factors, including neurotrophins (NTs) and urocortin, have been reported to be dynamically regulated. Furthermore, mental stress affects behavioral responses, such as smoking, alcohol abuse and the failure to engage in sufficient physical activity (**Table 2**). Moreover, mental stress may also be associated with poor adherence with taking medications. There is also an association between depression and an increased rate of smoking. For example, it has been reported that depression lowers the rate of success of smoking cessation programs among patients with coronary artery disease[20].

Table 2. Behavioral Responses Induced by Mental Stress

Smoking
Abuse of alcohol
Medical adherence ↓
Medical compliances ↓
Physical activity ↓

Mental stress and/or depression are associated with activation of the sympathetic nervous system (**Fig. 3**). Lambert *et al*. evaluated the pattern of sympathetic nervous firing in patients with metabolic syndrome and hypertension in relation to underlying psychological stress and found that a higher incidence of multiple firing of sympathetic nerves is associated with a higher level of affective depressive symptoms[21]. Activation of the sympathetic nervous system induces an increase in blood vessel tone, myocardial oxygen consumption and platelet activation, followed by activation of the renin-angiotensin system (RAS). Angiotensin II is a potent stimulator of NADPH oxidase, the primary enzymatic origin of reactive oxygen species (ROS) in the cardiovascular system, whose activation triggers oxidative stress. Enhanced oxidative stress induces endothelial dysfunction, as described in detail later in this review.

In addition, the hyperactivity of the HPA axis is one of the most reliable findings of the mental stress-induced physiological response (**Fig. 3**). The cortex of the brain perceives mental stress and then transmits signals to the hypothalamus, where corticotropin-releasing factor (CRF) is released, which binds to pituitary receptors, ultimately resulting in the release of cortisol from the adrenal glands into the systemic circulation. Lipid and/or glucose metabolism may be exacerbated due to the increased production of cortical hormones induced by activation of the HPA axis. Indeed, Pan *et al*. systematically reviewed 29 cross-sectional studies and found an association between depression and metabolic syndrome (unadjusted OR = 1.42; adjusted OR = 1.34)[22]. Therefore, alterations in these metabolic pathways may, in turn, be involved in atherogenesis.

The multiple factors mentioned above can affect the clinical courses and outcomes of patients with cardiovascular disease (**Fig. 3**).

Oxidative Stress Responses at the Cellular Level

It is important to note that the stress response occurs at different levels, that is, throughout the entire body or at the organ or cellular levels. An important example of the stress response at the cellular level is the cellular production of ROS. During normal cellular metabolism, various enzymes have the capacity to generate electrons that reduce oxygen, which leads to the production of a variety of ROS, including superoxide anion, hydrogen peroxide, peroxynitrite and other molecules[23]. These ROS are required for normal cell signaling events and the host defense system. However, when ROS are produced in excess for prolonged periods, the cellular antioxidant defense mechanisms fail to cope with the overproduction, resulting in a condition known as oxidative stress, wherein an excess of ROS causes cellular damage and ultimately cell death[24].

As described above, it is well known that major atherosclerotic risk factors, such as diabetes, smoking, hypertension and dyslipidemia, induce oxidative stress in the vasculature. With respect to atherosclerotic cardiovascular disease, one of the most important stimuli leading to excessive ROS production in cardiovascular cells is angiotensin Ⅱ, and the ROS production that occurs in response to the actions of angiotensin Ⅱ is primarily mediated by NAPDH oxidase (Nox). Recently, it has become evident that various isoforms of Nox play important roles in various pathophysiological mechanisms[25]. For example, the ROS produced by Nox are involved in endothelial dysfunction, atherogenesis, hypertension, blood vessel remodeling, cardiac enlargement and several other pathophysiological responses in the cardiovascular system. These untoward effects of the oxidative stress observed in response to angiotensin Ⅱ can be initially viewed as constituting phases 2 (initially adaptive) and 3 (failure) of Selye's model of general adaptation syndrome.

Stress-Responsive Humoral Factors and Mental Stress

In addition to the HPA axis and sympathetic nervous system, it has been reported that various systems are activated by mental stress, including NT and the CRF family of neuropeptides, such as urocortin1, urocortin2 and urocortin3 (also known as stresscopin). NTs also form a family of dimeric polypeptides that includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), NT-3, NT-4 and NT-5 in humans. NTs play critical roles in the survival, growth and maintenance as well as death of central and peripheral neurons[26]. Under psychological stress, the secretion of NTs from the hypothalamus, pituitary gland and central and peripheral nerves is markedly altered[27].

Among NT family members, the enhanced expression of BDNF in the brain is a well-recognized protective mechanism against stressful insults. BDNF protects striatal neurons from cell death by acting as an antioxidant[28]. Furthermore, there is growing evidence that the serum level of BDNF is negatively associated with the presence of depression[29]. It has been postulated that the dysregulation of BDNF plays a key role in the pathophysiology of depression. On the other hand, it was recently reported that BDNF causes oxidative stress in cortical cells via the activation of NADPH oxidase and overproduction of ROS[30]. We previously demonstrated an enhanced BDNF expression in human atherosclerotic coronary arteries obtained from autopsy cases (**Fig. 4**)[31]. Moreover, the coronary circulation of BDNF in patients with unstable angina is increased relative to that observed in patients with stable angina (**Fig. 5**)[31]. Furthermore, stimulation with BDNF significantly enhances the NADPH oxidase activity in association with the generation of ROS in cultured human coronary artery smooth muscle cells[31]. Recently, Amoureux *et al.* examined the vascular expression of BDNF and the superoxide production during the development of hypertension in spontaneously hypertensive rats (SHR)[32]. In the SHR, the expression of BDNF in the aortic wall was associated with enhancement of NADPH oxidase activity and superoxide production. These observations suggest that there is a close association between BDNF and oxidative stress. However, the pathophysiological roles of the BDNF expressed in the vasculature may be different from those of the BDNF expressed in the nervous system, since these findings are inconsistent with the observations of an inverse association between the serum BDNF level and depression. Further investigation is necessary to clarify the role of vascular BDNF in the stress response.

CRF, a 41-amino acid neuropeptide, plays a pivotal role in the control of the HPA axis under both basal and stress conditions and is involved in stress-related pathophysiology and behavior. Members of the CRF family of neuropeptides, including urocortin1-3, bind to the G protein-coupled, CRF type1 (CRFR1) and CRF type2 receptors (CRFR2). CRF has a relatively lower affinity for CRFR2 than for CRFR1. Urocortin 1 has an equal affinity for CRFR1 and CRFR2 and urocortin 2 and 3 appear to be selectively bound to CRFR2[33, 34]. It has been suggested that the CRF-

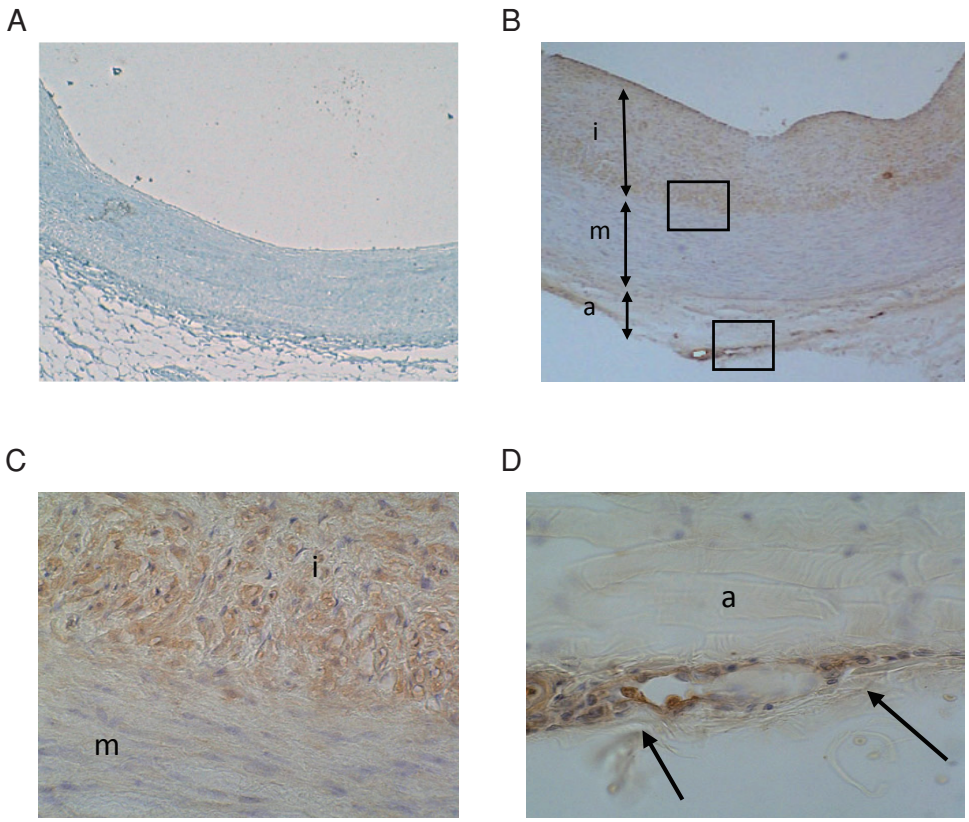

Fig. 4. Representative views showing the expression of BDNF in human coronary arteries obtained from autopsy cases.

A and B: The immunoreactivity for BDNF was negligible in the non-atherosclerotic coronary arteries (A), whereas intense BDNF immunoreactivity was observed in the atherosclerotic intima and adventitia (B).
C and D: A high-power view of the area indicated by the rectangle in (B) showing the expression of BDNF in the intima (C) and fibroblasts around the vasa vasorum in the adventitia (D). i, m and a indicate the intima, media and adventitia, respectively.

CRFR1 system is critical for the initiation of the stress response, while the urocortin-CRFR2 system plays an important role in the termination of the stress response[35]. Neufeld-Cohen *et al.* demonstrated that urocortin is an essential factor in the stress-recovery process using a triple knockout mouse model lacking all three urocortin genes[36]. We previously demonstrated that urocortin1 is also expressed in vascular endothelial cells and exerts potent antioxidative effects[37]. The pathophysiological roles of vascular urocortin in the stress response remain under investigation at present.

Interactions Between Stress Responses

The interaction between mental, oxidative and hemodynamic stress has been previously described. For example, it has been reported that ROS production is enhanced under high levels of mental stress in both animals and humans. Depressive symptoms are correlated with lipid peroxidation in human blood[38]. The levels of biomarkers of oxidative stress, such as 8-OH-dG, are increased in patients with depression[39]. In addition, Huang *et al.* demonstrated the activation of mast cells and increased serum levels of interleukin-6 in Apo E-deficient mice under conditions of high levels of mental stress[40]. Furthermore, Seo *et al.* reported that NADPH oxidase in the brain plays a pivotal role in depressive behaviors[41]. According to their investigation, repeated restraint-induced depressive behavior in mice results in the upregulation of the expression of the key subunits of NADPH oxidase, p47phox and p67phox, in the brain[41]. Moreover, the enhanced expression of NADPH oxidase is associated with the generation of ROS. Consistently, heterozygous p47phox knockout mice exhibit suppressed

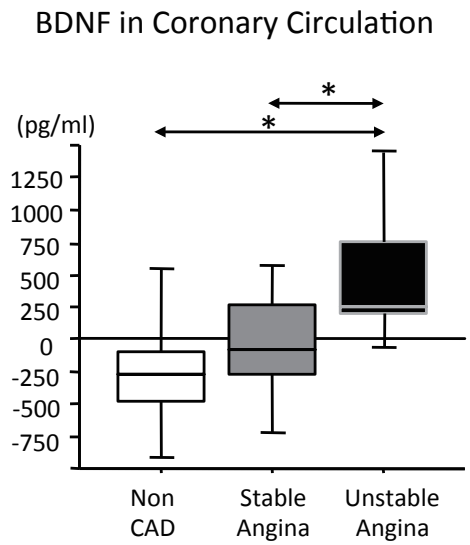

Fig. 5. Coronary sinus-aortic root (Cs-Ao) differences in the plasma BDNF levels across the coronary circulation. The Cs-Ao differences in the plasma BDNF levels were significantly greater in the unstable angina group (UAP) than in the stable angina (SAP) or non-coronary artery disease (non-CAD) groups. The UAP group consisted of 38 patients who experienced anginal episodes at rest or during a mild degree of effort within 48 hours of the initiation of the study, without a significant increase in the creatine phosphokinase level. The SAP group consisted of 45 patients exhibiting typical effort angina or positive treadmill exercise testing without episodes of angina at rest. The non-CAD group consisted of 24 patients with chest pain syndrome ($n=22$) and mitral valve prolapse ($n=2$). The data are expressed as medians, with 25th and 75th percentiles (boxes) and 10th and 90th percentiles (I bars). The asterisk indicates a p value of <0.01 for the comparisons between the UAP, SAP and non-CAD groups.

depressive behaviors. These experimental observations suggest that stress promotes depressive behavior via the upregulation of NADPH oxidase. The effects of psychological stress on the vascular expression of lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1), a key molecule linking oxidative stress and atherosclerotic cardiovascular disease[42], have been evaluated in rats. Interestingly, the expression of LOX-1 in the vessel wall was found to be upregulated in the rats by psychological stress via the formation of ROS[43].

Depression is closely related to oxidative stress. Therefore, the administration of antioxidative drugs may lessen the negative impact of depression on the occurrence of coronary artery disease. However, interventions addressing this hypothesis have not obtained conclusive results, although one small study showed that treatment with N-acetylcysteine, an antioxidant, suppresses depressive episodes in patients with bipolar disorder[44].

On the other hand, hemodynamic stress affects the degree of oxidative stress via the expression of antioxidative or pro-oxidative enzymes. For example, areas exposed to low levels of shear stress in the vascular bed are vulnerable to atherosclerotic changes, whereas high levels of shear stress exert protective effects against atherogenesis. This observation can be partly explained by experimental evidence indicating that high levels of shear stress induce the expression of protective enzymes, including superoxide dismutase and glutathione peroxidase, which are important antioxidative factors[45, 46]. Furthermore, the application of stretch forces on vascular smooth muscle cells accelerates the oxidative modification of low-density lipoprotein (LDL) via the production of ROS[47].

Therefore, the interactions between different types of stressors have a significant impact on the development of cardiovascular disease.

Social Stress in Super-Aging Societies

Social stress, including that due to a lack of support, social isolation or destitution, has a significant negative impact on the incidence of atherosclerotic cardiovascular disease. A previous study reported that living alone or experiencing a shortage of social support has an adverse effect on the development and progression of cardiovascular disease[48]. Social stressors are critical issues in aging societies, such as Japan. Aging societies are common worldwide; however, the aging of Japanese society is occurring at an unprecedented rate. Statistics published by the Japan Ministry of Health, Labour and Welfare indicate that the average life expectancy in this country is 86.39 years for women and 79.64 years for men. In addition, the number of individuals 100 years of age or more was over 40,000 in 2008. Having social support is essential for leading a healthy life and preventing various diseases among super-aging societies.

Recently, we analyzed the association between living alone and heart failure in elderly patients[49]. In order to clarify the clinical picture and socioeconomic characteristics of super-elderly patients with heart failure treated at our hospital, 380 patients with acute heart failure or acutely worsening chronic heart failure were divided into three groups according to age: those less 60 years of age, those 60-80 years of age and those 80 years of age or older (super-elderly group). The social backgrounds of the subjects varied widely

between the three groups in several respects. In particular, the number of patients living alone increased with age. Therefore, living alone itself is an important risk factor for cardiovascular disease in aging societies, such as Japan.

Recently, Kitamura *et al*. analyzed the results of the Osaka Acute Coronary Insufficiency Study (OACIS), a large-scale, prospective, multicenter observation study conducted in Japan and clearly demonstrated that living alone is an important risk factor associated with the prognosis of acute myocardial infarction[50]. According to their investigation, acute myocardial infarction survivors living alone were at a higher risk of cardiovascular events and death compared with those not living alone. The authors reported that living alone was found to be independently associated with a higher risk of the composite endpoint comprising major adverse cardiovascular events and total deaths. On the basis of their investigation, the multivariate-adjusted hazard ratio of the composite endpoint was 1.34 (95% CI: 1.08-1.68) for men and 1.31 (95% CI: 0.95-1.81) for women.

Social isolation, including living alone, may be associated with psychological factors, such as depression, which is a potent risk factor for various diseases, including cardiovascular and other diseases. Social isolation tends to be associated with higher risk behaviors, such as smoking, alcohol abuse or the failure to engage in sufficient physical activity, and living alone may be associated with poorer adherence with taking medications. Social stress due to insufficient public support is an urgent problem that must be addressed in a super-aging society such as Japan.

Residual Risks and Mental Stress

Recent progress in pharmacotherapy has achieved a drastic decrease in the incidence of atherosclerosis-based cardiovascular diseases. Accumulating evidence indicates that the use of statins prevents the primary and secondary onset of cardiovascular disease. Furthermore, as per the results of a previous study, the administration of statins with eicosapentaenoic acid was found to decrease the incidence of major coronary events by 19% in Japanese patients with a history of coronary artery disease[51]. However, treatment with these powerful medications cannot completely eliminate cardiovascular disease. Therefore, there is a significant residual cardiovascular risk even after the administration of optimum treatment for dyslipidemia. The precise reason for this residual risk remains to be clarified; however, mental stress may be one of the important factors involved because, as described above, the risk associated with mental stress is similar to that observed for a high cholesterol level.

To date, various interventions targeting mental stress have attempted to decrease the risk of cardiovascular disease; however, previous large, randomized, controlled trials have failed to find significant decreases in the incidence of cardiovascular events. For example, the ENRICHD study is a prospective study conducted to evaluate the effects of selective serotonin reuptake inhibitor (SSRI) intervention for psychological depression associated with myocardial infarction. Although SSRI therapy exhibited some beneficial effects with respect to depression, it did not reduce the onset of cardiovascular disease[52]. Therefore, the establishment of a therapeutic strategy for treating mental stress associated with cardiovascular disease remains an important goal for the reducing or eliminating residual risks.

Conclusion

More than a half a century has passed since the establishment of the concept of stress by Dr. Selye. However, his ideas continue to provide the basis for current research and are well accepted. The disturbance of homeostasis in the cardiovascular system induced by an imbalance between stressors and the stress response may be a trigger for the development of atherosclerosis-based cardiovascular disease, and various stressors play pivotal roles in the pathogenesis of these conditions via individual mechanisms. Evaluating the broadly interactive effects of stress may provide new insight into the pathogenesis of cardiovascular disease.

Conflicts of Interest

None.

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