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Cardiovascular Continuum, Common Pathogenetic Links of Syntropy

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ABSTRACT

In the review article, the authors studied the pathogenetic aspects of damage to the heart and blood vessels in hypertension and coronary heart disease, which constitute cardiovascular syntropy. During the systematization of studies by modern authors, it was found that patients with elevated VEGF levels have a high risk of developing and progressing cardiovascular pathology, namely fibrosclerosis and myocardial hypertrophy on the background of arterial hypertension, regardless of its severity.

The concept of the “cardiovascular continuum” has existed for several decades and has become a kind of symbol of the “route”, the inevitability of the development of non-infectious somatic pathology from its first functional changes to severe fatal complications. The continuum also seems to be a symbol of the sequence and continuity of pathological changes, their interrelation, and the multitude of vicious circles that ultimately ensure the disease itself. It includes both the action of risk factors (FR) and vicious circles that close when FR is finally realized in pathological processes. In the cardiovascular continuum, the sympathoadrenal system, endothelium, and juxtaglomerular apparatus of the kidneys play a role; “idiopathic” factors are important, i.e. not yet amenable to explanation: genetics (and epigenetics), stress, inappropriate lifestyle. An unconditional role is played by psychosocial factors, including loneliness and other negative socially directed emotions [16].

In clinical practice, the problem of multiple combined diseases has long been identified. Up to 80% of the healthcare budget of developed countries is spent on patients with four or more diseases. The most common term for this phenomenon is comorbidity. However, only that part of the combined diseases, which has a common genetic basis and a similar pathogenesis, refers to syntropies, diseases of "attraction", "mutual inclination" ("attraction"). There are many clinically proven syntropic diseases: immune-dependent diseases (allergic and autoimmune); endocrine diseases, including a combination of diabetes mellitus (DM2), autoimmune thyroiditis and gluten enteropathy, some forms of mental illness. Among them are cardiovascular diseases (CVD), united by the concept of the cardiovascular continuum (CSC) [8].

Over the past decades, the burden of coronary heart disease (CHD) in the world has been consistently decreasing. This decrease is explained by the improvement and improvement of measures for primary and secondary prevention of cardiovascular diseases (CVD). IHD is characterized by a wide range and associability of social and clinical-anthropometric factors

affecting the clinical course, the risks of complications and the social prospects of the subject in the situation of the disease [23].

Myocardial ischemia, as is known, leads not only to a deterioration in the quality of life of patients with coronary heart disease, but can be considered a risk factor for the development of adverse clinical outcomes associated with coronary heart disease. The risk of cardiovascular complications and death increases depending on the frequency of angina attacks. With the frequency of angina attacks more than 6 per week, patients have a 3-fold increased risk of developing cardiovascular complications (CVD). It is also generally recognized that the effect on myocardial ischemia can be an effective approach to reducing the risk of adverse outcomes. Achieving effective control of angina attacks is quite a difficult task. The symptoms of coronary heart disease persist, despite therapy with even several drugs. 86% of CHD patients continue to suffer from angina attacks, taking 2-3 antianginal drugs[2].

In modern literature, the term "remodeling of the heart" has appeared, which includes the whole complex of changes in the mass, volume and shape of the left ventricle due to cardiomyocyte hypertrophy, as well as hypertrophy and hyperplasia of interstitial cells and endothelium, leading to a violation of the biochemical and functional properties of the myocardium under the influence of various factors, including hypertension [10].

Age is a recognized risk factor for cardiovascular diseases and mortality, including in patients with hypertension. In many ways, this influence is realized through age-related changes in the structure and function of blood vessels [24].

The results of research in recent decades confirm the crucial role of vascular endothelium in the regulation of vascular homeostasis, while a significant contribution of endothelial dysfunction (ED) to the development of cardiovascular diseases (CVD) has been established, in particular, participation in the pathogenesis of hypertension. It is generally recognized that the endothelium maintains a balance between the processes of vasoconstriction and vasodilation, produces factors of inflammation and vascular proliferation, participates in vascular remodeling and thrombosis [12, 15].

Transforming growth Factor-β (TGF-β) is a cytokine, a protein growth factor that plays an important role in the regulation of cell growth, differentiation and regeneration of various tissues. In the heart, TGF-β1 is induced by MI, pressure overload, with the introduction of angiotensin II, norepinephrine and is inhibited by nitric oxide. In the myocardium, TGF-β1 is synthesized by fibroblasts and cardiomyocytes and plays a key role in the development of tissue fibrosis. Thus, along with the already "gold standard" biomarker of heart failure pro-BNP, new biomarkers are being intensively studied, such as markers of apoptosis, remodeling of connective tissue extracellular matrix and inflammation, which allow not only to more accurately diagnose, but also to determine the risk of developing or progressing heart failure and death [13, 18].

Arterial hypertension (AH) occupies one of the leading places in the structure of modern pathologies, while hypertrophy of the left ventricle (LVH), as a result of damage to target organs, gives a significant increase in cardiovascular risk in patients with AH. The “hypertensive heart” is characterized by both structural and geometric remodeling (SGR) - an increase in the mass and a change in the geometry of the LV, as well as changes in its electrophysiology (manifested by electrocardiographic (ECG) and vectorcardiographic (ECG) data). Prolongation of the QT interval is one of the indicators of electrophysiological remodeling, which has an important prognostic value in the etiology of sudden cardiac death [9].

Refusal to use or a significant reduction in doses of drugs that positively affect the course and outcomes of CVD in conditions where the risk of complications of existing CVD increases due to the occurrence of COVID-19 can lead to potentially adverse consequences. This applies

primarily to RAAS inhibitors and beta-blockers in CHF with a reduced left ventricular ejection fraction and in patients who have recently undergone MI, drugs to control myocardial ischemia, antiarrhythmic drugs necessary to prevent life-threatening or severe cardiac arrhythmias, as well as loss of control over blood pressure in patients with hypertension [22].

It was found that LV remodeling, especially its concentric type, increases the likelihood of arrhythmia, in particular ventricular extrasystole of high gradations. Concentric LV hypertrophy is associated with the severity of cardiac arrhythmia (LDC). Eccentric remodeling, in turn, contributes to the development of relative coronary insufficiency [4].

Despite the fact that over many years of research, scientists have figured out the mechanisms of development and progression of many cardiovascular diseases (CVD), in particular coronary heart disease and arterial hypertension (AH), the prevalence of these types of pathology is steadily increasing. In modern guidelines for the diagnosis and treatment of CVD, the main attention is paid to risk factors (FR) of their development. In 1991, V. Dzau and E. Braunwald formulated the concept of the cardiovascular continuum, which has become firmly established in scientific and medical practice over the past 20 years. In relation to practical medicine, a continuum (from the English continuous – "constant, continuous") means a continuous sequence of stages of the development of the disease: from FR to death. The main FR, such as magnesium deficiency, obesity, hypertension, diabetes mellitus (DM), atherogenic dyslipidemia, represent the initial stage of the cardiovascular continuum - a continuous sequence of pathophysiological events leading to progressive damage to cells of various organs, in particular to damage to the endothelium of the vascular wall, and ultimately to the manifestation of clinical manifestations of CVD [21].

Cardiovascular diseases are the result of various interrelated processes (arterio–, atherosclerosis, endothelial dysfunction), as well as, as numerous studies have shown, remodeling of the left chambers of the heart, which can increase the risk of cardiovascular complications. Various external and internal factors can influence the course of arterial hypertension (AH). Quite often, hypertension is associated with metabolic disorders: obesity, including abdominal, impaired glucose tolerance, dyslipidemia, etc. According to the literature, dyslipidemia with an increase in the level of atherogenic lipid fractions is often found in hypertension [17].

The cardiovascular continuum is a continuous chain of interrelated changes in the cardiovascular system from exposure to risk factors, through the gradual occurrence and progression of CVD to the development of terminal heart disease and death. A continuous chain of interrelated changes in the structure and function of several organs and systems of the body at once within the continuum suggests the presence of common pathophysiological processes, mechanisms of development and progression of organ damage [6].

Sexual and gender characteristics of men and women are manifested in differences in health status, including cardiovascular. Atypical symptoms of coronary heart disease are also more common in women, explained by different perceptions of pain. Nosocomial mortality after acute myocardial infarction remains higher among young women compared to male peers [20].

It is known that patients with CVD are at greater risk of developing COVID-19, especially in moderate and severe forms. According to repeated reviews and meta-analyses, ~40% of those infected with COVID-19 have concomitant CVD. Patients with pre-existing hypertension, diabetes mellitus and coronary heart disease are more likely to be hospitalized in the intensive care unit with subsequent severe and extremely severe course of the disease with the need for artificial support of respiratory function, including artificial ventilation of the lungs. The risk of death in patients with COVID-19 and CVD increases 5-10 times [5]. 5.

Myocardial remodeling includes cardiomyocyte hypertrophy, a change in the shape and an

increase in the volume of the heart chambers as a compensatory reaction aimed at maintaining cardiac output (CB). These changes occur under conditions of hyperreactivity of the sympathetic-adrenal (SAS) and renin-angiotensin-aldosterone system (RAAS). Structural changes of LV in hypertension according to echocardiography are classified into four geometric models based on myocardial mass and relative LV wall thickness: concentric hypertrophy (increase in myocardial mass and relative LV wall thickness); eccentric hypertrophy (increased myocardial mass with normal relative wall thickness); concentric remodeling (normal myocardial mass and increased relative wall thickness); normal LV geometry (normal myocardial mass and normal relative wall thickness) [3].

Remodeling of the heart, which occurs in response to damage leading to a change in its geometry, a violation of contractility, ultimately determines the prognosis of life in patients with chronic obstructive pulmonary pathology. At the same time, BA is not mentioned among lung diseases that lead to the development of heart remodeling. There is also no consensus on the nature of violations in both the right and left heart; their relationship with each other [14].

Myocardial remodeling in hypertension is one of the stages of progression of heart changes that lead to the formation of left ventricular dysfunction and, in the future, to the development of heart failure. According to modern concepts, there are four types of LV remodeling characteristic of patients with hypertension: 1) normal LV geometry; 2) concentric hypertrophy (increase in myocardial mass and relative LV wall thickness); 3) eccentric hypertrophy (increase in mass with normal relative thickness); 4) concentric remodeling (normal mass and increased relative wall thickness) [1].

Laboratory biomarkers are viewed with interest as tools for predictive stratification. In recent years, more than 100 new biomarkers have been evaluated in this regard, and more than 4,000 clinical studies have been published. Assessing the predictive accuracy of a new cardiovascular biomarker is very difficult. According to the principles of evidence-based laboratory medicine, a biomarker should not only be an independent predictor of the outcome in multiple regression models, but also influence patient management, which is a prerequisite for economic efficiency. As a result, very few new laboratory biomarkers are recommended for risk prediction. Several studies have demonstrated that cardiovascular risk progressively increases in the general population for cTn values well above the 99th percentile, the recognized threshold value for the detection of myocardial damage and/or diagnosis of myocardial infarction. Highly sensitive cTn methods make it possible to quickly identify patients at high risk of developing heart failure, which can lead to early diagnosis and improved prognosis of these patients [19]. 1

However, it is also noted that the degree of increase in blood pressure (BP) and the duration of the existence of hypertension do not correlate with the severity of remodeling processes. It has been established that the development of different types of remodeling is associated not only with increased hemodynamic load, but also with the influence of numerous neurohumoral factors on the heart, the degree of activity of which can be genetically determined [3,4]. In this regard, the search for candidate genes affecting the processes of myocardial remodeling is actively underway, and the study of the relationship of these genes with a specific type of remodeling. The genes encoding components of the renin-angiotensin system, genes of key sympathetic receptors, as well as genes whose defects can lead to endothelial dysfunction attract the most attention [8]. These genes are somehow related to the load on the heart, including blood pressure, vascular resistance, heart rate and other parameters [7].

Conclusion

Remodeling of the heart in hypertension, in fact, is a compensatory reaction that allows the heart to work in conditions of increased blood pressure. Risk stratification for the patient is an important goal, as it determines treatment and follow-up strategies, the ultimate goal of which is

to influence the natural course of the disease. There are two reasons for remodeling the heart in obesity – hemodynamic and metabolic. Basically, the whole variety of such mechanisms can be reduced to genetic, hemodynamic and neurohumoral factors. Among the latter, one of the central roles belongs to the activation of the renin-angiotensin-aldosterone system (RAAS), which can be traced at almost all stages of the cardiovascular continuum.

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