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Stress and arterial hypertension – from pathophysiology to pharmacology

Стрес и артеријска хипертензија – од патофизиологије до фармакологије

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Stress and arterial hypertension – from pathophysiology to pharmacology

Стрес и артеријска хипертензија – од патофизиологије до фармакологије

SUMMARY
Arterial hypertension is the most massive chronic non-infectious disease of mankind nowadays. It may remain undiagnosed for years, provoking later complications, such as acute heart failure, cerebrovascular stroke, myocardial infarction, renal failure, hypertensive retinopathy, or sudden death. Primary arterial hypertension is more common, while secondary occurs in about 5–20% of cases. The recent studies have shown that stress may be a core factor in development of essential hypertension in some patients. For the patients suffering from post-traumatic stress disorder, stress is the dominant etiological factor that leads to the disease. It has been proven that chronic stress can affect blood pressure regulation and endocrine-metabolic functions through the limbic-hypothalamic centers, therefore it can affect the arterial hypertension development. The strong association between stress and arterial hypertension have been also confirmed in preclinical and animal studies. For the pharmacotherapy approach, the most important are beta-adrenergic blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors) and AT1-receptor blockers (sartans). As a second line treatment, calcium channel blockers, diuretics, alpha-adrenergic blockers, and central antihypertensive agents may be required. The anxiolytics, such as benzodiazepines, should be considered if chronic anxiety and psychosomatic disorders are present.
Keywords: stress; arterial hypertension; therapy; anxiolytics

САЖЕТАК
Артеријска хипертензија је данас најмасовнија хронична незаразна болест човечанства. Може остати недијагностикована годинама, што изазива касније компликације, попут акутне срчане инсуфицијенције, можданог удара, инфаркта миокарда, бубрежне инсуфицијенције, хипертензивне ретинопатије или изненадне смрти. Примарна артеријска хипертензија је чешћа, док се секундарна јавља у око 5–20% случајева. Недавна истраживања показала су да стрес код неких пацијената може бити кључни фактор у развоју есенцијалне хипертензије. Код пацијената који пате од посттрауматског стресног поремећаја, стрес је доминантни етиолошки фактор који доводи до болести. Доказано је да хронични стрес може да утиче на регулацију крвног притиска, ендокрине и метаболичке функције путем лимбичко-хипоталамичких центара и самим тим да утиче на развој артеријске хипертензије. Снажна повезаност стреса и артеријске хипертензије потврђена је у претклиничким студијама и испитивањима на животињама. За фармакотерапијски приступ најважнији су бета-адренергички блокатори, инхибитори ангиотензин конвертујућег ензима (*ACE*) инхибитори и блокатори *AT*1 рецептора (сартани). Као друга линија терапије могу се користити блокатори калцијумових канала, диуретици, алфа-адренергички блокатори и централни антихипертензиви. Увођење анксиолитика, попут бензодиазепина, треба размотрити у случају хроничне анксиозност и психосоматског поремећаја.
Кључне речи: стрес; артеријска хипертензија; терапија; анксиолитици

INTRODUCTION

Arterial hypertension (AH) represents the most common illness from the cardiovascular diseases (CVD) group, and according to the latest data from the WHO 1.13 billion people worldwide is suffering from it, while in 2015 every fourth male and every fifth female suffered from AH. In such context, AH as a contributing factor of CVD is the most massive chronic non-infectious diseases of mankind nowadays [1]. AH can be primary and secondary; primary

is far more common (about 80–95%) and the cause is unknown, while secondary occurs in about 5–20% of cases and occurs as a consequence of other illnesses [2].

AH represents the most common risk factor for CVD. A study from March this year concluded that even stage 1 hypertension defined by ACC/AHA guidelines was independently associated with subclinical coronary atherosclerosis [3]. In the United States (US) considerably higher prevalence of AH has been noted in African Americans compared to other races. Thus, in a recent study conducted on a community-based cohort of African Americans, it was concluded that higher perceived stress over time is associated with an increased risk of developing hypertension [4].

Many organs participate in stress reactivity, however, the essential role is played by the hypothalamic-pituitary-adrenal (HPA) axis with corticosteroid secretion, as well as the neurovegetative system and the adrenal medulla with consequent secretion of catecholamines [2,5].

ARTERIAL HYPERTENSION AND STRESS

Stress has been noted in SCORE system as one of the contributing factors to CVD risk in the ESC/ESH guidelines for 2018 (Table 1). Blood pressure (BP) represents a circulatory parameter, which is controlled by baroreceptors. When the blood pressure rises, it affects the baroreceptors, which are most densely distributed in the bulbus of the carotid artery and the aortic arch, and their main characteristic is that they are sensitive to stretching. Stretching caused by an increase in blood pressure leads to transmission of information by baroreceptors along the vagal and glossopharyngeal pathways toward the nucleus tractus solitarius (NTS) in the brainstem, which makes single and multiple neural connections to pre-autonomic source nuclei in the brainstem and also to the forebrain. These structures have crucial role in regulation BP. Psychological stress has been shown to reliably reduce baroreflex sensitivity, specifically cardiovagal sensitivity [6].

Studies conducted on animal and human models have found that the network of cortical areas, limbic system and brainstem plays an important role in generating and regulating stress-

provoked cardiovascular reactivity. It should be noted that from the pathophysiological aspect, stress-induced cardiovascular reactions are a consequence of changes in the sympathetic and parasympathetic nervous systems, as well as the HPA axis that act on the heart and vasculature. Recent research has shown that higher levels of amygdala activity in rest predict the development of CVD over a period of 3.7 years. Increased amygdala activity is associated with changes in immune activity, and also with arterial inflammation and perceived stress, which provides evidence of potential pathways that support the development of CVD [7]. An animal model study published this year also confirms the link between stress and AH, with the very interesting conclusion that V1a and V1b receptors for vasopressin within the paraventricular nucleus contribute to hypertension in male rats exposed to chronic mild unpredictable stress [8].

The function of the HPA axis can be evaluated by measuring cortisol in the blood, saliva or urine. The recent data suggests the measurement of cortisol levels in the hair as a new biomarker of long-term HPA axis activity [9]. Some of the mechanisms that explain the development of cortisol-induced hypertension include its mineralocorticoid action in the form of sodium retention, then the expansion of plasma volume and inhibition of vasodilatory hormones [9]. There are several studies that have studied the ways in which stress can affect the epigenetic regulation of the HPA axis, so one of them states that DNA methylation of genes involved in the regulation of glucocorticoids is associated with arterial hypertension and subclinical atherosclerosis [10]. Short sleep and discontinuous rest, which are often found in women with depression, disrupt balance of the sympathetic and parasympathetic nervous system and are associated with hypersecretion of cortisol, thus increasing heart rate and blood pressure [11]. Furthermore, it is concluded that the intestinal microbiome disturbance, which can be a consequence of stress, is associated with AH, CVD and metabolic diseases [12].

A study by Rao et al. demonstrated that adrenergic polymorphism affects the human response to stress, and thus blood pressure levels and catecholamine secretion are influenced by genetic variation of the adrenergic pathway encoding catecholamine synthesis, specifically a step that limits the rate of synthesis, which is the enzyme tyrosine hydroxylase, or a genetic polymorphism for said enzyme [13]. Arosio et al. proved the existence of influence of mental stress on AH, but also the protective effect of AT1-receptor blockers on noradrenergic and adrenergic stress in hypertensive individuals [14].

The studies concerning stress and AH have been also conducted in animal models. Earlier publications have already established a cause-and-effect relationship between posttraumatic stress disorder (PTSD), where stress is the dominant etiological factor leading to the disease and AH. This was also confirmed in a recent study by Xue B et al. [15].

PHARMACOLOGICAL ASPECTS

The specificity of stress induced AH is that in addition to antihypertensive therapy, drugs that affect the patient's mental status, such as anxiolytics, may be recommended. There are non-pharmacological forms of treatment in the form of psychological support and psychotherapeutic techniques (relaxation techniques, stress management techniques, suggestion techniques, positive thinking and visualization techniques) [16]. For the pharmacological measures, there are available several groups of antihypertensive drugs. The most important, when treating the stress-induced AH, are beta-adrenergic blockers, ACE inhibitors and AT1-receptor blockers (sartans). In case of resistant AH, calcium channel blockers, diuretics, alpha-adrenergic blockers, and central antihypertensive drugs may be required. Moreover, some studies recommend that patients with impaired autonomic activity and stress induced AH be genetically profiled in relation to adrenergic pathways, and if a genetic risk is identified, it is considered that these patients would benefit from sympatholytic therapy [13]. The type of sympatholytic therapy most frequently mentioned in the literature recently is renal denervation (RDN). It is a minimally invasive therapeutic method based on catheter radiofrequency (although ultrasound or alcohol injection may be used) ablation of afferent and efferent renal sympathetic fibers, which is usually reserved for severe AH that is resistant to pharmacological treatment and AH with concomitant chronic renal failure, although it has recently been suggested to expand the indications to uncomplicated AH [17-19]. In March this year, the first study was published that proves the reduced efferent renal sympathetic innervation after chemical RDN in humans, as well as the positive effects of this procedure on AH [20].

Beta-adrenergic receptor blockers are not the first in line for antihypertensive therapy, due to the lower antihypertensive effect compared to some other antihypertensives, because of the negative chronotropic effect on the myocardium, which is not desirable in all hypertensive

patients, as well as due to the effect on beta2-adrenergic receptors in non-selective blockers, thereby reducing insulin secretion. However, for stress-induced AH, in addition to the antihypertensive effect beta-blockers also have an effect on reducing tachycardia, which is almost always present in these patients. These drugs antagonize the action of catecholamines and partially lead to patient's relaxation and stress reduction.

The effect of angiotensin-converting enzyme inhibitors **(**ACE inhibitors) is reflected in arterial and venous dilatation, reduction of peripheral vascular resistance, increase in minute volume, effort tolerance, the excretion of sodium and water by the kidneys, preventing the proliferation of the smooth muscle cells, reduction of the left ventricular hypertrophy. They have an important role in AH therapy, but also in cases of stress-induced AH [15]. The indications spectrum of AT1-receptor blockers (sartans) is identical to ACE inhibitors. They are introduced into therapy in case of intolerance to ACE inhibitors; dry cough as a consequence of bradykinin action caused by the action of ACE inhibitors, or reduced ACE inhibitors efficiency in situations of elevated plasma renin. The justification of their use in stress-induced hypertension can be found in the conclusion of the study by Arosio et al. [14], where it has been shown that AT1-receptor blockers act protectively in noradrenergic and adrenergic stress in hypertensive patients.

Calcium channel blockers lead to smooth muscle arteries cells relaxation, vasodilation, reduction of peripheral vascular resistance, and lowering the blood pressure. However, these drugs are not the first in line when treating stress-induced hypertension. It is similar when dealing diuretics and alpha-blockers, which have no significant application in this case, except when dealing with resistant stress-induced AH.

The use of anxiolytics should be considered only in the case of chronic anxiety and psychosomatic disorders. There are studies that indicate a favorable impact of GABAergic systems modulation in the treatment of anxiety with related cardiovascular diseases [21]. Benzodiazepines, as positive GABAergic modulators, are often prescribed with the internal medicine therapy and added to the treatment of chronic hypertension. Both quantitative and qualitative consumption data have confirmed this in practice [22]. The advantages of benzodiazepines are relatively safe pharmacological profile and low risk of serious side effects; however, they can produce tolerance and dependence after longtime treatment. The hypertension pharmacotherapy guidelines do not recommend routine use of benzodiazepines

except when associated with psychiatric comorbidities. Especially in the older population, simultaneous use of benzodiazepines has been shown to increase the risk of limb fractures and injuries, as well as reduced cognitive abilities [23]. The recent experimental studies have indicated that certain benzodiazepines, like midazolam and diazepam can be considered. It has been shown that midazolam induces arterial blood vessels vasodilation, most likely by of voltage-gated calcium channels modulation [24], while diazepam exerts its effect by alpha-1 receptors modulation [25]. However, their efficacy has neither been confirmed by meta-analysis or by long-term follow-up studies.

CONCLUSION

Nowadays, AH represents the most widespread, non-infectious disease of mankind. Chronic stress represents an increasingly common etiological cofactor, while in some situations it is the main cause of AH. Thus, it is necessary to consider and evaluate the presence of stress in the modern treatment. The decision which pharmacological agents shall be introduced into therapy depends on comorbidity, other CVD risk factors, and patient's age. There is a need to primarily introduce beta-adrenergic blockers, ACE inhibitors, or sartans for the stress-induced AH, while the use of anxiolytics should only be considered if chronic anxiety and psychosomatic disorders are present.

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Table 1. Risk modifiers that increase cardiovascular risk estimated by the Systemic coronary Risk Evaluation

Social deprivation, the source of many causes of cardiovascular diseases
Obesity (according to the body mass index) and central obesity (measured by waist circumference)
Physical inactivity
Psychosocial stress, including vital exhaustion
Family anamnesis of early cardiovascular disease (before the age of 55 in men and before the age of 60 in women)
Autoimmune and other inflammatory disorders
Major psychiatric disorders
HIV infection treatment
Atrial fibrillation
Left ventricular hypertrophy
Chronic kidney disease
Obstructive sleep apnea syndrome

