REVIEW ARTICLE

The relationship of stress and blood pressure effectors

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Abstract
Exaggerated cardiovascular response to acute and chronic stresses increases the risk for hypertension and cardiovascular disease. Stress also can be broadly defined as a disruption of homeostasis. The re-establishment and maintenance of homeostasis entail the coordinated activation and control of neuroendocrine and autonomic stress systems. Stressor-related information from all major sensory systems is conveyed to the brain. Brain activates neural and neuroendocrine systems to minimize the harmful effects of stress. Stress is generally thought to contribute to the development of hypertension. On the other hand, the evidence is still inconclusive. It is generally accepted that stress-induced hypertension occurs because of increases in sympathoadrenal activity, which enhances vascular tone, but complete α-adrenoreceptor blockade cannot prevent the long-lasting vasoconstriction induced by sympathetic nerve stimulation. That is why it is suggested that sympathetic nerve-mediated vasoconstriction may also be mediated by factors other than catecholamines. In this review, we aim to present the relationship between blood pressure effectors and stress altogether, along with evaluating the relationship between stress and blood pressure. In this respect, we have identified topics to explain the relationship between stress and the renin angiotensin aldosterone system, glucocorticoids, endothelial nitric oxide, endothelin-1 and L-type Ca^{2+} channels. Hippokratia 2015; 19 (2): 99-108.

Keywords: Blood Pressure, Stress, Acute Stress, Chronic Stress.

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Stress and Blood Pressure

High blood pressure is one of the established risk factors for cardiovascular diseases. Cardiovascular diseases associated with high blood pressure are more consistent and independent than other risk factors. The frequency of hypertension worldwide directly reflects the frequency of cardiovascular disease and heart attack[1]. Hypertension is an important risk factor because it takes first place worldwide as a preventable cause of death, in addition to its high prevalence. At the same time, hypertension ranks third place among the factors that adversely affect patients' quality of life. That is why reducing the risk of hypertension, which is a predicted risk factor, has importance for protection from disease and death[2,3].

Stress factors cause a series of reactions that change the dynamic steady-state condition in living organisms. The survival and welfare of all species require an appropriate physiological response to environmental and homeostatic problems. Acute stress is defined as a type of stress in which "fight or flight" response is observed as a result of exposure to stress by activation of the sympathetic nerve system (SNS). This response increases heart rate, contractility, vasoconstriction, the level of epinephrine and norepinephrine secreted by the adrenal medulla and sympathetic nerves, respectively[4] (Figure 1). Daily events cause chronic stress and have detrimental effects on the body (allostatic load) beyond the creation of "fight or flight" response against to acute stress. However, the hormones associated with stress protect the body in the short term and regulate adaptation (allostasis)[5].

It has been thought that stress contributes to the development of hypertension, although evidence from experimental studies is insufficient. It is accepted that increased sympathoadrenal activity, increased secretion of norepinephrine and epinephrine, and enhanced vascular tone cause hypertension, which occurs as a result of stress[6] (Figure 1). That is why the inhibition of the activated SNS provides clinical benefits for the treatment of heart failure[6-8] (Table 1). On the other hand, complete blockade of the adrenergic receptors cannot prevent prolonged vasoconstriction that occurs via activation of SNS. Therefore, it has been thought that there are other mediators rather than catecholamines mediating vasoconstriction through the SNS[9].

In general, chronic stress has various effects, such as increased risk of cardiovascular disease, decreased baroreceptor reflex response, increased blood pressure and neuroendo-

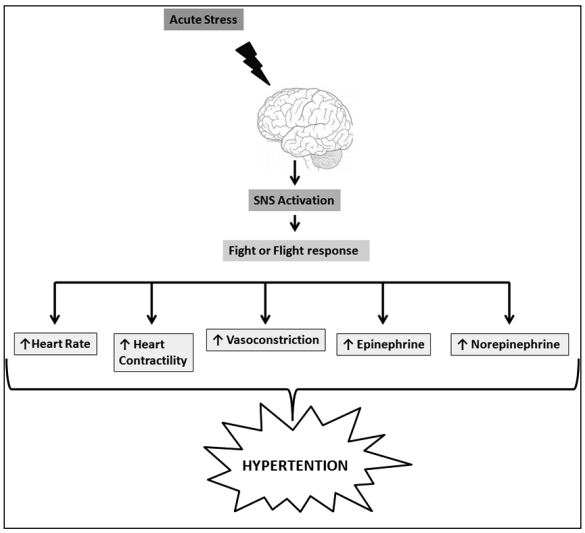

Figure 1: Schematic drawing demonstrating the response for acute stress.
SNS: sympathetic nerve system.

crine response against to new acute stress, decreased blood pressure and neuroendocrine response against to repeated stress, and increased basal blood pressure. These mechanisms work together harmoniously to help an organism survive under stress conditions and to prepare it for future threats. However, long-term activation of the stress circuit can cause many different health problems, including the increase of risk factors for cardiovascular diseases[10-12] (Figure 2).

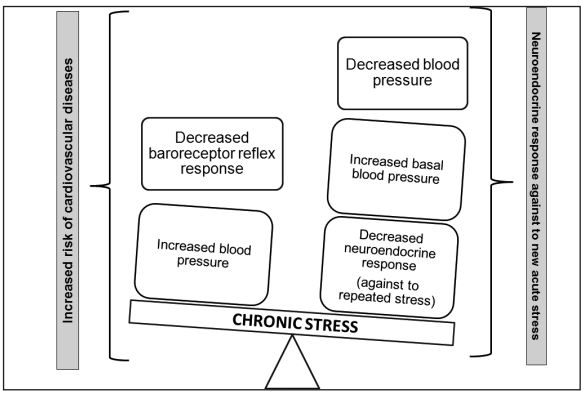

Figure 2: Schematic drawing demonstrating the effects of chronic stress.

Stress and renin angiotensin aldosterone system (RAAS)

Initially, heart failure was described as a clinical syndrome induced by reduced capacity of the heart. Later on, it was described as myocardial dysfunction and the continuous interaction between neurohormonal and activated balancing mechanisms. SNS, RAAS and cytokine systems are included in neurohormonal mechanisms. These systems can balance myocardial function, which is suppressed at acute phase and cardiovascular homeostasis. However, long-term activation of these systems has adverse effects on cardiac structure and function, which cause cardiac decompensation and progression of heart failure[13].

In the last two decades, important changes have emerged in the field of cardiology on the recognition of the effects of several activated neurohormonal axes including mainly SNS

Table 1: Proposed clinical approaches for stress management.

Proposed Clinical Approaches	
Mechanism	**Clinical Benefits**
Inhibition of SNS Inhibition of AngII	Treatment of heart failure
Modulation of inhibition/activation of neurohormones	Development of new and effective treatments for heart diseases
Blockade of ADRβ1	Improvement of left ventricular function Reducing the sudden deaths
Inhibition of ACE Blockade of AT-1R Inhibition of Renin Blockade of mineralocorticoid receptors	Preventing of cardiovascular diseases
Inhibition of ET-1	Preventing of hypertension, pulmonary hypertension, chronic heart failure and chronic kidney failure
ET-1 antagonists (Potential anti-arrhythmic agents)	Treatment of hypertension, pulmonary hypertension, chronic heart failure and chronic kidney failure Preventing of the development of vascular and myocardial hypertrophy in hypertension
ET-A receptor antagonists	Inhibition of hemodynamic and proliferative effects of AngII

SNS: sympathetic nerve system, AngII: angiotensin II, ADRβ1: beta1-adrenergic receptors, ACE: angiotensin converting enzyme, AT1-R: AngII type 1 receptor, ET-1: endothelin-1, ET-A: endothelin-1 receptor A.

and RAAS, on the developmental process of cardiovascular diseases, besides the pathologic changes of the integrity of the myocardial and vascular structures[14].

Cardiovascular diseases, which are promoted by atherosclerosis and left ventricular hypertrophy, cause a series of events such as thrombosis and myocardial infarction (MI), show progression in patients, and often cause death by heart failure. All these events have progressed before MI and heart failure, and are mediated by components of the neurohormonal system such as norepinephrine, angiotensin II (AngII) and aldosterone, which are components of SNS and RAAS. Recognition of the importance of these neurohormones provides great advantages for the treatment of the development of several diseases, which occur during cardiovascular processes. Therefore, the modulation of activation and inhibition of neurohormones has particular importance for the development of new and effective treatments for heart diseases (Table 1). Pathophysiological changes, which are affected by RAAS and SNS in heart diseases, include sodium retention, decreased cardiac contractility, and myocardial hypertrophy[14-17].

SNS is involved in the regulation of the cardiovascular system in the acute phase. On the other hand, the long-term activation of SNS causes heart failure. Increased sympathetic activity in heart disease results from various pathophysiological changes, including ventricular hypertrophy, sodium retention and vasoconstriction[14] (Figure 3). Increased plasma levels of norepinephrine, which result from central sympathetic outflow and activated sympathetic nerves, have been shown as evidence of sympathetic hyperactivity. At the same time, it has been emphasized that hyperactivity of SNS can increase the risk of cardiovascular disease, such as left ventricular diastolic dysfunction, in patients with hypertension[13].

The importance of cardiac toxicity, which occurs depending on catecholamines, was mentioned. Additionally, the importance of the hypothesis stating that "prolonged sympathetic activation causes myocardial toxicity" has been emphasized. An excessive amount of norepinephrine causes hypoxia, increased cyclic adenosine monophosphate (cAMP), formation of catecholamine metabolites and intracellular calcium overload, which occurs due to increased sarcolemmal permeability and ends in death of cardiomyocytes directly (Figure 3). Sympathetic activation, which occurs by increased secretion of norepinephrine, causes myocardial hypertrophy, increased apoptosis of the cardiomyocytes, and deleterious changes in contractile and metabolic proteins by differentiation of gene expression in cardiomyocytes, via enabling activation of adrenergic receptors[13,14,18]. Additionally, it has been shown that chronic administration of catecholamines in rats causes interstitial fibrosis, beta-adrenergic receptor-mediated decrease in inotropic responses, myocyte apoptosis and increased pumping function disturbances that occur via particularly left ventricular dilatation[19,20].

Sympathetic hyperactivity that is observed in heart diseases is closely related to abnormalities in cardiovascular reflexes. Sympathoinhibitory cardiovascular reflexes, such as the arterial baroreceptor reflex, are suppressed significantly along with sympathoexcitatory reflexes such as cardiac sympathetic afferent and the arterial chemoreceptor reflex that are increased in case of sympathetic hyperactivity[21]. The central nervous system receives information from different sources of the body and active mechanisms, which play a major role in cardiac remodeling and in the development of dysfunction. Additionally, it causes the development of systolic heart failure, which occurs by production of AngII and aldosterone locally in the brain and by activation of sympathetic nerve system[22,23]. AngII causes increased production of superoxide anion, mediated by increased AngII type 1 receptor (AT1-R), inhibited nitric oxide (NO) and reduced nicotinamide adenine. It will also lead to increased development of disease mediated by increased sympathetic stimulation[24,25] (Figure 3).

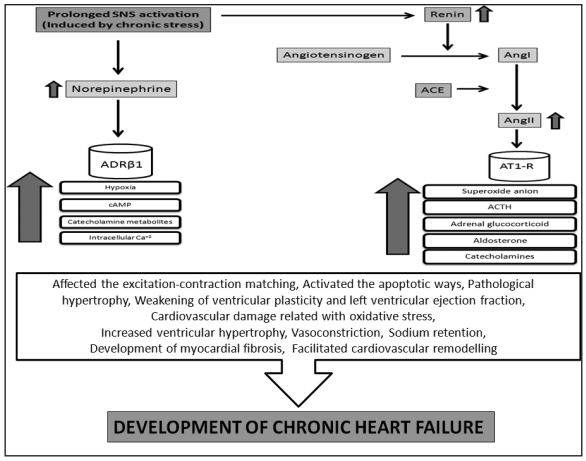

Figure 3: Schematic drawing demonstrating the effects of prolonged SNS activation.
SNS: sympathetic nerve system, ACE: angiotensin converting enzyme, AngI: angiotensin I, AngII: angiotensin II, AT1-R: AngII type 1 receptor, ACTH: adrenocorticotropic hormone, ADRβ1: beta1-adrenergic receptors, cAMP: cyclic adenosine monophosphate, Ca^{+2}: calcium ion.

It is reported that prolonged activation of the sympathetic nervous system negatively affects the excitation-contraction matching and activates the apoptotic ways, which play a central role in the development of chronic heart failure (Figure 3). It is supported by the fact that although human beta1-adrenergic receptors (ADRβ1) initially improve cardiac function, this event causes pathological hypertrophy and heart failure in later times[26,27] (Figure 3). The overexpression of ADRβ1 results in weakening of ventricular plasticity and left ventricular ejection fraction in animal models. It has been reported that the blockade of ADRβ1 in patients with systolic dysfunction, improves left ventricular function and reduces the sudden deaths[14,28,29] (Table 1). Signalization of ADRβ2 can lead to an increase in the level of inhibitory G-protein (Gi), so that it can activate the protective anti-apoptotic pathways, which regulate the increase in catecholamines. MI size and apoptotic signalization significantly increase with selective inhibition of Gi signaling in the response, which occurs against myocardial ischemia[30]. It is reported that the absence of ADRβ2 is associated with increased levels of catecholamine, cardiac hypertrophy, fibrosis and finally with congestive heart failure[13]. There is no information stated on the role of beta3-adrenergic receptors (ADRβ3) in heart failure. On the other hand, the increase in

ADRβ3 signalization, which shows a transient negative inotropic effect of the increase in NO production and pathways that inhibit the passage of calcium, is mentioned in heart failure[31,32].

The increase in sympathetic activation during stress leads to an increase in renin production. The increase in renin production results in a higher level of blood AngII. The increase in circulating AngII increases the stimulation of physiologically active AT-1R and consequently anterior pituitary gland contributes to the formation and release of adrenocorticotropic hormone (ACTH), adrenal glucocorticoid, aldosterone and catecholamines[33-35] (Figure 3).

Although cardiovascular diseases progress in stress, especially in depression, the role of the RAAS in the stress response is generally neglected. Later studies have shown the basic role of RAAS in the development and progression of cardiovascular diseases. RAAS is one of the most important systems in the development of the pathogenesis of cardiovascular diseases. The activation of RAAS under stress conditions stimulates a series of processes such as oxidative stress related to cardiovascular damage, inflammation and insulin resistance[33]. Especially, the blockade of RAAS can stop the molecular and cellular mechanisms related to cardiovascular remodeling and the maintenance of high blood pressure. Therefore, the substances that are commonly used for the prevention of cardiovascular diseases are angiotensin converting enzyme (ACE) inhibitors and AT-1R blockers, direct renin inhibitors, and mineralocorticoid receptor antagonists[36-41] (Table 1).

Symptoms of depression, which are related to stress and social interaction disorders, are risk factors for cardiovascular diseases. Additionally, it has been reported that the physiological response to acute stress in depressed people is not the same compared to healthy individuals. Especially, the symptoms of social isolation and depression are reported as biological and behavioral risk factors which show a negative development for cardiovascular diseases and accompanied deaths. It refers to the evidence that the activation of the hypothalamic-pituitary-adrenal (HPA) axis in depressed patients, the changes in the autonomic control of the heart, sympathoadrenomedullar system and behaviors are related to stress. The increased response to stress in the absence of sensorial information resources, which provide acute or chronic stress adaptation, is shown as the cause of increased mortality rates in socially isolated individuals[33]. It has been shown that individuals who have depressed symptomatology and hypertension have a higher risk of mortality compared to individuals who have only one symptom[42]. It has been suggested that the underlying mechanism for this event can be related with increased RAAS activity[43]. The pathophysiological effects of RAAS on the cardiovascular system are formed by AngII and aldosterone. It is known that the production of AngII and aldosterone increases the expression of norepinephrine (NE) and inhibits the uptake of NE from the nerve endings[13,14].

The cardiovascular effects of AngII are similar to the sympathetic activation and excessive release of NE. Chronic exposure to the excessive amount of AngII causes exaggeratedly increased ventricular hypertrophy, vasoconstriction, and sodium retention (Figure 3). It has been discovered that chronic benefits of ACE inhibition in patients with heart failure depend on the increase of bradykinin not on the chronic inhibition of AngII production[44-47] (Table 1). The selective implementation of mineralocorticoid receptor antagonists after the initiation of ischemic damage in animals prevents ventricular dilatation and the decrease in systolic function in control animals (Table 1). It has been reported that these findings are clinically valid for human cardiovascular diseases[14].

Angiotensin converting enzyme 2 (ACE2) is a membrane-transitive type 1 glycoprotein, which is an element of the RAAS and is expressed and active in many tissues. The maximum expression of ACE2 was observed in the kidneys, endothelium, lungs, and heart. The domain of the ACE2 enzyme, which represents catalytic activity, has the same morphology with an ACE enzyme in the rate of 61% but shows different functional properties. While ACE2 is functioning as dipeptidase, ACE2 functions as a carboxypeptidase. The main substrate of ACE2 is AngII; otherwise, the substrates, which ACE2 has low interest, are composed of AngI, vasoactive bradykinin, apelin13 and 36. Angiotensin 1-7 (Ang 1-7), which is the main product of ACE2 activity, shows antioxidant and anti-inflammatory effects, contrary to AngII. The balance between AngII and Ang1-7 plays an important role in guiding the development of vascular diseases[48]. In one study it has been shown that the decrease in the level of ACE2 expression, increases the formation of atherosclerotic plaques[49]. Some of the studies in the literature are trying to explain the relationship between the lack of ACE2 and development of systolic hypertension. The increase in hypertensive responses that develop against the application of AngII, excessive accumulation of AngII in kidney and development of early cardiac hypertrophy have been reported in rats that ACE2 gene is silenced[50,51]. The importance of ACE2 is impressed for balanced work of RAAS. Especially, ACE2 is more important than ACE in the regulation of the cardiovascular system. Because local levels of AngII and Ang1-7 are regulated by ACE2 in balanced work of RAAS[48]. The effect of chronic moderate exercise on the elements of RAAS has been studied in rats that were submitted to chronic moderate exercise for 16 weeks. A significant increase in the amount of ACE2 in the brains of rats that were submitted to chronic moderate exercise, was observed compared to the sedentary rats. It is thought that these data provide some of the parameters, which will explain the positive effect of long-term exercise on blood pressure[52].

Aldosterone plays many important roles in the brain, vascular physiology, and heart, besides its effectiveness in sodium transport in the kidney. It affects cardiovascular diseases such as hypertension, MI, and heart failure. Therefore, the necessity for the prevention of pathophysiological side effects of aldosterone is emphasized in the development of the treatment of cardiovascular diseases[14]. The level of aldosterone was found 20 times higher in patients with heart failure than in normal individuals. It is thought that this increase is due to the increased production of aldosterone in the adrenal glands and subsequently high AngII concentration. Aldosterone has electrolytic and metabolic effects, stimulating the development of myocardial fibrosis and facilitating cardiovascular remodeling and development of disease processes (Figure 3). Aldosterone has a negative effect on endothelial function as well as inhibition of NE uptake, but it increases the level of plasminogen activator inhibitor-1. The positive effects of aldosterone antagonists have been re-

ported in heart failure, and this effect has been attributed to the effect of aldosterone on NE[13] (Table 1).

It has been reported that inhibition of ACE is essential and adequate for limiting the production of aldosterone in cardiovascular diseases. AngII can increase the production of aldosterone; besides this, it is also known that there are several mediators, which can regulate the expression and production of aldosterone. As a result of the series measurement of aldosterone concentration, it is noted that the concentration of circulating aldosterone is temporarily suppressed by inhibition of ACE. This is called "aldosterone escape". It is emphasized that this event shadows the significant clinical benefits provided by the inhibition of ACE. Consequently, the insufficiency of ACE inhibitors, AngII receptor antagonists, and neurohormonal inhibition strategies related to ADRβ blockers has been reported to reduce the amount of circulating aldosterone in heart diseases with left ventricular systolic dysfunction[14].

Stress and Glucocorticoids

The role of glucocorticoids in the mechanism of cardiovascular responses to stress has not yet fully understood. It is thought that the glucocorticoids show their blood pressure increasing effects against many physical stressors by supporting the peripheral effects of catecholamines[53].

Exposure to stress activates the hypophysiotrophic neurons in the paraventricular nucleus of the hypothalamus by stimulating the HPA axis[54]. These neurons secrete releasing hormones such as corticotropin releasing factor into the portal circulation of the median eminence. These releasing hormones provide the secretion of the adrenocorticotropic hormone by affecting the anterior pituitary gland. This hormone stimulates the synthesis and secretion of glucocorticoid hormones (e.g. corticosteron in rats, cortisol in human) by affecting the internal part of the adrenal cortex (zona fasciculata)[4].

The activation of the HPA axis results in increased amount of circulating glucocorticoids. The achievement of glucocorticoid levels to the highest plasma level occurs within minutes after the onset of stress. The two-step hormonal mechanism of HPA stimulation acts slowly compared to the waiting period of the synaptic mechanism that initiates the sympatho-adreno-medullar activation. Thus, releasing regions with a relatively long-term and strong effect are involved in this two-step mechanism. Subsequently, glucocorticoids potentiate numerous sympathetically-mediated effects such as the mobilization of the stored energy and peripheral vasoconstriction. Additionally, the adrenal cortex is directly innervated by the sympathetic nervous system, and this innervation can regulate the release of the corticosteroids. Therefore, the HPA axis and central nervous system have many complementary effects, including the provision of energy and the continuity of blood pressure during stress[4].

Glucocorticoids produce both genomic and non-genomic effects in the body. Their genomic effects occur by binding to glucocorticoid receptors (GR) and mineralocorticoid receptors (MR) in some tissues. These receptors affect transcription factors as ligand-dependent and thus show their effects in the long term by causing a change in gene transcription[55]. MR show a great interest to the endogenous glucocorticoids, which are secreted by the circadian rhythm. GR show a low interest to corticosteroids and bind to corticosteroids if an increase in the amount of corticosteroids exhibit in stress response. In contrast, the non-genomic effects of glucocorticoids may occur within minutes, and thus the non-genomic signalization for the rapid negative feedback inhibition of HPA axis occurs with the rapid increase of circulating glucocorticoids within minutes. The non-genomic effects most likely occur as a result of target cell membrane interaction[4].

It has been stated that the increase of chronic and systemic glucocorticoids causes an increase in cardiovascular and catecholamine responses to acute physiologic stress. Because cardiovascular responses are generated against new and life-threatening stresses if these stresses are experienced before. The prolongation of chronic stress may lead to a sustained attention that includes a normal blood pressure increase. The literature includes little information related to the central effects of chronic increase of glucocorticoids in cardiovascular regulation, during stress. There is significant variability between people in terms of sensitivity to stress and glucocorticoids. Therefore, some people are sensitive to the negative effects of stress, but others are resistant. The importance of understanding the interacting roles of glucocorticoids, stress, and genetic predisposition in the development of cardiovascular diseases is essential for the development of new methods of treatments to be implemented and precautions to be taken against cardiovascular diseases[53].

Stress and nitric oxide synthetase (NOS)

There are three different NOS, which synthesize nitric oxide (NO) in mammals. The first information related to the synthesizing of NO has been obtained from the observations made on the immune system (inflammatory) cells. While NO is not detected in inactive inflammatory cells, it was found that NO is secreted by the activation of these cells. For this reason, NOS in inflammatory cells is called as "inducible NOS" (iNOS). Subsequently, unlike inflammatory cells, the endothelial and neuronal tissues were found to produce and secrete NO continuously, and in earlier times NOS in these tissues was called "constitutive NOS" (cNOS) while later, they were called as endothelial NOS (eNOS) and neuronal NOS (nNOS) according to the tissue of origin[56]. All isoforms of NOS have a regulative role in the cardiovascular system. eNOS is the most important isoform, which regulates blood pressure by keeping blood vessels in the dilated form and showing several vascular protective and anti-atherosclerotic effects[57].

NO is also known as an endothelium-derived relaxing factor. It is a small molecule, which is described as a free radical and consisting of a nitrogen and an oxygen atom, containing unshared electron, acting as a weak oxidant or reductant component that affects many reactions. As an uncharged molecule, it passes the membranes easily and enters the reaction quickly because of having an unpaired electron. Its half-life is about 20-30 seconds[56].

Endothelium is a large paracrine organ, which regulates vascular tone, cell proliferation, thrombogenesis, and the interaction between leukocytes and platelets by secreting a number of factors. Endothelium responds to internal and external stimuli by secreting complex cell membrane receptors, signal transduction mechanisms, vasoactive and thromboregulatory

substances and growth factors. It adjusts the flow and distribution of blood according to the local environmental changes by organizing its own tone. Most vessels give a dilatation response to flow increase (shear stress). This is called as flow-mediated dilation (FMD). The main mediator of FMD is an endothelium-derived NO[58].

NO is synthesized from its precursor L-arginin by the enzymatic activity of eNOS that is located in *caveolae* which is formed by invagination of the cell membrane in endothelial cells. Caveolin-1 binds to calmodulin and inhibits the activity of eNOS. The binding of calcium (Ca^{+2}) to calmodulin separates caveolin-1 and leads to the production of NO by activating eNOS. Cofactors like tetrahydrobiopterin (BH4) and nicotinamide adenine dinucleotide phosphate (NADPH) play a role in the production of NO. Caveolae is rich from cholesterol and sphingolipids but poor from phospholipids. Caveolae is a structure in which receptors like G protein and protein kinase are clustered. Factors that cause differences in the lipid composition of cell membrane such as hypercholesterolemia may adversely affect NOS activity by disrupting the function of caveolae[59,60].

NO is an important endothelium-derived vasodilator and causes vasodilatation by resisting the effects of endothelium-derived vasoconstrictors such as AngII and endothelium. The main indicator of endothelial dysfunction is the impairment of endothelium-derived vasodilatation caused by NO[61,62]. Any impairment in NO production or activity causes effects that increase atherosclerosis, i.e. vasoconstriction, platelet aggression, proliferation of smooth muscle cells, leukocyte adhesion and oxidative stress[63].

In basal conditions, endothelium functions to keep the vein relatively dilated. However, the endothelium has the capacity to react to various physical stimuli such as shear stress. The endothelial cell membrane involves specialized ion channels such as "potassium channels activated by calcium". Calcium intake is increased when the endothelium gets hyperpolarized when faced with shear stress. Calcium, mediated by calmodulin, activates eNOS and initiates NO production[59,64].

Many intracellular and extracellular molecules stabilize NO or break it chemically. It is supposed that the effects of NO, whose intracellular location is instable, are controlled by NOS, and many studies were conducted about this. NOS was not found in the cell nucleus, although it was proved that NO increases the transcription of many genes, including the guanylate synthase genes, in the cell nucleus. It was found that NOS is seen in mitochondria, endoplasmic reticulum, and Golgi apparatus, but its functionality could not be explained clearly. It was also reported that NOS is related to cytoskeleton molecules. It is estimated that this relation functions as a mechanoreceptor for shear stress[56].

In various shear stress cases, eNOS has some significant physiological effects such as acute and chronic regulation of vein diameters, control of cardiac inotropic, lusitropic and chronotropic situations under stress conditions; and cell stimulation for the restructuring of heart. In genetic studies, the gene that codes eNOS is indicated as a gene that changes pathological conditions such as chronic adaptation that develops against hemodynamic forces or peripheral vascular resistance stimulated by exercise. These data support the relationship between eNOS and human diseases. Although there is no evidence that endothelial NOS is a gene associated with diseases, many cardiovascular risk factors cause oxidative stress, eNOS reduction, and endothelial dysfunction[57].

eNOS mediated chemical events are among primary homeostatic mechanisms required for the regulation of blood pressure and organ blood flow. Any change in blood pressure stimulates systemic and local physiological regulation mechanisms. The regulation of myogenic tonus, local functions of catecholamine, and RAAS occur when NO produces paracrine from endothelium. The speed of the effects of these feedback mechanisms on blood pressure may vary considerably compared to each other[57].

Barbieri et al[65] had recourse to Western Blot analyses to determine the increase in eNOS level related to the increase in vascular endothelial growth factor (VEGF) in mice exposed to chronic restraint stress. In this study, there was a significant increase in eNOS level in tumor samples from the stress group compared to the control group. Chronic stress did not stimulate tumor growth in mice where eNOS gene is mutated. These findings are considered evidence for the fact that eNOS enzyme plays a role in tumor growth induced by stress[65].

Stress and Endothelin-1

The vasoactive substances secreted from endothelium for the generation of vascular tone are not only mediators with dilating effects but also vasoconstrictor mediators. The best-defined vasoconstrictor mediator is endothelin (ET). ET is divided into three, namely ET-1, 2 and 3, each of which is a peptide family consisting of 21 amino acids. ET-1 is found most in endothelial cells, and is the strongest vasoconstrictor agent. It is also produced in the heart, kidneys, central nervous system, and posterior lobe of the pituitary gland. ET-2 is mostly produced in endothelial cells, the heart, and the kidneys. ET-3 is produced in the gastrointestinal and central nervous system along with endothelial cells[66].

ET-1 production is increased by many factors, including vasoactive hormones, growth factor, hypoxia, shear stress, lipoproteins, free radicals, and endotoxin. The suppression of ET-1 production is caused by endothelium-derived NO, nitrovasodilators, natriuretic peptide, heparin, and prostaglandins[66]. There is evidence that ET-1 production is increased in hypertension model[67].

ET-1 synthesis is complicated. ET-1 is synthesized by a precursor molecule, named pre-proendothelin that converts into a larger endothelin and finally becomes active ET-1 by means of endothelin-converting enzymes (ECE-1 and 2). Contrary to NO, oscillated rapidly in response to vasodilators and inactivated in seconds, ET-1 related construction starts slowly and continues for hours, even for days. The primary role of ET-1 in the regulation of vascular tonus is dependent on the vasoconstrictor effect[66-69].

The complex vasoactive effects of ET-1 accrue by means of two receptors, i.e. Endothelin-A (ET-A) and Endothelin-B (ET-B). ET-A, existing in smooth muscle cells of veins, is responsible for vasoconstriction. ET-2 and 3 cause a temporary vasodilatation mediated by NO and prostacyclin before a long-term vasoconstriction that occurs through ET-A. ET-B receptor, existing in venous endothelial cells, plays a role in vasodilatation by mediating the oscillation of

endothelium-derived vasodilators. Studies have shown that NO and ET-1 controls each other through the autocrine feedback mechanism[66,69].

The physiological effects of ET-1 mediated by ET-A receptor are important for the maintenance of blood pressure. The total physiological effects of ET-1 tend to increase blood pressure. ET-1 has cardiovascular effects as a result of the balance between ET-A and ET-B receptor-mediated effects, which is why, with the changes in numbers and functions of receptors, the cardiovascular effects of endogenous ET-1 are likely to vary. For instance, in case of endothelial dysfunction related to a decrease in NO activity, ET-B receptor-mediated vasodilation may be reduced, and ET-A receptor-mediated vasoconstriction may be increased. The number of endothelial receptors is dependent on many factors. AngII and phorbol esters reduce the number of endothelial receptors and increase the number of ischemia and cyclosporine endothelial receptors[66].

In addition to its vasoactive characteristics, ET-1 stimulates smooth muscle cell proliferation through same receptors. Thus, it contributes to vascular restructuring and leukocyte adhesion. ET-1 also shows inotropic, chemotactic and mitogenic characteristics. Additionally, it plays a role in the regulation of water and salt homeostasis by affecting RAAS, vasopressin and atrial natriuretic peptide and stimulating the sympathetic nervous system. ET-1 generally tends to increase blood pressure and venous tonus. That is why ET-1 antagonists play a significant role in the treatment of cardiovascular and kidney diseases such as hypertension, pulmonary hypertension, chronic heart failure, and chronic kidney failure, which develop because of local and systemic vasoconstriction and cell growth[66-69] (Table 1).

It is reported that the mitogenic effect of ET-1 contributes to the development of atherosclerosis. The vasoconstrictor and mitogenic effects of ET-1, mediated by sympathetic nervous system and renin-angiotensin activation, show that ET-1 is likely to be a component in the pathogenesis of cardiovascular diseases. ET-1 causes an increase in human vascular smooth cells which occurs through platelet-derived growth factor, fibroblast growth factor and epidermal growth factor as a result of the response to ET-A receptor. That is why anti-endothelin treatment may not be only anti-hypertensive but also anti-atherosclerotic[66,70,71] (Figure 4).

Under *in vitro* conditions, ET-1 has positive inotropic and chronotropic effects. In animals, low-dose endothelin has positive inotropic effects while high-dose ET-1 has negative inotropic effects. The latter is probably due to myocardial ischemia resulting from high afterload and coronary vasoconstriction. The systemic administration of ET-1 in human beings reduces cardiac output. This effect is probably caused by increased afterload and baroreceptor-mediated reduced heart rate[66].

Endothelin-1 contributes to the pathogenesis of significant diseases such as arterial hypertension, atherosclerosis and heart failure. The level of ET-1 was found high in patients with atherosclerotic vascular disease[68]. The injection of ET-1 into heart causes coronary vasoconstriction, which results in the development of myocardial ischemia and deadly arrhythmia. That is why ET-1 antagonists have the potential of being antiarrhythmic agents[66]. There are many studies on ET receptor

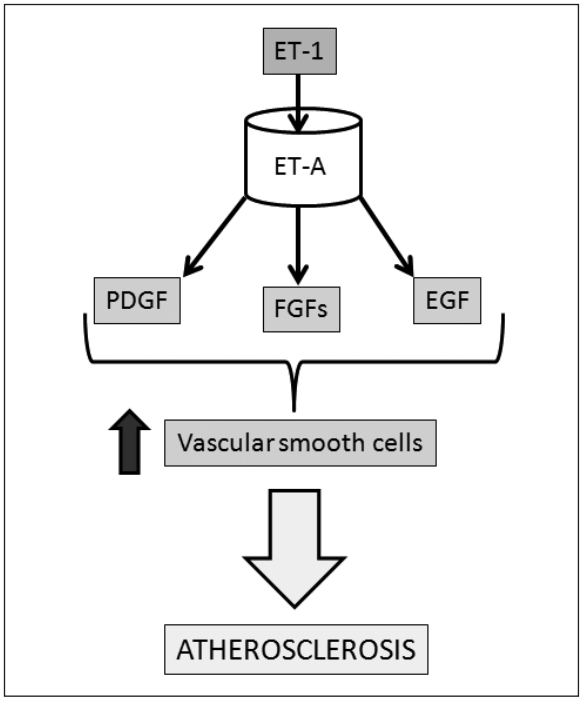

Figure 4: Schematic drawing demonstrating the atherosclerotic effect of endothelin-1 (ET-1).
ET-A: endothelin-1 receptor A, receptor PDGF: platelet-derived growth factor, FGFs: fibroblast growth factors, EGF: epidermal growth factor.

antagonists in cardiovascular disease models. ET receptor antagonists prevent the development of vascular and myocardial hypertrophy in hypertension (Table 1). It has experimentally been shown that ET receptor blockade prevents endothelial dysfunction and structural vascular changes that develop because of hypercholesterolemia in atherosclerosis. In an experimental ischemic study, the administration of ET receptor antagonists reduced the infarct size and prevented remodeling of the left ventricle that developed after myocardial infarction. The use of BQ123, the specific ET-A receptor antagonist, increased the survival rate significantly in experimental heart failure model. In several clinical cases such as congenital heart failure and arterial hypertension, the single or combined use of ET receptor antagonists resulted in recovery of patients' clinical symptoms. In cases of scleroderma, which is associated with primary pulmonary hypertension, treatment with ET receptor antagonists resulted in recovery in exercise capacity. ET receptor antagonists, complementing the use of RAAS antagonism, are considered new and promising therapeutics used in heart failure treatment. Therefore, they are seen as potential agents used for promising treatment of cardiovascular diseases. Clinical studies continue to provide detailed explanation in relation to the effects of ET receptor antagonists on diseases and death[66,68].

Long-term anti-endothelin treatment may contribute to the elimination of symptoms and prevent the progress of heart failure. It is also reported that endothelin contributes to the development of sclerotic renal changes in end-stage renal diseases. The use of anti-endothelin in its treatment may provide benefits, additional to the useful and known effects of RAAS inhibition for chronic kidney failure. Clinical

studies show the potentially useful effects of endothelin antagonists in patients with essential hypertension, pulmonary hypertension and heart failure[66].

Endothelin-1 increases ECE activity in endothelial cell culture and tissue RAS in the mesenteric tissue of isolated rats. It additionally increases aldosterone oscillation in isolated cortical zona glomerulosa cells and adrenaline secretion from medullar chromaffin cells. AngII increases the ET-1 level and ECE activity at the level of tissues. Hemodynamic and proliferative effects of AngII may be blocked by ET-A receptor antagonists (Table 1). These results suggest that, in diseases such as heart failure, there is a relationship between AngII and ET-1, which is based on a positive feedback mechanism. It is reported that the suppression of the endothelin system may be a complementary method of treatment in patients with permanent RAAS activation resisting to an ACE inhibitor or angiotensin receptor blockade[66].

Stress and L-type Calcium (Ca^{+2}) channels

L-type Ca^{+2} channels exist in many tissues, including heart and smooth cells. These channels are highly sensitive to dihydropyridine, phenylalkylamine, and benzodiazepine. L-type Ca^{+2} channels consist of various subunits such as alpha-1, alpha-2, beta, gamma and delta. The function of L-type Ca^{+2} channels is regulated by the second messenger system particularly in the heart muscle. Therefore, various drugs are likely to change channel functions indirectly by affecting receptor proteins or activating second messengers. It is known that L-type Ca^{+2} channels play a role in determining the characteristics of normal physiological functions in cardiac myocytes. L-type Ca^{+2} channels also play an important role in several cell functions including incidents such as membrane excitability, Ca^{+2} homeostasis, protein phosphorylation and gene regulation[72].

Depolarization mediated by L-type Ca^{+2} channels leads to the plateau phase of action potential in the heart and the pacemaker potential in node cells. The entry of calcium ions into cells through L-type Ca^{+2} channels is of great importance for the occurring of excitation-contraction coupling in heart[73,74].

L-type Ca^{+2} channel is a protein that involves multiple passage of alfa-1c (α1c) subunit in pore structure in the membrane and that consists of regulatory alfa2/delta (α2/δ) and beta (β) subunits. The α1c subunit is the voltage-gated part of L-type Ca^{+2} channels and involves receptor areas for different classes of calcium channel antagonists/agonists. Therefore, α1c subunit plays a role in determining main electrophysiological properties of L-type Ca^{+2} channels[75].

In many cases of heart diseases, changes in the function or intensity of L-type Ca^{+2} channels are reported. The change in the function or intensity of L-type Ca^{+2} channels, plays a part in the occurrence of several heart diseases, including atrial fibrillation, heart failure, and ischemic heart disease. That is why there is a relationship between cardiovascular diseases and pathophysiological changes in Ca^{+2} homeostasis regulated by L-type Ca^{+2} channels. Furthermore, it is emphasized that the impairment of Ca^{+2} regulation mediated by L-type Ca^{+2} channels is required for the pathogenesis of cell death. However, it is still unclear whether L-type Ca^{+2} channels play a role in cardiomyocyte damage induced by restraint stress, and to which extent channel intensity and function are affected by any possible stress[76].

It has been found that acute restraint stress increases L-type Ca^{+2} current (ICa-L), which refers to an increase in activation characteristics of calcium channels. This reversible incident culminates first in temporary calcium overload, then in apoptosis and eventually in cardiomyocyte damage. However, L-type Ca^{+2} channel changes resulting from chronic stress could not be explained[77].

Zhao et al showed in their study that restraint stress caused cardiac dysfunction and structural changes in the heart. It was also found that severe cardiomyocyte apoptosis and necrosis occurred after restraint stress. Related to stress-induced cardiovascular damage and diseases, cardiomyocyte death is considered the most significant cellular event. The pathological mechanism of cardiomyocyte damage caused by stress is nevertheless not known[78].

Another study revealed, once again, that acute restraint stress caused an increase in L-type Ca^{+2} channel current (ICa-L). This increase is associated with the increase in Ca^{+2} channel activation character. In the same study, they used the patch-clamp technique to show the ventricular myocyte ICa-L change in rats exposed to chronic restraint stress. The results indicate that chronic restraint stress increases ICa-L. In addition, reverse transcriptase polymerase chain reaction (rtPCR) and Northern Blot analyses suggest that, after chronic restraint stress, the messenger ribonucleic acid (mRNA) of α1c subunit in ventricular L-type Ca^{+2} channel increased significantly. Western Blot analyses have also been used to determine the increase in the amount of α1c subunit protein. In exposure to chronic stress, the increase in the expression of α1c subunit in L-type Ca^{+2} channel contributes to changes in ICa-L, unlike the regulatory mechanisms that cause changes in protein-kinase-A (PKA) dependent channel activation, induced by acute stress. However, the increase in the number of channels is not associated with the changes in channel activation and inactivation characteristics. The results of this study indicate that chronic restraint stress causes an increase in the channel current by increasing the expression of α1c subunit in L-type Ca^{+2} channel. This causes cardiomyocyte damage, which occurs as a result of stress-induced changes in calcium uptake. In acute restraint stress, the increase in current takes place by means of PKA activation. The findings of this study, while offering new approaches to understand the mechanism of stress-induced cardiomyocyte damage, may suggest that L-type Ca^{+2} channels cause cardiomyocyte damage induced by chronic stress. The results obtained in this study may contribute to the treatment of and prevention from cardiovascular diseases[76].

Conclusion

Stress is a state characterized by an impairment of homeostatic balance as a result of various factors. Because of balance disorder in the body in case of stress, the risk of developing hypertension and cardiovascular diseases increases. With regard to the duration of exposure to stress, stress is as acute or chronic. In both cases, the responses of central nervous and endocrine systems tend to recover the impaired balance of the body. Defining the bodily responses under various stress conditions is of particular importance for the treatment of stress and accompanying disorders.

Conflict of interest
The authors report no conflict of interest.

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