World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-4, November 2021
ISSN: 2749-3644

BASIS OF PATHOGENESIS OF CHF WITH PRESERVED EJECTION FRACTION

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Article history:

Received: August 24st 2021
Accepted: September 20th 2021
Published: November 11th 2021

Abstract:

Despite numerous studies of CHF with preserved EF, the mechanism of its formation and progression is not fully unexplored. In addition to age and concomitant diseases, microvascular dysfunction plays an important role. An actual task is to study the combination of risk factors, as well as to determine the leading link in the pathogenesis of CHF with preserved EF. In the pathogenesis of CHF in men and women, there are key differences that can affect not only the clinical course of the disease, but also its short-term and long-term prognosis, since women more often experience concentric LV remodeling and, as a consequence, the formation of heart failure with preserved EF, whereas for men, the formation of heart failure with low EF is more typical[1]. Nowadays, the problem of heart failure (HF) has become a global public health problem, given the fact that its prevalence is constantly increasing. The number of patients with heart failure worldwide is about 26 million, of which 50% are patients with heart failure with preserved ejection fraction(HFpEF)[2].

Keywords: Chronic Heart Failure, Ejection Fraction, Diastolic Dysfunction, Renin-Angiotensin-Aldosterone System

INTRODUCTION:

Despite numerous studies on chronic heart failure with preserved EF, the mechanism of its formation and progression has not been fully understood. In addition to age and concomitant diseases, microvascular dysfunction plays an important role. It is an urgent task to study the complex of risk factors, as well as to determine the leading link in the pathogenesis of CHF with preserved PV. In the pathogenesis of CHF in men and women, there are key differences that may affect not only the clinical course of the disease, but also its short- and long-term prognosis, as women are more likely to have concentric LV remodelling and, consequently, to form heart failure with preserved EF, while men are more likely to form heart failure with low EF [1]. Today, the problem of heart failure (HF) has become a global public health issue, given the fact that its prevalence is constantly increasing. The number of patients with heart failure worldwide is about 26 million, of whom 50% have heart failure with preserved ejection fraction. (CHF) [2].

Arterial hypertension (AH) and age are known to be major risk factors for CHF. Activation of the renin-angiotensin-aldosterone system (RAAS) leads to increased synthesis of angiotensin II (AT II), causing a number of undesirable effects (myocardial and vascular wall cell proliferation and hypertrophy, aldosterone secretion, sodium retention, increased collagen synthesis, reduced NO formation, endothelin-1 synthesis, etc) [3]. At the same time, some comorbid conditions including obesity, type 2 diabetes mellitus (DM2), chronic obstructive pulmonary disease, chronic kidney disease and anaemia are considered to be factors that together accelerate the development of CHFV as they increase systemic vascular inflammation. [4]. The latter is considered as one of the main mechanisms leading to the development of endothelial dysfunction and endothelial damage, given that a number of experimental studies have proved the effect

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of microcirculatory bed rarefaction: reduction of capillary wall density on the background of increased platelet adhesion, as well as oxidative stress, as shown in the works of S. Mohammed et al. [5] and F. Crea et al. [6]. Oxidative stress impairs endothelial homeostasis by reducing nitric oxide (NO) bioavailability, leading to endothelial dysfunction (ED) and endothelial damage. [7]. On the other hand, the development of CHFV is directly influenced by age and hypertension experience, which, as risk factors, alter the metabolism of myocardial stroma and the medial vessel wall, leading to increased stiffness with accumulation of extracellular matrix, in which myocardial and vascular myocytes change their phenotype to collagen-secreting myofibroblasts [8,9,10]. Despite the importance of CHFV, there are currently no effective treatments for the disease. All classes of prognostic drugs (reninangiotensin system blockers, beta-adrenoblockers, neprilysin inhibitors) have proven ineffective in CHFV, which seems to be due to the different mechanisms of these two forms of heart failure. In SNFV, cardiomyocyte death is the underlying cause; in SNFV, the main pathophysiological changes are delayed relaxation and reduced left ventricular compliance, with myocardial microvascular inflammation playing a key role. This concept is now supported by most experts and is supported by a range of clinical evidence.

The main pathophysiological mechanisms of myocardial damage are interstitial fibrosis, inflammation, endothelial dysfunction, impaired microvascular autoregulation and increased end-diastolic left ventricular myocardial stiffness. [11,12,13]. Left ventricular (LV) ejection fraction (EF), which characterises ventricular ejection, that is, changes in ventricular volume, should not be considered as the only measure of contractility, as it can remain unchanged when there are significant changes in overall LV systolic function [14]. An important role in the pathophysiology of this process belongs to endothelial dysfunction, accompanied by an increase in endothelial metabolic activity, leading to an increase in vascular stiffness, changes in cardiovascular conjugation, consisting in an increase in effective arterial and vascular stiffness, a decrease in LV end-systolic elasticity. Normal diastolic function depends on myocardial relaxation, LV compliance, left atrial (LV) function and heart rate (HR). The development of LV stiffness is preceded by changes in extracellular myocardial matrix and changes in the ratio of collagen synthesis, whereby type I collagen begins to predominate over type III collagen with age, and accumulation of collagen type Collagen I occurs due to decreased activity of matrix metalloproteinases and increase in their tissue inhibitors. [15]. Clinically, CHF with preserved PV is manifested by increased fatigue, decreased exercise capacity, dyspnoea, palpitations, swelling of the lower extremities; in later stages, moist rales may appear in the lungs and paroxysmal nocturnal dyspnoea may occur. [16]. Some scientists believe that poor exercise tolerance and increased fatigue are related to microvascular endothelial dysfunction. Kitzman M.D. et al. studied microvascular function in the skeletal muscles of the thigh in patients with CHF with preserved ejection fraction and found a significant decrease in capillary density, which subsequently reflected the degree of reduced physical activity. [17]. Diastolic dysfunction (DD) has long been thought to be the underlying mechanism of CHF development, based on delayed LV myocardial relaxation in diastole with increased myocardial and vascular wall stiffness due to activation of fibrosis processes [18]. Echographic criteria have been proposed that, in addition to normal or slightly reduced LV EF (>50%), structural or functional signs of myocardial LD or hypertrophy are required to confirm the diagnosis of LVSFV, which include: left ventricular dilatation atrial cavity-LV (LV index≥34 m/m2), LV hypertrophy (LV mass index≥115 g/m2 for men and 95 g/m2 or more for women) or E/e'≥13 [19]. Microvascular endothelial inflammation is accompanied by oxidative stress, which triggers the proliferation of vascular myocytes and activates fibroblasts, while reducing the bioavailability of nitric oxide (NO), which decreases cyclic guanosine monophosphate formation. (cGMP) and protein kinase G (PKG) activity [20]. The progression of oxidative damage alters the secretory phenotype of myocytes, turning them into myofibroblasts. These changes to the medial membrane of the small resistive vessels are due to changes in the vasa vasorum. Further differentiation of myofibroblasts is provided by signalling factors, including transforming growth factor b1. (TFR-b1) [21].

CONCLUSIONS:

Thus, changes in myocyte function lead to changes in the extracellular matrix (ECM) both in the myocardial interstitium and in the outer and middle sheaths of arterial vessels of the muscular-elastic and muscular type. These processes consist in changing the diffusion abilities of glucosaminoglycans and proteoglycan hydrogel, compacting it, thereby impairing its diffusion abilities and feeding the surrounding cardiomyocytes and myocytes of the vascular wall, leading to the development of myocardial fibrosis, increasing vascular stiffness, leading to increased pulse wave velocity (PWV) and increased pulse pressure (PP). When remodelling processes are triggered, components of VCM are degraded, in which matrix metalloproteinases (MMPs), enzymes whose activity begins to increase during

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tissue remodelling or inflammation, play an important role. For example, in a study by Spinale et al. (2013) found that during pressure overload in the LV, MMP-2 levels increase and are higher than MMP-9 and, conversely, are higher than MMP-2 levels in end-stage CHF [22]. At the same time, oxidative stress damages the sarcoplasmic reticulum, increasing the activity of Ca2+ ions, thereby causing a delay in ventricular relaxation in diastole. Increased arterial stiffness, as evidenced by recent published work by A.Pries, L.Badimon (2015), is directly related to changes in small vessels (100-500 μm diameter microcirculatory bed). This statement is the most likely, as this network is one of the most branched muscular terminal vessels in terms of area. These changes at the arteriolar level probably primarily lead to remodelling of the indicated vascular bed fragment with an increase in its tone, which creates conditions for a retrograde pressure increase in the entire vascular system. On the one hand, due to the wide representation of this segment of the vascular system in the blood supply of any organ, including the heart, it leads to the deterioration or appearance of microcirculatory disorders at the systemic level, on the other hand, it contributes to the increase of intraventricular pressure and deterioration of subendocardial and intramural blood flow [23]. Due to the increase of LV BP, LV pressure increases, which leads to the expansion of its cavity (observed in about 1/2 of all patients with CHFV), the development of atrial fibrillation, which is an independent predictor of mortality and rehospitalization in patients with CHFV, becomes a frequent complication of CHFV. [24]. Due to LV pressure and volume overload, the pressure in the small circle of the circulation increases, leading to the formation of pulmonary hypertension, which with progression of heart failure leads to right ventricular dysfunction, which is an unfavourable prognostic criterion for CHFV [25].

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Volume-4, November 2021
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