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SIGNIFICANT PATHOGENETIC FACTORS IN THE DEVELOPMENT OF CHRONIC HEART FAILURE WITH PRESERVED EJECTION FRACTION

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ABSTRACT:

Chronic heart failure (CHF), being an outcome of cardiovascular continuum, leads to worsening of the course of not only the causes of the disease, but also to its decompensation, rehospitalizations, which leads to difficulties in the care of these patients and becomes a socio-economic problem. The prevalence of CHF in Western countries ranges from 1% to 2% in the general population, reaching 10% in those over 70 years of age. In the Russian Federation, the EPOHA study data show an incidence of CHF of 7-10%. In Uzbekistan, CHF is also one of the leading complications of cardiovascular disease (CVD). The presence of strict diagnostic positioning criteria increases the number of patients with CHF III-IV, and the use of softer criteria sharply expands the population of patients with CHF I-II.

Keywords: chronic heart failure with preserved ejection fraction, diastolic dysfunction, quality of life

RELEVANCE:

The main etiologies of CHF in the Russian Federation, Europe and the USA are arterial hypertension (AH) (95.5%) and coronary heart disease (CHD) (69.7%), including more than half of patients with CHF. In Uzbekistan, along with the above-mentioned causes, valvular heart disease plays a role. Over the last 10 years, the "competing" causes of CHF have been myocardial infarction (19.7%) and diabetes mellitus (22.7%). The outcome and course depend on a variety of adverse factors, including anaemia.

Decompensation of CHF is the reason for hospital admission in one in two patients (49%), and the diagnosis of CHF is made in 92% of hospitalised patients (2,38). This determines the high overall mortality of patients with CHF (6%), which is 10 times higher than in the population (OR=10.1;p<0.0001). Life expectancy in patients with CHF class I-IV is 7.8 years, and among patients with CHF class III-IV - 4.8 years.

Studies have shown a clear association

between impaired diastolic function and preserved contractility in more than half of all cases of CHF. Moreover, diastolic dysfunction (DD) of the heart tended to develop before the decline in myocardial contractility, i.e. occurring in the early stages of CHF. One obvious variant of cardiac DD is AH; the ESSE-RF study confirms its presence in 44% of the population over 15 years of age in Russia. Currently, AH is the only cause of CVD in 40-50% of cases. Epidemiological study conducted in Russia, among patients being treated for chronic heart failure in II-IV class, showed that 9% of patients had decreased VEF (nFVL<40%), 20% had "intermediate" VEF (nFVLV 40-60%), and most patients (71%) - so called "hyperkinetic" type of contraction (sFVLV>60%). An even higher prevalence of cFVLV reached -78%, among all patients with CHF I-IV FK. A similar prevalence of CCFVL in Russia (84.1%) was found in another population-based IMPRDVEMENT HF study (Russian part of the study). According to the results of the Russian CHF registry, patients with CHF class I-IV also predominated among the examined patients with LVEF (83%), and systolic LV dysfunction was observed in only 17% of patients. Patients with CHFsFV are characterized by a significant decrease in exercise tolerance, frequent hospitalizations, and reduced quality of life.

The process of myocardial remodeling in CHFsFV differs from that in CHFsFV and includes 2 interrelated processes, representing the basis of VD: 1) decrease in elasticity and relaxation of LV myocardium, which is caused by imbalance of mechanical properties of cardiomyocytes.2) state of extracellular matrix. The molecular basis for these changes is impaired calcium transport, regulation of fibrillar collagen synthesis and transformation, and changes in cardiomyocyte cytoskeleton due to increased expression of a stiffer isoform of the cardiac muscle stiffening sarcomeric titin protein. Massive studies have proved the role of immune inflammation in the development and progression of CHF and, in particular, CHFsFV. The role of proinflammatory cytokines (interleukin (IL)-1, IL-6, TNF-α, etc.) involved in cardiac dysfunction and the progression of CHF has been identified. Chemokines such as IL-8 are also involved in cardiac dysfunction and are identified as markers of tissue destruction. Adhesion molecules, autoantibodies, nitric oxide (NO), endothelin-1 and acute inflammatory proteins (C-reactive protein (CRP), fibrinogen, complement system) have also been shown to be involved in the pathogenesis of CHF. The data collected support the current concept of interconnection and interdependence between such systems as the sympathetic-adrenal (CAC), renin-angiotensin-aldosterone (RAAS), endothelin system, immune and inflammatory systems in the pathogenesis of CHF. They create an intricate, multidimensional network of cooperation, including different types of cells (monocytes, macrophages, T- and B - lymphocytes, endothelial cells) and biologically active substances. One of the early triggering factors in CHF is CAC hyperactivation, which has a positive adaptive-compensatory effect in the early stages. It ensures pumping function of the heart by increasing heart rate and myocardial contractility, stabilises BP under reduced cardiac output (CV) by activating arteriolar constriction, and induces venoconstriction to ensure venous return and increase filling pressure in the heart. In the early stages, this will be a manifestation of compensatory systems aimed at maintaining the contractile function of the heart. Increased CAC activity manifests itself in positive inotropic and chronotropic effects on the heart, whereas the RAAS maintains vascular tone, blood pressure and circulating blood volume.

Over time, CAC hyperactivation begins to have a negative effect and contributes to the progression of CHF due to extreme vein and arteriolar constriction, which increases pre- and post-load and decreases tissue perfusion. At the same time, norepinephrine (NA) inhibits sodium salts, increases the ROS and increases the myocardial load, stimulating circulating RAAS activity, resulting in low cardiac output. It has been shown that chronic cardiac patients with severely elevated plasma catecholamine (PA) levels (especially those with HA above 600 pg/ml) have a much poorer prognosis, with a 2.3-fold increase in mortality. An increased level of HA determines a significant restructuring of the myocardial receptor apparatus. Thus, the number of β1 receptors is significantly reduced. This process is known as down regulation. It occurs because the receptors are coupled with HA molecules. In this case, a contradictory situation occurs: myocardial contractility decreases against the background of excess HA. An excess of HA circulating in the blood involves an increase in endothelial production of constrictive factors (endothelin, thromboxane A2, superoxide anion, endoperoxide), thus increasing peripheral blood flow resistance, impairing microcirculation (especially in the heart and kidneys), causing progressive remodelling of the heart and vessels. Thus, CAC hyperactivation promotes further myocardial hypertrophy and remodelling, the development of diastolic and systolic LV dysfunction with progression of CHF. Among a large number of biomarkers involved in CHD, the most studied are natriuretic peptides (NUPs), markers of myocardial fibrosis, and biochemical markers of renal damage (renal dysfunction and ischaemic damage). These include atrial ANP, urodilantin (isoform of ANP), brain BNP, C-type ANP (CNP) and D-type ANP. The main biological essence of these neurohormones is to increase sodium excretion in the distal parts of the nephron. ANP and BNP are produced in response to myocardial dilatation under pressure or volume overload and are produced in atrial and ventricular myocytes. In addition to natriuresis, ANP and BNP induce vasodilation, providing haemodynamic "unloading" of the myocardium under adverse haemodynamic changes. In the development of CHD, the protective effect of NUP is offset, including through CAC and RAAS activation and increased sodium reabsorption in the proximal nephron. Thus, despite a significant increase in blood concentrations of these biomarkers, no natriuresis occurs. The concentration of ANP and BNP in the blood increases in proportion to the degree of haemodynamic overload of the heart chambers (both left and right). In CHF, in general, an increased concentration of NUP reflects the level of haemodynamic abnormalities and is correlated with the incidence of adverse outcomes. In CHF, the significance of NUPs is even greater, as their increased concentration in blood is one of the criteria for the diagnosis of questionable EchoCG results. The signs of LD (impaired active LV myocardial relaxation, decreased wall elasticity) were recommended only for the diagnosis of obvious clinically pronounced DSH. Zile et al. confirmed that all patients with CHFV showed LD on Doppler. However, they concluded that the sensitivity and specificity of these parameters are rather low for the diagnosis of CSFV. This is due to the fact that EchoCG does not always detect the key passive component of diastole, as it is labile (Doppler wave peak amplitudes), associated with age, hypertension and other comorbid conditions. Some sources indicate that, even in the presence of a strong symptomatic CSFV, many patients are not confirmed to have type 2 or type 3 DM on Doppler. DD may not always be present or fully explain CHNSFV. In connection

with these data, new diagnostic criteria for CHF have appeared, in which the obligatory presence of DD, LV and LV hypertrophy, and increased BNP have not been highlighted. In 2013, criteria based on several features (presence of typical symptoms and signs of CH; normal or near-normal LVEF; absence of other causes, including valve pathology, explaining CH symptoms) were proposed. Further studies of patients with a history of HF and a PVLV greater than 50% have shown that many patients have moderate resting VD. Arterial stiffness is an independent marker of CVDs, including CHFV, and mortality; it develops in the early stages of these diseases and progresses rapidly with the duration of the disease. Transformation of the vascular wall is accompanied by collagen accumulation and decreased elasticity, vascular conduction and damping function are impaired, pulse wave velocity increases, the aortic root dilates and its stiffness increases. As a result, there is an early return of the reflected wave in late systole, LV LV DA is formed, postload increases, oxygen demand increases, coronary perfusion is impaired, and myocardial hypertrophy and microcirculatory disorders develop. The recommendations of the European Society of Cardiology (ESC) Working Group state that the diagnosis of primary (isolated) diastolic HF is eligible when the following criteria are mandatory :

1. Clinical signs of CHF;
2. Normal (LVEF 55% or >), mildly reduced (LVEF 50-54%) and moderately reduced (LVEF 40-49%) myocardial contractility;
3. Increased levels of BNP (BNP more than 35 pg/ml and/or NT-proBNP more than 125 pg/ml) in serum;
4. Other functional and structural changes underlying the development of CHF;
5. In case of doubt, a stress test or invasive detection of increased LV filling pressure.

The implementation of optimal LV shock volume delivery to body tissues requires a commensurate interaction between the LV and the arterial system. This interaction between the LV as a pump and the vascular system as a load has been termed the left ventricular-arterial coupling (LVAC) and is measured as the ratio of arterial elastance (Ea) to end-systolic ventricular elastance (Ees).

The concept of LJAS is important in the concept of CVD formation. Normally, the interaction between the LV and the arterial system ensures that LV shock work is transmitted as efficiently as possible to the vessels. In HF, this interaction is impaired. In impaired LV energy and mechanical efficiency decreases, especially with a decrease in LVEF. Analyses of LHAS suggest the efficacy of cardiovascular interaction, remodelling and fibrosis. Increased arterial stiffness has been shown to be a predictor of CVD and one of the main factors influencing LJAS. At the same time, the relationship between aortic stiffness and CHF has not been sufficiently studied, although this issue is also significant.

Thus, the pathogenesis of CHF illustrates the multiple changes occurring in the body, from disturbances in the immune and CAS systems to changes in LVA with arterial stiffness, which in turn is a predictor of CVD and its complications.

CONCLUSION:

CHF is the major complication of CVD and is the cause of hospital admission in every 2 patients (49%). The main causes of CHF are AH (95.5%), CHD (69.7%), and their combination. More than 50% of CHF cases are associated with cardiac fibrillation while the heart retains its contractility. Cardiac DD usually precedes myocardial impairment, i.e. occurs in the early stages of CHF. A significant decrease in exercise tolerance, frequent

hospitalisations and reduced quality of life are typical of patients with CHFsFV. The modern concept of CHF pathogenesis indicates interrelation and interdependence between such systems as CAC, RAAS, endothelin system, immune and inflammatory. In recent years, attention has been drawn to the increase in GAS, vascular load and disruption of ventriculo-vascular interaction, which determine LV myocardial remodelling and the development of CHF.

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