Stress-induced blood pressure reactivity and cardiovascular disease risk

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Abstract People are exposed to various acute and chronic stressors in daily life. Usually, blood pressure increases quickly in response to acute physical and psychological stressors. The pressor response to acute stress is explained primarily by cardiovascular regulatory mechanisms of the sympathetic nervous and endothelial systems. It has been found, by long-term follow-up studies across a wide range of generations, that exaggerated blood pressure reactivity to acute stress is an independent risk factor for cardiovascular disease (CVD), including hypertension. The association between exaggerated blood pressure reactivity to acute stress and increased future CVD risk may be explained by sympathetic effects, mechanical effects, and prothrombotic changes. Consequently, it is possible that stress management, such as cognitive behavioral therapy and improvement in the psychosocial environment, may be effective, at least in part, against future CVD due to the weakening of stress-induced blood pressure reactivity from childhood to adulthood.

Keywords: acute stress, blood pressure reactivity, cardiovascular disease

Introduction

People are exposed to various stressors in daily life. Usually, cardiovascular parameters such as blood pressure and heart rate (HR) increase quickly in response to acute stress. It has been shown that these responses are in excess of what would be expected based on metabolic demand for adaptive behavioral action, particularly in the case of psychological stress1-4). In addition, it has been widely accepted that there is a clear individual difference in the magnitude of the response, or reactivity, of cardiovascular parameters5-7). The individual difference in cardiovascular reactivity, especially blood pressure reactivity, to acute stress has been reported to be associated with the risk for cardiovascular disease (CVD), including hypertension5,8). In this review, we describe the blood pressure response to acute stress, its regulatory mechanisms, and the association between blood pressure reactivity and future CVD risk in healthy humans, focusing on physiological aspects.

Blood pressure response to acute stress and regulatory mechanisms

Laboratory stress tests have been recognized as important tools for examining stress-induced cardiovascular reactivity9). These tests can be classified into two main categories5). One type of test induces stress mainly by physical stimuli, for example, with the application of cold water to an extremity or the forehead or with isometric handgrip exercise. The other type of test induces psychological stress that involves the emotional aspect of the individual, for example, the mental arithmetic test, the conflict color-word test (CWT) developed by Stroop10), the reaction time test, or the interpersonal speech test. Usually, the cold-pressure test (CPT)11), which is a representative physical stress test, is performed by immersing the extremity in cold water for 1-2 min. Subsequently, blood pressure markedly increases and attains the maximal value within 30 s. After the test, blood pressure decreases quickly, and returns to the pre-test value within 2 min. Of the two dominant factors determining blood pressure (cardiac output [CO] and total peripheral resistance [TPR]), the pressor response during CPT usually occurs due to a consistently increased TPR, or vascular mechanism, while there is little change in CO1,2). On the other hand, psychological stressors such as those mentioned above (up to ~10 min) usually increase blood pressure and HR. The pressor response is due to a cardiac mechanism1,3,14), although it has been suggested that when the duration of the stress test is longer (such as with mental arithmetic), CO recovers to the baseline level, and the vascular mechanism becomes dominant, resulting in a sustained pressor response1,15).

Cardiovascular responses to acute stress are induced mainly by activation of the sympathetic nervous system.
(SNS) through cardiac and vascular adrenergic receptors. Activation of the β-adrenergic receptor influences the cardiac chronotropic and inotropic actions, and tends to result in increased CO. The β-adrenergic receptor on the systemic blood vessel mediates vasodilatation and acts to decrease the TPR, while activation of the α-adrenergic receptor on the blood vessel induces vasoconstriction and acts to increase the TPR. As described above, the CPT and psychological stress tests, such as the mental arithmetic test and the CWT, usually induce different hemodynamic responses, as the former does not greatly induce the β-adrenergic-mediated myocardial response, and typically induces the α-adrenergic response concomitant with the TPR increase; whereas the latter (for ~10 min) typically induces the β-adrenergic response concomitant with increased CO and the combined β-adrenergic vasodilatation and α-adrenergic vasocostriction concomitant with the inconsistent TPR response.

The endothelial system, which is another fast-responding vascular-regulatory system, may also be associated with the TPR and blood pressure responses to acute stress. Nitric oxide (NO) is a vasodilator released from the endothelium that acts quickly as an endothelium-derived relaxing factor and is important for regulating vasomotor tone and therefore TPR. The magnitude of endothelium-dependent arterial dilatation (EDAD), which emerges during reactive hyperemia and is measured noninvasively by using echography, has been used as a direct index of the functional state of the endothelium. The validity of the EDAD magnitude as an endothelial functional index was supported by a previous study that demonstrated the importance of NO for flow-dependent dilatation of large conduit arteries using the NO synthase inhibitor Nω-monomethyl-L-arginine. It has been found that the EDAD magnitude is inversely associated with the TPR and blood pressure responses to acute stress. It has been indicated that NO inhibits α-adrenergic vasoconstriction and that vasodilatation through β-adrenergic receptor activation (e.g., with the use of the β-adrenergic agonist isoproterenol) is inhibited by the inhibition of NO formation and at least partly depends on endothelial vasodilatory function. Thus, as a mechanism by which the endothelial system is associated with vascular regulation during acute stress, it is thought that the endothelial system modulates the adrenergic vascular regulation of SNS activation.

The association between stress-induced blood pressure reactivity and future CVD risk

The cardiovascular reactivity hypothesis, which states that persons with exaggerated cardiovascular reactivity to acute stress are at an increased risk for CVD development, was previously proposed. Most studies that followed individuals for a long period (over 10 years) found that the exaggerated increase in blood pressure to laboratory acute stress tests, such as the CPT, mental arithmetic test, and reaction time test, was associated with an increased future CVD risk even after adjusting for confounding factors, such as resting blood pressure, age, degree of obesity, smoking history, and familial hypertension history, in individuals across a wide age range from childhood through adolescence and adulthood at the time of initial testing. A recent study, which examined the association between the cardiovascular response to mental arithmetic at home and CVD mortality for the subsequent 16 years in the elderly (~63 years, including individuals with disease), also found a positive association between stress-induced cardiovascular reactivity and CVD mortality. In addition, it has been indicated that cardiovascular reactivity, especially systolic blood pressure (SBP) reactivity, to speech and other psychological stressors was associated with carotid artery intima-media thickness, a valid index of generalized sub-clinical atherosclerosis in other vascular beds (such as the coronary, aortic, and peripheral arteries) and the early pathogenesis of CVD. These previous findings support the cardiovascular reactivity hypothesis. It is also suggested that the stressor inducing the relationship between blood pressure reactivity and future CVD risk is not limited to the specified one. Reactivity parameters to psychological stress (such as mental arithmetic) mediated predominantly by the β-adrenergic mechanism may more accurately predict future CVD risk than may reactivity parameters related to the CPT. In relation to the hypothesis, it is necessary to confirm the reproducibility of stress-induced blood pressure reactivity and to determine the differences in blood pressure reactivity caused by laboratory and real-life stressors. Relatively good stability of laboratory stress-induced blood pressure reactivity over time has been observed. It has also been found that ambulatory blood pressure, which usually cannot be measured under resting conditions, is a stronger predictor than is the blood pressure measured at rest. Finally, blood pressure reactivity to laboratory stress tests corresponds to blood pressure reactivity to challenges in daily life during ambulatory blood pressure monitoring.

Both baseline (resting) blood pressure and stress-induced blood pressure reactivity are blood pressure variables. An increase in resting blood pressure, even within the normal range, is a primary independent risk factor for essential hypertension and coronary heart disease. The relationship between stress-induced blood pressure reactivity and future CVD risk has been observed even after adjusting for baseline blood pressure. It has also been reported that the measurement under stress-loaded conditions is a more valid predictor of future blood pressure than is the measurement under resting conditions. Some studies have suggested that blood pressure responses to an acute stressor (e.g., the CPT) may be affected by genetic factors associated with CVD pathogenesis, which
does not affect baseline blood pressure. Additionally, the regulatory systems of the baseline blood pressure and stress-induced blood pressure reactivity may be different; the former is due to long-term regulation, and the latter is affected by the acute sympathetic activation, as noted above.

With regard to the cut-off value for blood pressure hyper-reactivity to acute stress, the longest follow-up study to date (45 years) reported that 71% of hyper-reactors in whom the increases in SBP or diastolic blood pressure (DBP) were >25 or >20 mmHg, respectively, at the time of initial CPT and 19% of normoreactors, in whom the SBP and DBP responses were smaller, developed hypertension. In other studies using the CPT, the cut-off values of SBP and DBP reactivity were 15 - 20 and 20 mmHg, respectively, and future hypertension and coronary heart disease risks increased clearly in hyper-reactors who showed reactivity over these cut-off values. However, studies also showed that the increased disease risk is clear when individuals become more prone to developing hypertension and is more dominant in individuals with hypertension at an earlier age. It is thought that the relationship between stress-induced blood pressure reactivity and future CVD risk tends to be observed more easily for SBP than for DBP, since DBP reproductibility is lower than SBP reproductibility. Regarding the psychological and physical stress tests, future hypertension risk has been shown to clearly increase in hyper-reactors who show reactivity of >75% above the sample mean. A follow-up study in elderly people has applied the same cut-off values for reactivity to mental arithmetic. The results indicated greater CVD mortality in hyper-reactors compared with that in normoreactors. Although some studies have suggested that the aggregate reactivity of cardiovascular variables for some acute stress tests are better indices of future CVD risk and carotid intima-media thickness, the cut-off values have not been examined.

Mechanism underlying the association between stress-induced blood pressure reactivity and future CVD risk

The mechanisms underlying the association between stress-induced blood pressure reactivity and future CVD risk have been generally explained as follows, although further examination is necessary. The cardiovascular response to acute stress is dominantly regulated by the SNS, as described above. It has been found that the artery subjected to a sympathetic stimulus induces remodeling, increasing the wall-to-lumen ratio, and the TPR increases partly due to structural factors. It has also been demonstrated by an 18-year follow-up study that blood catecholamine concentration, an index of sympathetic activity, during psychological stress (e.g., mental arithmetic) contributes substantially and significantly to predicting future blood pressure. In this previous study, blood pressure, HR, and catecholamine during stress were better indicators of future blood pressure compared with those at rest. Consequently, in hyper-reactors who would be subjected repeatedly to increased sympathetic activation, it has been thought that the sustained TPR increase and subsequent CVD development may be induced easily by sympathetic mechanisms.

It has been considered that the exaggerated stress-induced blood pressure reactivity repeated in daily life injures the peripheral vessel endothelium due to a turbulent blood flow pattern, which promotes shear stress, particularly at the branch, and is associated with atherosclerosis development. This consideration is supported by the following findings. In vitro, shear stress through flow produces a strong vasoconstrictor, endothelin, which increases vascular tone over a long period of time, proliferates smooth muscle at the affected site, and increases intima hypertrophy, resulting in decreased production of the NO relaxing factor. Such change of the arterial wall may induce sustained increased vascular resistance. It may also induce increased sensitivity to vascular constriction and act to sustain high blood pressure, even in non-stressful conditions. Increased endothelial transparency to circulating lipoprotein, release of mitogen substances from newly regenerated endothelial cells, and proliferation of intimal smooth muscle cells would be associated with atherosclerosis due to the peripheral vessel’s endothelial injury induced by repeated exaggerated blood pressure responses. Taken together, the dispositional tendency that the exaggerated stress-induced cardiovascular responses, particularly blood pressure, induced repeatedly, may injure the vasculature. This response may increase the atherosclerosis and CVD risks.

It has been suggested that increased stress-induced blood pressure increases hematocrit and blood viscosity and decreases clotting time, producing the state regarded as the prothrombotic state. Therefore, the exaggerated stress-induced blood pressure reactivity may be comitant with a greater prothrombotic change. Acute stress can be associated with triggering clinical events in individuals with sub-clinical or established coronary heart disease by pressor-related hemodynamic or vasoconstrictive factors. For instance, the acute increase in blood pressure may destroy fragile plaque, leading to blood clot formation and embolus.

Previous studies using experimental animals indicate that a sustained increase in blood pressure does not occur from a temporary blood pressure increase, although careful attention is necessary before applying these findings to humans. It has also been suggested that in animal models, endothelial injury observed by exposure to psychological stress under normal conditions (no blockade) is inhibited and does not produce atherosclerosis under β-adrenergic blockade. Thus, the degree of developed atherosclerosis is associated with HR reactivity (blood pressure reactivity was not measured in the previous...
study). Consequently, it is suggested that the increased sympathetic activation to acute stress increases stress-induced hemodynamic response and is linked to developing atherosclerosis. The promotion of coagulation is linked to increased shear stress. Thus, it is thought that the mechanisms described above do not act alone but interact with each other, resulting in future CVD.

Hypertension and CVD progress slowly for decades. Although the disease is usually initiated at an early age, it is usually only confirmed clinically in late middle age. The traditional risk factors, such as family history, obesity, smoking, diabetes, and hyperlipidemia, can predict only about 50% of future CVD. Exaggerated stress-induced blood pressure reactivity is believed to be included as a risk factor in addition to those noted above. As described above, laboratory stress tests can provide a measurement of stress-induced cardiovascular reactivity that corresponds with that obtained during ambulatory monitoring, and they have been recognized as important tools for measuring stress-induced reactivity. A person with vascular hypertrophy would show hyper-reactivity to acute stress in cardiovascular parameters that would increase blood pressure predominantly through vasoconstrictive mechanisms and not through cardiac mechanisms. To examine such individual differences associated with regulatory mechanisms, usage of some laboratory stress tests with different regulatory mechanisms would be useful.

Finally, although stress-induced blood pressure reactivity is influenced by many factors, such as baseline blood pressure, familial disease history, age, gender, and obesity, we have suggested greater reactivity in thin youth (body mass index < 18.5 kg/m²), particularly in younger generations in Japan (unpublished data). Although previous findings are not consistent regarding the effects of fitness and regular exercise on stress-induced cardiovascular reactivity, we have found that, in experimental animals, spontaneous and continuous exercise for 10 weeks attenuated cardiovascular responses to acute stress (cage-switch stress and immobilization stress). Although negative studies exist for predicting future CVD risk due to stress-induced blood pressure reactivity, recently, as a result of meta-analysis, the effect of cardiovascular reactivity on future CVD occurrence has been shown to be present, even if the effect is not large. If so, the management of stress-induced cardiovascular reactivity due to cognitive behavioral therapy, proper weight control (not underweight nor obese), and perhaps regular exercise, among other aspects would be useful for preventing and treating CVD. Previous study has shown that a high daily stress level affects the prediction of future blood pressure increases due to exaggerated stress-induced cardiovascular reactivity, and the relationship between blood pressure reactivity and future CVD risk has been found even in children. Thus, because the psychosocial environment (i.e., a stressful situation) may interact with cardiovascular reactivity across a wide range of generations, more attention should be paid to its role in relation to cardiovascular health.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this article.

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