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Pathogenic mechanisms of arterial hypertension in patients with chronic psychoemotional stress

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Abstract

The article is based on literature review and describes the implication of psycho-emotional factors in the development of arterial hypertension (HTN). HTN and its cardiovascular complications take a leading place among the causes of high mortality and disability in the adult population. High blood pressure (BP) is known to be a major modifiable risk factor for premature death, myocardial infarction, stroke and other cardiovascular diseases. The pathogenesis of HTN is complex and multifactorial with a significant variability of the involved mechanisms in individual patients. In this regard, the determination of specific pathogenic mechanisms underlying stable BP elevation would substantially individualize therapeutic approaches, and hence increase the effectiveness of treatment. The role of psycho-emotional stress has been recently reassessed and it is widely discussed as a factor contributing to the HTN formation. Global urbanization, sedentary lifestyle, daily work-related stress, lack of physical activity and social support lead to increased anxiety, uncertainty, and finally to chronic mental and emotional stress. This review analyzes the main physiological markers of chronic stress, neuroendocrine and immunological mechanisms underlying the development of HTN. The role of endothelial dysfunction as a binding link between chronic stress and high BP is also discussed.

Key words: arterial hypertension, psychoemotional stress, pathogenesis, cortisol, C-reactive protein, endothelial dysfunction

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Патогенетические механизмы формирования стойкой артериальной гипертензии при хроническом психоэмоциональном напряжении

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Резюме

Статья представляет собой обзор литературы, в котором обсуждается значимость психоэмоциональных факторов в формировании стойкой артериальной гипертензии (АГ). АГ и ассоциированные с ней сердечно-сосудистые заболевания занимают лидирующее место среди причин высокой смертности и ранней инвалидизации взрослого населения. Как известно, повышенное артериальное давление (АД) является основным модифицируемым фактором риска преждевременной смерти, инфаркта миокарда, мозгового инсульта и других сердечно-сосудистых осложнений. Патогенез АГ является сложным и многофакторным с существенной вариабельностью задействуемых механизмов у каждого конкретного больного. В этой связи определение конкретных патогенетических механизмов, лежащих в основе развития стойкого повышения АД у отдельного пациента, позволит существенно индивидуализировать терапевтические подходы, а следовательно, и повысить эффективность лечения. Среди факторов, способствующих становлению АГ, в последнее время вновь стало широко обсуждаться влияние психоэмоционального стресса. Глобальная урбанизация, малоподвижный образ жизни, ежедневный стресс на рабочем месте и отсутствие социальной поддержки приводят к повышенной тревожности, неуверенности и, наконец, к хроническому психо-эмоциональному напряжению. В данном обзоре проанализированы основные психофизиологические маркеры хронического стресса, а также нейроэндокринные и иммунологические механизмы, лежащие в основе формирования АГ. Обсуждается роль эндотелиальной дисфункции в качестве связывающего звена между хроническим стрессом и стабильным повышением АД.

Ключевые слова: артериальная гипертензия, психоэмоциональный стресс, патогенез, кортизол, С-реактивный белок, эндотелиальная дисфункция

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Introduction

Nowadays, arterial hypertension (HTN) and associated cardiovascular events take the leading positions among the main causes of mortality and early disability. According to the World Health Organization, about 17 mln fatal cases result from cardiovascular diseases annually, and 9.4 mln of deaths are related to HTN complications [1].

HTN is the leading risk factor of coronary heart disease and cerebrovascular diseases, determines 45 % of deaths caused by heart diseases and 51 % of fatal cases due to stroke [2]. The national epidemiological study ESSE-RF demonstrated that 48.1 % males and 40.7 % females have elevated blood pressure (BP) in the Russian Federation, but HTN-related mortality rate is 4.7-fold higher in males compared to females [3, 4]. High rates of morbidity and mortality may be due to various factors: population aging, environmental factors, behavioral characteristics, such as excessive consumption of salt and alcohol, smoking, overweight, hypodynamia, continuous stress [5, 6].

HTN pathogenesis is complex and related to multiple factors, with a substantial variability of the involved mechanisms in each patient. In this regard, the identification of specific pathogenic mechanisms underlying the development of BP increase, will allow to individualize therapeutic approaches and, therefore, increase treatment efficiency.

Role of chronic psycho-emotional stress in the development of arterial hypertension

Recently, the influence of psycho-emotional stress has been widely discussed again among the factors contributing to HTN [7–11].

Within the WHO program "MONICA-PSYCHOSOCIAL", 657 men aged 25–64 years, residents of one of the Novosibirsk districts, were examined to assess the contribution of stress in the family and at work to the risk of HTN development in open male population. Based on the 14-year monitoring, the greatest risk of HTN in open male population under stress at work and in the family was found during the first 10 years, and was 5–7 times higher than the risk in subjects without stressful situations [12].

M. Timio et all (1996) observed the nuns, who lived in solitary and changeless environment in the monastery, and a control group of females living in the same region outside the monastery. During the 20-year period, a significant increase in systolic and diastolic BP was found in the control group compared to the nuns, due to the reliable psycho-emotional protection of the latter, preventing HTN [13].

In the population study by N. Granado et all. (2009), after several years of service and participation in military actions, 6.9 % previously healthy servicemen developed HTN confirming the role of psycho-emotional stress associated with military environment in the HTN development [14].

Hans Selye's theory was the first step of stress research as a general adaptation syndrome [15]. The concept of stress is characterized by the condition occurring due to exposure to adverse environmental factors, emergency events and circumstances. Stress is usually considered as any stimuli (physical, social, and psychological) leading to the state of high tension, physical and mental discomfort, and depression [16]. In response to acute exposure to stress factors, the hypothalamic-pituitary-adrenal axis and sympathoadrenal system are immediately activated to maintain homeostasis, which is a necessary protection mechanism. However, upon constant exposure to stress factors or long-term readiness for stress, the allostatic load state is achieved, which is manifested in mental stress, negative emotional experience, anxiety, and deadaptation. Currently, psycho-emotional stress is considered as subjective reactions related to internal mental tension and excitement. Long-term psycho-emotional stress leads to a decrease in adaptation and contributes to the development of somatic disorders, including cardiovascular and endocrine diseases [17–19].

Restrained negative emotions leading to long-term psycho-emotional stress, associated with the lack of adequate physical exercise caused by lifestyle or professional activities, are one of the key factors underlying the formation of psychosomatic disorders [20]. Lifestyle changes and negative behavioral characteristics such as smoking, alcoholism, excessive consumption of carbohydrates and fats, and hypodynamia, play an important role in the negative influence of psycho-emotional stress on the cardiovascular system [11, 19]. Lack of physical exercise hampers

efficient response to the emotional stimuli, leading to violation of the evolutionary mediated relationship between the anxiety reaction and subsequent functional activity in motor movements [20, 21]. When physical exercises are performed, biological mechanisms (sympathoadrenal and pituitary-adrenal axis, cardiovascular system) are activated, along with the changes at the cellular and molecular levels. These changes are similar to activation induced by stress. Thus, under the influence of regular physical exercise, favorable conditions for the cross-adaptation and increased resistance to stress are developed [22–24]. S. Toker et all. in a prospective study showed that regular physical exercise reduced the risk of depression and occupational burnout [25]. Meta-analysis by K. Forcier et all assessed correlation between physical activity, cardiovascular stress reactivity and recovery period and showed that adequate physical training correlated to lower indicators of heart rate and systolic BP in response to stress, as well as was associated with quicker recovery of baseline heart rate [26]. Meta-analysis by D. Gasperin et all (2009) showed that healthy persons with higher BP level during the performance of psychologically stressful tasks (stress reactivity tests) and after them (recovery period), were subsequently more prone to the HTN development [27]. As known, recurrent episodes of hyper-reactivity of the cardiovascular system and delayed recovery period can lead to HTN due to vascular remodeling and long-term BP dysregulation [28, 29]. Thus, physical exercises have a favorable impact on cardiovascular reactivity, mitigate negative consequences of stress, and facilitate recovery after stress. Besides, physical exercises have immediate psychological benefits as compared to other procedures, and, therefore, they can serve as efficient adjuvant therapy [28].

The leading role of psycho-emotional factors for HTN development was studied in early 20th century by Russian scientists G. F. Lang and A. L. Myasnikov. According to their ideas, the formation of a pathological dominant in the brain and BP central dysregulation in subjects with frequent psycho-emotional overloads was the main reason of HTN [30, 31]. Subsequently, based on the experimental models, the neurogenic HTN concept was investigated by foreign scientists, such as B. Folkov, G. Noll, J. Henry and others [32, 33]. Currently, this theory remains relevant due to a high proportion of negative psychosocial factors in the modern society and their role for somatic disorders.

The interaction between psycho-emotional stress and HTN is not easy to establish due to the lack of specific standard techniques for stress evaluation. Some researchers observe physiological changes upon exposure to stress factors, associated with activation of the hypothalamic-pituitary-adrenal and sympathoadrenal axes, assess the serum levels of catecholamine [34, 35], cortisol [36], and dehydroepiandrosterone [37, 38]. For example, M. Esler et all (2008), by measuring the concentration of noradrenaline and its lipophilic metabolites in the internal jugular vein, determined the circulation of noradrenaline in subcortical structures of the brain. They showed increased noradrenaline circulation in the hypothalamus and amygdaloid nucleus in hypertensive patients and patients with panic disorder confirming the role of psycho-emotional factors in HTN pathogenesis [35] M. S. Gadinger et all. (2011) showed association of high emotional tension at work with higher cortisol/dehydroepiandrosterone index and, the decrease in circulating dehydroepiandrosterone, as compared to less stressful working conditions [38].

As hyperactivation of the sympathetic nervous system (SNS) under stress is undoubted, heart rate and BP variability are widely investigated. Thus, army officers with HTN, who have specific work-related stressful situations, showed sinus tachycardia at rest, a greater index of tension of regulatory systems, and higher autonomic rhythm indicator as compared to the control group [39]. Meta-analysis conducted by J. Thayer et all (2012) confirmed a potential role of heart rate variability as a marker of stress [40]. The authors detected the relationship between activation of some brain structures, namely the amygdaloid nucleus and medial prefrontal cortex that are responsible for threat and security perception, and heart rate variability. Meta-analysis of 22 cross-over studies conducted by P. Landsbergis et all (2013) demonstrated that significant emotional stress at work several years later resulted in increase of systolic BP by 11 mmHg and diastolic BP by 7 mmHg compared to the control age-matched

group. However, this relationship was significantly stronger in males than in females [41]. Another study revealed that psycho-emotional stress at work was associated with disruption of normal circadian BP rhythms. A lower decrease of systolic BP during nocturnal sleep was found in males experiencing high stress at work, as compared to those who had never experienced stress at work [42]. Thus, the cardiovascular system state is a universal indicator of adaptive reactions of the organism, and associated disorders of heart rate variability, BP and its circadian rhythms are markers of sympathetic dysfunction which plays the key role in HTN genesis [43]

Psychological scales and questionnaires are another common method to estimate emotional stress. There is a wide variety of these psychological scales. Perceived stress scale (PSS) [43] includes 10 questions about thoughts and feelings of a patient during the last month, and characterizes the frequency of certain emotions and intensity of individual perception of stressful situations. There are two main models to study the degree of psycho-emotional stress at work: "demand–control" occupational stress model of R. Karasek [45] and "effort–reward" imbalance model of J. Siegrist [46]. These models describe chronic stressful situations at work, associated either with high requirements and impossibility of independent control over situation, or with imbalance between efforts and the corresponding reward. M. Gilbert-Ouimet et all (2014) in their systematic review established a close correlation of "demand–control" and "effort–reward" occupational stress models with the HTN development [47]. MMPI test [48] consisting of 13 scales is used to assess the psycho-physiological profile. The interpretation is performed according to 10 basic scales: overcontrol, pessimism, emotional lability, impulsiveness, masculinity/femininity, rigidity, anxiety, individualization, optimism, and social introversion. PSM-25 Lemyre–Tessier–Fillion scale adapted by N.Ye. Vodopyanova (2009) is designed for measuring phenomenological structure of feelings (16) and determines the integral index of mental tension which correlates to the Hamilton's scale for anxiety and depression [49] and Spielberger–Khanin's scale for personal and reactive anxiety [50]. In most studies, increased level of anxiety and depression is considered as an equivalent to psychological stress and tension. Thus, influence of personal anxiety on the 16-year relative risk of HTN was studied in the open population of females aged 25–64 within the framework of the WHO "MONICA-psychosocial (MOPSY)" program. High level of personal anxiety was found among females and was associated with the increased HTN risk, especially in the first 5 years of follow-up. In another study, mental stress was assessed in patients with various HTN severity degrees and stages by psychological questionnaires, including the PSM-25 scale [52]. The significant increase in the stress level was found in patients with HTN stage 1 and 2; increase in neuroendocrine responses was also shown, manifested by elevated levels of cortisol and adrenocorticotropic hormone.

Chronic psycho-emotional stress, elevated levels of anxiety and depression are independent risk factors for adverse events in patients with HTN. O. V. Antonisheva demonstrated that high levels of depression and increased level of reactive and personal anxiety in HTN led to the increase in the incidence of unstable angina, hypertensive crisis and hospitalization [53].

Biomarkers of chronic psycho-emotional tension

Immunological biomarkers of psycho-emotional tension and arterial hypertension

Current literature provides convincing data in favor of influence of psycho-emotional tension on the immune system [54–57]. The occurrence of systemic inflammation is considered as a possible mechanism underlying the link between chronic stress and HTN [58, 59]. Psycho-emotional stress contributes to the activation of the hypothalamic-pituitary-adrenal and sympathoadrenal systems, thereby causing the release of cortisol and catecholamines, which, in turn, cause inflammatory reaction with production of cytokines and acute phase proteins. In case of long-term exposure to stress, a chronic subclinical inflammation develops, leading to endothelial dysfunction (ED) and atherosclerosis development [60]. As a result of inflammation modified proteins are produced in the vascular system, which are recognized by T-cells as foreign substances. This, in turn, leads to migration of macrophages, white blood cells, and the liquid portion of blood into the vascular wall, production of cytokines and free radicals,

proliferation of smooth muscle cells in the media, ultimately leading to vasoconstriction and vascular remodeling [61, 62].

Numerous studies indicates the relationship of psycho-emotional stress with a variety of immunological markers, such as the number of T-lymphocytes, natural killer cells, the level of interleukin-6, and the ratio of CD4/CD8 [63–65]. Changes in immunological parameters and subclinical inflammation are frequently found in people experiencing stress at work [66, 67]. Thus, the study of P. Marvar (2012) showed activation of T-lymphocytes and vascular inflammation induce d by repeated daily stress that might contribute to the HTN development [65]. A systematic review by A. Nakata in 2012 [66] also provided evidence that stress at work, especially high requirements and inadequate social support, is associated with the increased levels of immunological markers, namely the increase in C-reactive protein (CRP) serum level.

In recent years, the correlation between systemic chronic inflammation and HTN has been studied actively [68–71]. However, there is no definite answer to the question whether inflammatory reaction is a cause or consequence of HTN and the variety of the cause and effect relations of these factors is unclear.

Inflammation is an evolutionary protective and adaptive reaction occurring in response to potentially harmful external and internal factors. This is a complex process of a cascade of consecutive reactions including identification of the affected area and elimination of foreign substance by immune cells and subsequent tissue regeneration. Any inflammatory response includes interactions of the cell surface, matrix, and cytokines [72].

CRP is the most extensively studied immunological marker associated with cardiovascular diseases, including HTN [73–76]. CRP is an acute phase protein which activates the complement system, enhances phagocytosis and stimulates production of proinflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-alpha, and IL-1β. In several studies, a close relationship between the CRP content in the serum of patients and HTN and its complication was established. Thus, L. M. Vasilets et all (2012) found higher levels of cytokines — IL-6, tumor necrosis factor-alpha and CRP — in patients with HTN compared to the control group, and the multivariate analysis showed that CRP is a predictor for HTN [77]. Another study assessed the relationship of the cytokine level with BP elevation and HTN stage. An increase of CRP levels in subjects with metabolic syndrome and more severe HTN was found [78]. The increase in CRP was shown to be associated not only with HTN but also with pre-hypertension [79, 80]. In the CRISPS (Cardiovascular Risk Factor Prevalence Study) cohort study, the CRP plasma level was shown to be an independent risk factor for HTN in the future [81].

Moreover, CRP is widely used in epidemiological studies as an immunological marker upon exposure to stress factors [82–84]. Thus, M. K. Wium-Andersen et all (2013) in a cross-over study showed a strong relationship between the increased CRP level and increase of the risk of psychological distress and depression [85]. W. E. Copeland et all (2012) noted influence of anxiety disorders on the increase of the CRP level [86].

There are also data showing higher levels concentrations of IL-6 in patients with HTN as compared to normotensive patients [77, 87, 88]. O. A. Radaeva in a (2012) prospective study showed that change of the IL-6 level in patients with HTN is a risk factor of the development of cardiovascular events [89]. L. Lukic et all (2014) demonstrated that HTN development in patients with overweight and type 2 diabetes mellitus depends on the increase of insulin resistance and IL-6 [90].

M. Hamer et all (2007) showed that adequate physical training is associated with lower levels of IL-6 ($\beta = 0.24$; $p = 0.005$) and tumor necrosis factor-alpha ($\beta = 0.27$; $p = 0.002$) in response to stress, thus emphasizing a leading role of physical exercise as a mechanism that mitigates the cardiovascular risk [91].

Neurohumoral biomarkers of psycho-emotional tension and arterial hypertension

The dysfunction of the sympathetic nervous system is the most likely pathophysiological mechanism linking psycho-emotional stress and HTN. It is, characterized by excessive sympathetic activation and parasympathetic suppression [43]. Sympathoarenal overactivity place extremely important role in HTN pathogenesis [92–94]. Psycho-emotional tension is one of the most wide-

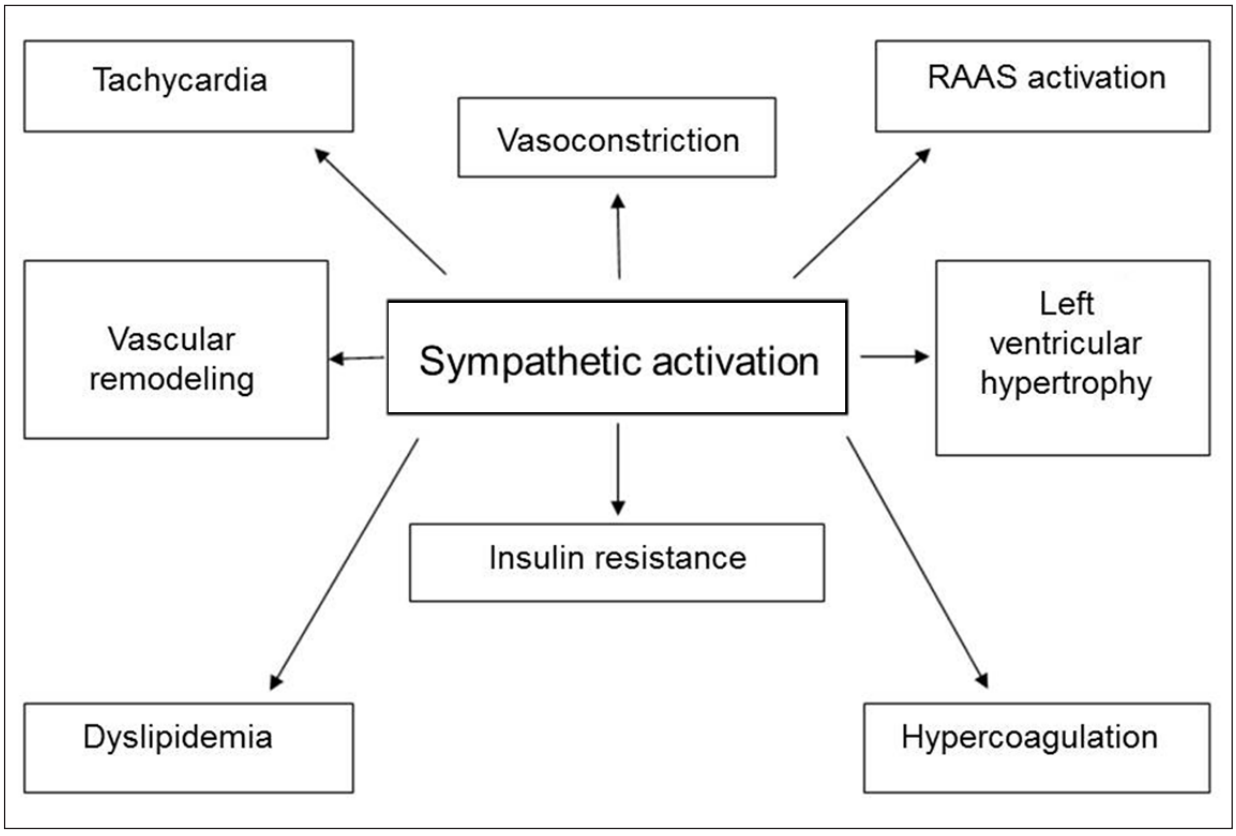
spread causes of SNS activation. Mechanisms underlying sympathetic hyperactivity associated with chronic stress are either directly related to the central autonomic dysregulation or influence of stress on lifestyle. Overweight, hypodinamia, hyperinsulinemia, and hyperleptinemia are known factors enhancing SNS activity [95].

SNS activation contributes to the BP increase and subsequent formation of resistant HTN. Moreover, it enables vascular remodeling and stimulates the growth of smooth muscle cells and the development of LV hypertrophy [34]. Also it contributes to the release of renin and activation of the renin-angiotensin-aldosterone system, leading to the increase of peripheral vascular resistance, retention of sodium and water, and, ultimately, to the BP elevation. In turn, angiotensin II may stimulate SNS, increasing the release of noradrenaline in sympathetic nerves [96]. The main effects of the SNS upon hypertension are presented in Figure 1.

Determination of catecholamines in plasma or urine is insufficiently to assess the sympathoadrenal activity with regard to the local response in various organs [94].

The hypothalamic-pituitary-adrenal axis and sympathoadrenal system are the main neuroendocrine components for stress response. The hypothalamus responds to a stress factor with secretion of corticotropin releasing hormone and vasopressin, stimulating the production of adrenocorticotropic hormone (ACTH) by the pituitary and the activation of noradrenergic neurons of the subcortical brain structures. ACTH contributes to synthesis of cortisol in the cortical adrenal zone. Under normal conditions, the production of corticotropin releasing hormone and ACTH is inhibited by high blood levels of cortisol by a feedback mechanism. Chronic and recurrent stress leads to dysregulation of the hypothalamic-pituitary-adrenal axis, increase of cortisol secretion, and decrease of secretion of dehydroepiandrosterone (DHEA) which is also synthesized in the adrenal cortex and has a common precursor with cortisol — pregnenolone. There is evidence that recurrent long-term stress

Figure 1. Adverse cardiovascular effects associated with sympathetic hyperactivation in arterial hypertension



Note: RAAS — renin-angiotensin-aldosterone system.

eventually lead to exhaustion of the mechanism and reduction in the corticosteroids production [37].

Numerous studies are devoted to changes in the level of cortisol, DHEA and their ratio as markers of psycho-emotional tension, as well as to their relationship with HTN. Thus, M. Esler et all. (2008) found significantly higher plasma levels of cortisol in patients with HTN and patients with panic disorder compared to the control group. These results prove psycho-emotional tension in patients with HTN [35]. V.I. Khasnulin studied manifestations of stress among residents of the North with HTN. Along with high levels of cortisol, a higher level of psycho-emotional tension based on the psychological questionnaires and excessive free-radical lipid oxidation were found in hypertensive inpatients [97]. M.A. Yermakova (2014) demonstrated significantly higher values of occupational burnout, index of fatigue and stress (by standardized scales) in hypertensive patients subject to psycho-emotional tension at work. The indices correlated with the increased levels of cortisol and adrenocorticotropic hormone [98]. J. Gonzales-Cabrera et all (2014) found a significant increase of the anxiety level, associated with the increased level of cortisol in saliva in students who had been studying for an important exam for several months [99]. S. Izawa et all (2012) showed that increase of the cortisol level in saliva and decrease of the DHEA level are present not only during stress perception, but also after the elimination of stress factor [100].

Nerve growth factor is another biomarker, attracting the attention of researchers and considered as a marker of stress. For the first time, this protein was discovered by E. Alleva et all (1996) in blood of mice with isolation-induced aggressive behavior [101]. In subsequent studies, changes in the level of the nerve growth factor in people experiencing acute stress, anxiety, fear, as well as mental illnesses, were found, thereby confirming the role of the nerve growth factor in pathophysiological response to stress [102]. The nerve growth factor is one of the main neurotrophic mediators involved in neurohumoral mechanisms of adaptation. Its highest concentrations are detected in the cerebral cortex, hippocampus, pituitary gland, basal ganglia, and thalamus. It is also involved in the activation of the hypothalamic-pituitary-adrenal axis, representing a link between neuroendocrine and immune mechanisms. In addition, the nerve growth factor participates in the regulation of immune cells, beta cells of the pancreas, cardiomyocytes, endothelial cells, and adipocytes [103].

S. Yanev et all (2013) discussed the potential role of the nerve growth factor in pathogenesis of cardiometabolic diseases such as atherosclerosis, HTN, diabetes mellitus, and neuropsychiatric pathology, as well as on the possibility of using neurotrophic factors in treatment of these diseases [104]. M. Esler et all (2008) measured the concentration of the nerve growth factor in walls of small veins in patients with HTN, patients with mental disorders and healthy individuals [35]. The nerve growth factor exerts trophic effect on sympathetic innervation of veins. Using the Western blotting procedure, the authors showed an increased concentration of the nerve growth factor in patients with HTN and in patients with panic disorder as compared to the control group and confirmed the role of this factor as a biomarker of emotional stress and for HTN development.

Endothelial dysfunction in arterial hypertension and psycho-emotional tension

The endothelium is a continuous layer of cells lining the inner surface of blood vessels. For many years the endothelium was considered only as a passive barrier between blood and the intercellular space of the vascular wall. However, this theory was revised after discovery by J. Vane and S. Banting et all (1976–1977) of prostaglandin X, which was subsequently called prostacycline. Their work demonstrated the role of the endothelium in the synthesis of vasoactive substances that contribute to relaxation of smooth myocytes and inhibition of platelet aggregation [105, 106].

Currently, endothelium is recognised as an important neuroendocrine organ that supports homeostasis by modulating vascular tone, transporting biological substances into cells, protecting blood vessels, and regulating inflammatory and reparative processes in response to damage. The endothelium produces a variety of biologically active substances, so called endothelial vasodilators and vasoconstrictors. The balance between them determines vascular tone and local blood circulation [107].

Endothelial vasodilators include nitric oxide (NO), prostacyclin, and endothelial hyperpolarizing factors (hydrogen sulfide, hydrogen peroxide, carbon monoxide, etc.).

NO is the strongest endogenous vasodilator. Penetrating from endothelial cells to smooth muscle cells of the vascular wall and binding with the guanylate cyclase, NO leads to the release of cyclic guanosine monophosphate and stimulation of protein kinase G, resulting in reduced intracellular calcium concentration, as well as vasorelaxation. In addition, NO has anti-inflammatory properties and inhibits cytokine synthesis and migration of white blood cells into the vascular wall, suppresses proliferation of smooth muscle cells and platelet adhesion [108–110].

Among the main endothelial vasoconstrictors, endothelin-1 and angiotensin II are the most powerful vascular constrictors. The effect of angiotensin II, mediated through angiotensin receptors type 1, is manifested not only in significant vasoconstriction but also in the increase of hypertrophy of smooth muscle cells, stimulation of aldosterone secretion and free radical formation, constriction of efferent arterioles of glomeruli and SNS activation [111]. In addition, endothelin-1 stimulates proliferation of smooth muscle cells, inhibits fibrinolysis, enhances the activity of the renin-angiotensin and sympathoadrenal systems [112].

The endothelial dysfunction is considered to be associated with imbalance between endogenous factors of vascular relaxation and constriction, with a predominance of the latter. Undergoing structural and functional changes, the endothelium loses its protective and antithrombotic function, activates the proliferation processes and remodeling mechanisms, acquires proatherosclerotic features. Endothelial dysfunction is associated with the production of substances with adverse effects on the vascular wall, such as endothelin-1, thromboxane A2, prostaglandin H2, and free radicals [113, 114].

The major cardiovascular risk factors including age, smoking, hyper- and dyslipidemia, diabetes mellitus, and HTN are considered as typical reasons leading to ED. However, ED itself is a risk factor for diabetes mellitus, atherosclerosis and HTN, being both a consequence and a possible pathogenic mechanism for their occurrence and progression [115, 116].

Various mechanic and pharmacological stimuli can lead to the release of factors synthesized by the endothelium. Vasomotor response to these stimuli can be estimated by changes in the artery diameter and linear blood flow velocity in a test with reactive hyperemia and nitroglycerin test. A common way to measure endothelium-dependent vasodilation is ultrasound scanning of the brachial artery diameter before and after transient ischemia (reactive hyperemia test) causing the increase in shear stress. Shear stress is the main physiological stimulus for the release of vasoactive factors by the endothelium and changes in vascular tone. Endotelium-independent vasodilation represents a functional state of vascular smooth muscle cells and is estimated by changes in the brachial artery diameter after sublingual intake of 500 μg of nitroglycerin [117, 118]. The described techniques are non-invasive and easy to perform; so they are widely used to determine ED.

To date, the evidence of a negative impact of psycho-emotional stress on endothelial function has been acquired [119–122]. ED may be an important pathogenic mechanism linking stress and cardiovascular morbidity associated with HTN, insulin resistance and atherosclerosis [121, 123–125]. In a study by V. Mausbach et all (2010), individuals exposed to chronic stress due to continuous care after a sick family member, showed significantly worse endothelium-dependent vasodilation in comparison with persons without stress. These findings confirmed a close relationship of psycho-emotional stress with ED [126]. I. S. Lutsky et all (2014) believe that chronic stress promotes the expression of specific NO-synthetase genotypes, leading to changes in secretion of vasoactive substances by the vascular endothelium towards higher production of vasoconstrictors and decrease in NO (main vasodilator) [127]. H. S. Kim et all (2013) examined 64 females and divided them into 2 groups according to the Global Severity Index applied for establishing psychological distress level [128]. Females with an index ≥ 50 (high distress level) had a reduced flow-dependent vasodilation compared with participants with the score < 50 (6.6 ± 2.2 and $9.5 \pm 2.9\%$, respectively, $p < 0.001$); similar results were observed in a test with nitroglycerin (14.6 ± 4.7 and $18.0 \pm 5.8\%$, respectively, $p = 0.016$). A. Non et all (2014) measured concentration of soluble cell adhesion molecules (slCAM-1)

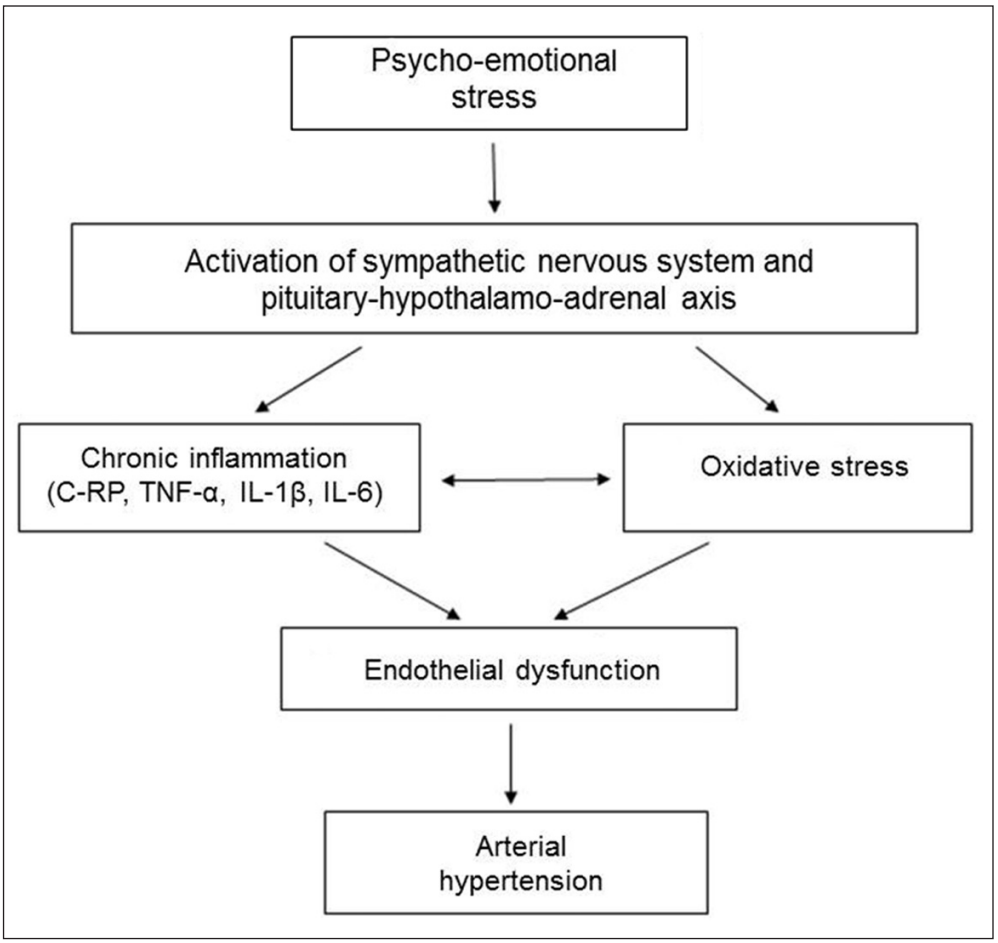
and soluble vascular cell adhesion molecules (sVCAM-1) that stimulate the migration of white blood cells to the artery walls, contributing to inflammation and atherosclerosis. They showed that males experiencing frequent stress at work or at home had higher levels of slCAM-1 and sVCAM-1, which confirmed the association of ED with psycho-emotional tension [60].

Numerous studies confirm the key role of ED in pathogenesis of cardiovascular diseases, including HTN [116, 129–131]. ED often precedes HTN onset and is also diagnosed in individuals with hereditary predisposition for HTN [132–134]. The reduction in NO release is only one way of ED to be involved in HTN; the increased degradation of NO and active local secretion of endothelin-1 and angiotensin II are also considered [135]. In recent years, the role of oxidative stress in the ED-associated pathological processes is discussed. Oxidative stress is the result of a wide range of factors, including HTN [136]. Therefore, the differentiation between ED as a cause or a consequence of HTN is quite difficult, since both processes are interrelated and occur simultaneously. The mechanisms that show the relationship between psycho-emotional stress and HTN are shown in Figure 2.

Conclusions

Thus, the available evidence shows the growing interest to the interaction of HTN with psycho-emotional stress, primarily in chronic forms. Global urbanization, sedentary lifestyle, daily stress at work and lack of social support lead to increased anxiety, insecurity, and, finally, to chronic psycho-emotional tension. Thus, one of the key factors underlying pro-hypertensive effect of stress in the modern society is the lack of conjugation of anxiety and stress reactions with physical activity that initially is genetically

Figure 2. The mechanisms of hypertension in chronic psycho-emotional stress



Note: CRP — C-reactive protein; TNF-α — tumor necrosis factor alpha; IL-1β — interleukin 1β; IL-6 — interleukin-6; ED — endothelial dysfunction.

programmed as a response aimed at survival in the natural wildlife (avoidance of danger, food procurement, etc.).

Specific molecular and cellular mechanisms, underlying the development of HTN in chronic stress, represent a set of complex interaction of neuroendocrine and immune factors and are not entirely understood. So further research to establish the key determinants of high BP and, therefore, to prevent HTN, individualize diagnostic algorithms, and decrease the risk of cardiovascular events is needed.

Conflict of interest
The authors declare no conflict of interests.

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