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LEFT VENTRICULAR REMODELING IN HEART FAILURE (PART I): CURRENT UNDERSTANDING OF PATHOMECHANISMS AND RELATED MYOCARDIAL DYSFUNCTION

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Summary

Aim: to provide a literature review of the current data on various pathomechanisms of left ventricular (LV) remodeling in heart failure (HF) patients and their role in the development and progression of myocardial dysfunction. This paper is a first part of the review, devoted to the current state of pathophysiology of LV remodeling in HF.
Material and methods. The thematic scientific papers, published during the last decade, constituted the study material. The research methodology involved bibliosemantic method and structural and logical analysis.
Results and discussion. LV remodeling is the result of complex changes at the molecular, cellular and tissue levels, affecting the myocardial mass, geometry and performance, and ultimately leading to HF development and progression. LV systolic dysfunction occurs through the numerous mechanisms, including the defects in sarcomere function, abnormal excitation-contraction coupling and calcium homeostasis, ion channel dysfunction, mitochondrial and metabolic abnormalities, depressed cardiomyocytes survival signaling, redox pathobiology, inflammation and inadequate vasculogenesis. The term «LV diastolic dysfunction» covers the alterations in diastolic distensibility, filling or relaxation of the LV, regardless of whether LV (global) systolic function is normal or abnormal, and regardless of whether the patient has clinical manifestations of HF. The up-to-date pathophysiological paradigm of the development and progression of HF with LV diastolic dysfunction and preserved LV (global) systolic function considers systemic inflammation as a key pathomechanism of structural and functional changes of the myocardium, promoted by various cardiovascular and extracardiac conditions. In its turn, the systemic inflammation promotes endothelial dysfunction, contributing to multiple end-organ damage.
Conclusion. The deepening one`s knowledge of various pathomechanisms of LV remodeling and related myocardial dysfunction in HF patients is an important prerequisite for identifying new perspectives on further fundamental research and more rational designing of future clinical trials.

Key words: **left ventricle, remodeling, heart failure, pathophysiology, pathomechanism, myocardium, dysfunction**

INTRODUCTION

Heart failure (HF) remains a substantial problem for the healthcare system, particularly due to rapid pandemic-like increasing of its incidence, and a significant economic burden of HF-related health expenditures. Despite evident progress in HF treatment, the morbidity and mortality rates are still high, and the quality of life of such patients is poor [1-8].

Among the major conceptual advances in the field of HF, it should be highlighted the recognition of HF progression that is based on structural and functional abnormalities, occuring in the heart in response to hemodynamic, neurohormonal, epigenetic and genetic factors. Cardiac remodeling is a fundamental pathophysiological stage of the cardiovascular continuum and the backgroung for HF manifestation [1, 2, 9, 10].

To date, the majority of available studies on cardiac remodeling relate to structural and functional changes in the left ventricle (LV). Although the complex of changes regarding LV (adverse) remodeling has traditionally been described from the anatomical point of view, current scientific evidence suggests that this process is secondary to alterations in the biological properties of cardiomyocytes, histological changes of the myocardium (myocytes and nonmyocyte compartments), along with macroscopic changes in the geometry and architecture of the LV chamber [1, 2, 11].

The available classical pathophysiological models cannot fully cover the rapidly emerging data on new pathomechanisms of LV remodeling and HF development and progression. At the same time, current progress in fundamental research and the growing body of clinical evidence warrant the systematizing of the obtained knowledge, aiming at filling the gaps and updating of existing concepts, as well as developing new conceptual approaches to the vision of the studying object. Deepening the understanding of the pathophysiological mechanisms of myocardial remodeling is a valuable addition to the accumulated wealth of clinical data, potentially favoring better HF prevention, more rational description of the «portraits» of patients, appropriate for the certain treatment modality, along with highlighting novel therapeutic targets [1, 2, 12, 13].

This three-part review is devoted to the current state of pathophysiology of LV remodeling in HF. This first part will focus on its prominent pathomechanisms and their role in the development and progression of LV dysfunction.

AIM

This paper aims to provide a literature review of the current data on various pathomechanisms of LV remodeling in HF patients and their role in the development and progression of myocardial (LV) dysfunction.

MATERIAL AND METHODS

The thematic scientific papers, published during the last decade, constituted the study material. The literature search was conducted by the use of Google Web Search and PubMed search engines by the following keywords: left ventricle, remodeling, heart failure, pathophysiology, pathomechanism, myocardium, dysfunction, as well as their combinations. The research methodology involved bibliosemantic method and structural and logical analysis.

REVIEW AND DISCUSSION

The pathomechanisms of LV remodeling: from molecular alterations to cardiac dysfunction. The process of LV remodeling is treated as the changes in its mass, volume, shape and composition in response to mechanical stimulation and systemic neurohormonal activation. Conceptually, these alterations are observed at different LV structural levels, including cardiomyocytes, histological structure of the myocardium (involving cardiomyoctyes, non-cardiomyocytes and extracellular matrix), and the LV chamber as a whole [1, 2, 10, 14, 15].

The changes in the biological properties of cardiomyocytes are multiform, and include the following processes: cell hypertrophy; reactivation of fetal genes, accompanied by α-myosin heavy chain gene expression decrease with concomitant increase in β-myosin heavy chain expression; β-adrenergic desensitization; progressive loss of myofibrils and disarray of the cytoskeleton; the changes in excitation-contraction coupling, with consequent alterations in the contractile properties of the myocyte; and modifications of myocyte metabolism. All these molecular changes of the failing cardiomyocyte, as a result, lead to progressive deteriortion of its contractile function (decrease shortening) and delayed relaxation [1, 2, 9, 10, 16, 17].

The hypertrophic response of the cardiomyocyte is one of the prominent characteristics of LV remodeling, being associated with the expression of fetal gene isoforms and coordinated by several signaling pathways. Moreover, the activation of fetal gene portfolio may also affect the contractile properties of the failing cardiomyocyte. At present, various stimuli are known for the genetic reprogramming of the cardiomyocyte, including mechanical stretch/strain of the cell, neurohormones, inflammatory cytokines, other peptides and growth factors, and reactive oxygen/nitrogen species (RONS). These stimuli exert local myocardial (autocrine/paracrine) and systemic (endocrine) effects [1, 2, 10, 18].

At the histocellular level, the alterations in the failing myocardium may be classified into those occuring within the cardiomyocytes compartment, non-cardiomyocytes compartment (including fibroblasts, endothelial and immune cells), extracellular matrix (ECM) and the myocardial microvasculature. In general, both cardiomyocytes and non-cardiomyocytes interact closely with each other, responding to cardiac damage, neurohormonal activation and stress [1, 2, 9, 10].

The fundamental alteration of the cardiomyocytes compartment of myocardium is progressive myocyte loss, leading to both LV remodeling and dysfunction. Besides non-programmed cell death, subsequent studies demonstrated that, under specific conditions, cell death is regulated by the certain signaling pathways and is known as programmed cell death, including apoptosis, ferroptosis, pyroptosis, autophagy-dependent cell death (particularly, autosis) and necroptosis. However, despite the existence of distinct types of cell death in the failing myocardium, one should most likely recognize a continuum of cell death responses, contributing to progressive cardiomyocytes loss and HF progression [1, 2, 19].

Alterations in ECM constitute the second important myocardial histological modifications, occuring during

cardiac remodeling, and are represented by the changes in the following aspects: the overall collagen content, the relative contents of different collagen subtypes, the collagen cross-linking, and the connections between cells and ECM via integrins. In particular, the activation of cardiac fibroblasts leads to excessive collagen deposition and fibrosis, either reactive (as a direct response to damage) or replacement (to replace the loss of cardiomyocytes). Furthermore, there is a growing evidence that the three-dimensional organization of ECM is an important regulator of the structural and functional state of the myocardium in HF [1, 2, 9, 10].

In the context of alterations in the myocardial microvasculature, it should be noted that endothelial dysfunction is positioned as one of the leading pathophysiological mechanisms of HF development and progression. Microvascular endothelial dysfunction promotes RONS production, enhances leucocyte infiltration and leads to capillary rarefaction and tissue hypoxia. Along with ECM changes, microvascular remodeling is also a component of histological modifications of the failing myocardium, characterized by a number of structural structural abnormalities, particularly medial hypertrophy, intimal hyperplasia, interstitial fibrosis and disarray of vascular smooth muscle cells. These morphological alterations precipitate coronary flow reserve impairment, which can be associated with specific circulating proteomic profiles, narrowing of resistance vessels and disturbed capillary growth. Vascular remodeling may jeopardize local tissue oxygen supply, impair fluid homoeostasis and alter LV wall compliance, thus contrubuting to the development and/or progression of HF [1, 2, 9, 10, 18, 20-25].

The above mentioned changes in the biological properties of cardiomyocytes and histological modification of the myocardium form the background for alterations in LV chamber geometry, consisting in its progressive dilation, increased sphericity of the ventricle, LV wall thinning and formation of mitral valve incompetence («functional mitral regurgitation»). In general, many of the structural changes of LV chamber may contribute to deterioration of HF natural course [1, 2].

In general, the technological progress in recent years has significantly deepened the understanding of molecular substrates of cardiac remodeling in HF, in particular the role of non-coding genome, extracellular particles (vesicles) and alterations in mitochondrial bioenergetics [1, 2, 9, 10, 19, 16, 17, 26].

Thus, it has become known that cardiomyocytes release extracellular vesicles and non-coding RNAs that mediate autocrine and paracrine effects on cardiomyocytes and non-cardiomyocytes [10]. Non-coding RNAs include small interfering RNAs, microRNAs, linear long noncoding RNAs and circular non-coding RNAs, and, despite being considered ealier as a «transcriptional noise», have emerged as potential biomarkers and therapeutic targets in HF. Particularly, a number of microRNAs are involved in cardiac remodeling, hypertrophy and HF pathogenesis, have diverse and sometimes opposite effects, either by inhibiting or activating of various processes, e.g., cardiomyocyte hypertrophy, cell death, neovascularization and fibrosis [1, 2, 10, 16, 17].

Extracellular vesicles are released by different cardiac cells and contain a variety of receptors, lipids, proteins and RNAs (both messenger and non-coding RNAs). Extracellular vesicles are positioned as potential mediators in cardiovascular diseases and prominent participants in intercellular communication [1, 2, 10, 26].

In the main, the intercellular cross-talk among different cell types in the myocardium is carried out in a complex manner through cytokines, growth factors, non-coding RNAs and mechano-transduction pathways [1, 2, 6, 9, 10, 23].

While studying mitochondrias in yeast, it has been demonstrated that uphold of normal mitochondrial morphology and function is determined by the dynamic balance of mitochondrial fusion and fission (division), collectively termed as «mitochondrial dynamics». However, the issue of the contribution of abnormalities in mitochondrial fission/fusion in HF pathogenesis remains unresolved to date, given the limited data on the causal relationships of mitochondrial dynamics with myocardial injury [1].

To date, there are four standard phenotypic variants of LV geometry, based on LV mass and relative wall thickness, namely normal geometry, concentric remodeling, concentric and eccentric hypertrophy [1, 6].

The mentioned two basic patterns of LV hypertrophy occur in response to hemodynamic overload. In pressure overload hypertrophy (e.g., in case of aortic stenosis or hypertension), the increase in systolic wall stress promotes the addition of sarcomeres in parallel, an increase in myocyte cross-sectional area, and, consequently, precipitates LV wall thickening. This pattern of LV remodeling has been referred to as concentric hypertrophy, and has been related to the alterations in calcium/calmodulin-dependent protein kinase II-dependent signaling. As distinct from pressure overloading, in volume overload hypertrophy (e.g., in patients with aortic and mitral regurgitation), the increase in diastolic wall stress gives a rise to an increase in cardiomyocyte length with the addition of sarcomeres in series, thus engendering progressive LV dilation. This pattern of LV remodeling has been referred to as eccentric hypertrophy (or a dilated phenotype) and has been linked with protein kinase B (Akt) activation [1, 2].

At the same time, one should consider that the heart remodeling is an extremely complex process, characterized by a wide spectrum of structural and functional changes, ranging from minor functional adaptations to significant

modifications of the cellular morphology and functions, myocardial architecture, the heart shape and physiology. Cardiac mechanotransduction is considered as the basic biological mechanism of particular sequences of actions, which unequivocally determine the adjustments and modifications, occuring in the heart, being exposed to the altered wall and/or tissue stress. Definitely, various molecular pathways, predominantly «orchestrated» by mechanotransduction, are jointly involved in the processes underlying heart remodeling, and aimed at achievement of myocardial adaptation to modified biomechanical and hemodynamic conditions, as well as maintaining and/or correction of cardiovascular homeostasis [6].

However, in cardiological practice, one can observe far more individual configurations of remodeled heart. In this regard, it is possible that there is a much wider range of phenotypes of slightly or substantially different «hearts», which are formed against the background of various combinations of effects of pressure or volume loading. Moreover, even with similar wall and cardiomyocyte stress, the «hypertrophic» (remodeling) response of the myocardium to certain biomechanical stimuli can be quite variable [6, 27].

From the clinical perspective, LV remodeling refers to the changes of the ventricle`s structure and function over time, with a progressive deterioration of myocardial performance, leading to HF development (adverse remodeling) or vice versa a recovery in response to HF treatment. On a more fundamental perception, LV remodeling is the result of complex cascades of transcriptional, signaling, structural and functional events at the cellular and tissue levels, affecting cardiac dimensions, mass, geometry, function and electrical activity. Initially, these responses are adaptive in nature, but, when sustain over time, acquire maladaptive propeties, with further aggravation of myocardial damage in a vicious circle manner. In a broader context, besides the mentioned aspects of LV structural and functional alterations, the left atrium and, in the long term, even right heart chambers are also involved in the heart remodeling process. In addition, adverse LV remodeling is a predictor of a worse prognosis, whilst its reversibility is associated with better clinical outcomes. Generally, myocardial remodeling can occur and deteriorate across the entire HF spectrum, thus being a reasonable target for drug and/or device treatment [1, 2, 10, 19, 27, 28].

It has been long recognized, that LV EF is one of the most widely used parameters of myocardial function, and remains the «cornerstone» of HF diagnosis, phenotyping and prognostic stratification. Importantly, LV EF appears to be among criteria that determine the strategy and effectiveness of treatment. However, LV EF characterizes the global systolic (pump) function of the ventricle, but not its contractility. Moreover, given the results of advanced multivariable data analytics (like machine learning and other methods for patients clustering and phenotyping) of the wide spectrum of parameters characterizing the LV performance, LV EF should not be used alone for an appropriate calibration and discrimination for survival in HF patients. Nevertheless, LV EF remains the basic parameter for HF characterization and the primary inclusion criterion for clinical trials devoted to different aspects of HF [1-5, 7, 13, 27, 29].

It is widely accepted, that, according to LV EF value, HF is classified into HF with reduced LV EF (HFrEF) (LV EF ≤40%), HF with mildly reduced LV EF (referred earlier to as «mid-range» EF) (HFmrEF; LV EF 41-49%), and HF with preserved LV (HFpEF) (LV ≥50%). At that, HFmrEF is usually considered as a dynamic «intermediate» stage on the trajectory to improvement from HFrEF or to deterioration to HFrEF [1-5, 7, 29, 30].

Despite the fact that LV EF-based HF categorizing provides a valuable insight into the HF pathophysiology, such an approach leads to an enormous oversimplification of understanding of HF as an extremely complex condition [31]. There can be many explanations for this, e.g., in the context of well known morphological properties of the myocardium. In particular, the LV myocardium consists of subendocardial and subepicardial longitudinal fibers, and circumferential fibers in the mid-wall layer. HFrEF usually develops on the background of transmural abnormalities in all three layers, caused by conditions such as acute myocardial infarction, dilated cardiomyopathy, myocarditis or toxic damage (for instance, alcohol or chemotherapy). Accordingly, abnormal LV function is first detected in the subendocardial layer, and afterwards extends to the mid-wall (in the absence of transmural damage) in HFpEF and HFmrEF patients. Therefore, there is an opinion than HFpEF and HFmrEF patients should be better characterized as having «HF with preserved subepicardial myocardial function» rather than «HF with preserved (non-reduced) EF», and that the «non-reduced» LV EF value (>40%) is dependent on the extension from subendocardial to mid-wall myocardial lesions [29]. Finally, the currently available data suggest the overlapping of contractile and dyastolic abnormalities in the myocardium, irrespective to LV EF value, that demands an integral assessment of overt and/or sublte alteriations in myocardial performance by the use of modern diagnostic techniques [27, 29, 31].

LV systolic dysfunction. The suppression of LV systolic function, being a basic manifestation in nearly half of all HF patients, occurs through the numerous mechanisms, including the following: defects in sarcomere function, abnormal excitation-contraction coupling and calcium homeostasis, ion channel dysfunction, mitochondrial and metabolic abnormalities, depressed cell survival signaling, enhanced autophagy and mitophagy, abnormal proteostasis, redox pathobiology, inflammation, signal transduction abnormalities and vascular insufficiency (inadequate vasculogenesis). The alterations in myocardial contractile

properties are also impacted by cross-talk between the cells and signaling from the ECM and cardiomyocytes. Finally, the net systolic performance can potentially be influenced by the series of external factors, particularly an abnormal venous (preload) and/or arterial (impedance) loads, pericardial constraints, neurological controls etc. [1, 2].

The currently approved HF classification, based on LV EF value, is convenient for clinicians, but also arbitrary, and does not take into account a number of important characteristics of myocardial systolic function. For example, one can onserve the reduced LV EF in either myocardial infarction or dilated cardiomyopathy. However, these two hearts can be characterized by disparate myocardial properties, particularly the loss of a regional contractility of the infarcted area (replaced by scar), or a diffuse cardiodepression, respectively [1, 2, 27].

Over the last decade, significant progress has been made in understanding the pathophysiology of HF, in particular through the deepening of knowledge about its molecular-cellular determinants and their impact at the organ level. Most of this information is based on the results of basic research with genetic manipulations, including those related to sarcomere proteins, which play a central role in systolic dysfunction. In particular, such a research revealed HF causing mutations that depress molecular motors, as well as numerous posttranslational modifications that alter their function. Importantly, in HF there is also a disruption of intermediate filament proteins that structurally couple the sarcomere to the cell membrane. Moreover, the abnormalities of calcium homeostasis constitute another major cause of LV systolic impairment, invovling the ion channels at the plasma membrane, intracellular proteins and calcium storage systems (such as the sacroplasmic reticulum) [1, 2, 9, 10, 19].

To date, the genetic gain and loss-of-function studies have been manipulated with myriad molecular signaling abnormalities in the failing heart, revealing their role in contractile dysfunction. In addition to specific genes and proteins, the wide spectrum of epigenetic transcriptional regulators, including BET-bromodomains (gene readers) and non-coding RNAs, are also involved in systolic depression pathogenesis. Lastly, the systemic inflammation, being presented in case of obesity, diabetes mellitus and proinflammatory diseases, alter the metabolic and signaling conditions in which the failing heart operates. The changes in the global biochemical milieu, namely the high-energy phosphate metabolism and fuel substrate utilization, have a major impact on systolic function and reserve [1, 2, 16, 17, 19, 32].

Up to now, little is known about the precise reasons why some patients with LV systolic dysfunction remain asymptomatic or minimally symptomatic after the initial decline in the ventricle`s pumping capacity, or the clinical manifestation occurs only after the dysfunction has been persisted for some time. Among the potential explanations, one could assume that a number of compensatory mechanisms, being activated in the setting of cardiac injury or cardiac output decline, are sufficient to modulate LV function within a physiologic/homeostatic range, thus the patient`s functional capacity remains preserved (or depressed only minimally) for a certain period of time. However, at some time point, the aggregated changes within the cardiomyopathic ventricle may progress and reach the state where no amount of neurohormonal stimulation can maintain cardiovascular homeostasis, i.e., HF may deteriorate independently of the patient`s neurohormonal status [1].

At present, three main conceptual HFrEF models have been proposed, namely cardiorenal, cardiocurculatory (hemodynamic) and neurohormonal ones, which explain the pathophysiology of HF with LV systolic dysfunction and serve as a basis for developing strategies for its treatment. However, despite repeated attempts to integrate these pathophysiological concepts and propose a unifying hypothesis, none of these models has understood the test of time [1, 2, 13].

Particularly, it has been long recognized that the neurohormonal concept explains many aspects of disease progression in the failing heart. At the same time, the growing body of clinical evidence suggests that current neurohormonal models fail to completely explain the basis for HF progression. Currently available neurohormonal antagonists may stabilize the clinical course of HF or, in some cases, cause the reversal of the certain aspects of its progression. However, in the vast majority of patients, HF still progresses, albeit more slowly. Moreover, as HF progresses, the significant proportion of patients become resistant to conventional treatment regimens and require their revision. Because the exact mechanisms of reduction or loss of efficacy of neurohormonal antagonists are yet to be deeply elucidated, the accumulated data suggest that LV remodeling is directly related to further deterioration in LV performance and a less favorable HFrEF clinical course, irrespective to neurohormonal status at a certain point in time, demanding to explore the new pharmacological approaches [1, 2].

Among the reasons for the above features of HFrEF pathogenesis, it should be considered that the development and progression of HF in patients with LV systolic dysfunction represent the complex interplay between structural and functional biological changes occurring in the heart (with the engage of cardiomyocytes and ECM), autonomic nervous system, kidneys, peripheral vasculature and skeletal muscles. Importantly, numerous factors affect these biological changes, including aging, genetic background, comorbidities, nutrition, along with nonbiological environmental factors, adding to the complexity of understanding the pathophysiology of HF. Moreover, a detailed analysis of the obtained evidence is strongly demanded in the cases, where recent successes in

clinical trials do not fit existing models, in order to identify areas where further refinement of current paradigms may be needed [1, 2, 9, 10, 13, 19].

LV diastolic dysfunction. The term «LV diastolic dysfunction» covers the alterations in diastolic distensibility, filling or relaxation of the LV, regardless of whether LV EF is normal or abnormal, and regardless of whether the patient has clinical manifestations of HF [1, 2]. As indicated in recently published guidelines, although the classic clinical signs and symptoms of HF, together with LV EF of 41% to 49% or ≥50%, respectively, are necessary for the diagnosis of HFmrEF and HFpEF, the requirements for additional objective measures of cardiac dysfunction can improve the diagnostic specificity, i.e., the supporting the diagnosis by the data of spontaneous (at rest) or provokable (e.g., during exercise, fluid challenge) increased LV filling pressures (e.g., elevated natriuretic peptide, noninvasive/invasive hemodynamic measurement) [4].

Despite the theoretical usefulness of categorizing the LV dysfunction patterns, which emphasizes whether the primary problem is defective pumping or filling, clinical practice and current diagnostic techniques suggest that LV systolic and diastolic dysfunction are rarely isolated and often both contribute to HF clinical manifestation. Although systolic and diastolic variants of LV dysfunction are often coexist in HFpEF, it is the latter one that is positioned as the primary contributor to the development and clinical presentation of HF [27, 33].

From a hemodynamic perspective, the fundamental disorder in HFpEF patients is LV end-diastolic filling pressure elevation (with resultant left atrial pressure elevation) at rest or with exertion, being related to increased LV stiffness. In the absence of specific endocardial or pericardial diseases, high diastolic LV stiffness is originated from the increased myocardial stiffness, which is regulated by cardiomyocytes and ECM [1, 2, 5, 29, 33, 34].

The cardiomyocyte-based stiffness is mainly regulated by the giant elastic sarcomeric protein titin, which functions as a spring in bidirectional manner, and is responsible for early diastolic recoil and late diastolic distensibility. Cardiac titin stiffness is regulated by the certain cardiomyocyte signaling pathways. The stiffening of titin, leading to increased passive intrinsic stiffness of cardiomyocytes, is a result of multiple mechanisms, involved in HFpEF pathogenesis. Interestingly, it was demonstrated recently that the family of small heat shock proteins, including HSP27 and αB-crystallin, provide myofilamentary protection against cardiomyocyte damaging factors [1, 35].

In its turn, ECM-based stiffness is predominantly regulated by collagen. In HFpEF, the increased endothelial expression of adhesion molecules intesify myocardial infiltration by monocytes/macrophages, that secrete transforming growth factor β, favouring converting of fibroblasts to myofibroblasts. Additionally, the ECM degradation is decreased because of altered expression of matrix metalloproteinases and upregulation of their tissue inhibitors. The mentioned processes thereby enhancing interstitial collagen deposition and promoting interstitial myocardial fibrosis [1, 2].

Despite the fact that abnormal myocardial relaxation and reduced LV chamber compliance are the predominant pathomechanisms of HFpEF development and progression, the current body of data allows to interpet HFpEF as a systemic syndrome with multiple cardiovascular and extracardiac pathophysiologic mechanisms beyond diastolic dysfunction [1, 2, 5, 29, 33, 34].

From the cardiovascular perspective, such ancillary mechanisms include systolic LV dysfunction, left atrial dysfunction, ventricular-vascular stiffening (with consequent abnormal ventricular-arterial coupling), impaired systemic vasodilatory reserve, chronotropic incompetence, pulmonary hypertension, right ventricular (RV) dysfunction and chronotropic incompetence. It is worth noticing, that, despite normal LV EF, the sublte contractile dysfunction is often present in HFpEF patients, and could only be detected with advanced imaging techniques [1, 2, 5, 6, 19, 36, 37].

Considering the cardiac and extracardiac factors, contributing to LV diastolic dysfunction, it should be considered, that HFpEF patients population is characterized by the substantial burden of cardiovascular risk factors and diseases, namely hypertension (with increased central aortic stiffness), coronary artery disease, atrial fibrillation, obesity and type 2 diabetes mellitus, as well as by the high prevalence of comorbidities (extracardiac conditions), including pulmonary disorders (chronic obstructive pulmonary disease and chronic bronchitis, central and obstructive sleep apnea), chronic kidney disease, impairment of structure and function of skeletal muscles (sarcopenic obesity, i.e., a loss of skeletal muscle and increased intramuscular adiposity), liver disorders (nonalcoholic fatty liver disease, primary cirrhosis) and anemia. In addition, HFpEF patients are generally older and more often female, indicating the importance of age and sex factors in HFpEF pathogenesis [1, 2].

Under the certain conditions, HFpEF may be considered as a maladaptive response to environmental modifiers, causing premature and pathological aging of the heart [38]. In this respect, the abnormalities in the protein folding process (deficiency of the unfolded protein response) have been observed during the abnormal aging of the heart, being a part of the HFpEF pathomechanisms pool. This phenomenon was reffered to as «Alzheimer`s of the heart» [39]. The neurological paradigm of dementia is suited to explain HFpEF, which may be, at least partially, considered as a maladaptive response of the myocardium to aging. Interestingly, telomere damage, being a cellular hallmark of aging, has been related to molecular and mitochondrial abnormalities, in a vicious circle involving

oxidative stress and activation of pro-apoptotic signalling pathways [8, 37, 38].

Given the current advances in the understanding of LV diastolic dysfunction and HFpEF pathogenesis, a novel paradigm of HFpEF development and progression has recently been proposed, considering systemic inflammation as a key pathomechanism of structural and functional myocardial remodeling, promoted by the above-mentioned cardiac and extracardiac conditions. In its turn, the systemic inflammation promotes endothelial dysfunction, affecting the multiple organs throughout the body, including myocardium, lungs, skeletal muscle and kidneys. Such specific features of HFpEF pathophysiology constitute the basis for the diversity of HFpEF phenotypes, which are characterized by multiple manifestations of the end-organ damage, particularly by the variable amounts of myocardial remodeling and dysfunction, pulmonary hypertension, renal sodium retention, deficient skeletal muscle oxygen extraction during exercise, etc [1, 2, 37].

In particular, systemic inflammation promotes coronary microvascular endothelial inflammation and dysfunction. This affects LV diastolic dysfunction through the aforementioned mechanisms, and can result in subendocardial ischemia, particularly during exertion. Endothelial inflammation also causes increased RONS production and reduced nitric oxide (NO) bioavailability, resulting in depressed soluble guanylate cyclase activity, lower cyclic guanosine monophosphate (cGMP) content and reduced protein kinase G (PKG). The upregulation of iNOS and downregulation of myocardial cGMP-PKG signaling, being evident in HFpEF, are related to the reduced myocardial brain natriuretic peptide expression and increased microvascular inflammation and oxidative stress, which impair both «natriuretic peptides-cGMP» and «NO-cGMP» cascades. Reduced cardiomyocyte cGMP-PKG signaling aggravates the cell intrinsic stiffness through hypophosphorylation of titin, and enhances cardiomyocyte hypertrophy related to the impaired PKG-mediated antihypertrophic activity. Besides, coronary microvascular dysfunction on its own can contribute to RV dysfunction, irrespective to the increased RV afterload [1, 2, 10, 19-23, 40].

Among the additional molecular pathomechanisms of LV diastolic dysfunction, which have been investigated in HFpEF/HFmrEF preclinical studies, are abnormal cardiomyocyte calcium handling, lipotoxicity and metabolic defects in fuel utilization and efficiency. Overall, insufficient evidence is available on the molecular mechanisms of HFmrEF due to the lack of basic science studies of this HF phenotype [1, 30].

Thus, HFpEF represents a complex clinical syndrome, in which multiple cardiovascular risk factors, cardiac and vascular disorders, and overlapping extracardiac comorbidities may be present in various combinations. These particular properties make HFpEF highly heterogeneous, which forms the basis for the existence of multiple HFpEF subphenotypes. Therefore, creating a rationale, unified HFpEF classification system remains a challenge. However, a number of approaches to the classification of HFpEF have been proposed, aiming to optimize the management of such patients, in particular according to the following principles: clinical subtypes (based on etiologic and echocardiographic features); predominant HFpEF pathomechanisms; hemodynamic/clinical presentation (exercise-induced left atrial pressure elevation, overt volume overload, or pulmonary hypertension/RV failure); and extent of cardiac (vs. extracardiac) involvement. These and other stratification approaches, focusing on the identification of myocardial structural and functional abnormalities in the individual HFpEF patient, could be a highly relevant tool for predicting the potential response to certain treatment modality, i.e., could be used to optimize the choice of appropriate treatment strategies [1, 2, 5, 6, 29, 33, 34, 37].

To date, insufficient evidence is available on the underlying pathophysiology of HFmrEF, because the detailed studies in this HF subtype are lacking. Given the mildly reduced LV EF, HFmrEF share some pathophysiologic similarities with HFrEF patients. As compared to HFpEF, HFmrEF is characterized by more exaggerated longitudinal systolic dysfunction (i.e., by abnormal LV global longitudinal strain) and impaired contractile reserve. At the same time, the profile of comorbidities in HFmrEF patients may resemble that of HFpEF, thus both HFmrEF and HFpEF may be characterized by a number of common pathophysiological features, including systemic and coronary endothelial dysfunction, abnormal ventricular arterial coupling and chronotropic incompetence. It is worth noting, that biomarkers and proteomic signatures might be a useful tool for further highlighting the differences across the LV EF-based HF phenotypes [1, 7, 30]. In particular, the existing data suggest that patients with HFmrEF have an intermediate profile between HFrEF (cardiac stretch) and HFpEF (inflammation), which has been demostrated by the use of a multiple biomarker approach in acute HF [41]. Additionaly, the spectrum of LV EF phenotypes is characterized by the high proteomic variability, with the mildly LV EF reduced category being heterogeneous and resembling HFpEF more than HFrEF [42].

In the context of comparing the pathophysiological features of HF with the opposite LV systolic function patterns, it is important to note that the above phenotypic heterogeneity is likely far greater in HFpEF than in HFrEF, which may be a significant factor, determining the failure of HFpEF clinical trials. In addition, to date, the HF treatment strategy has been based on a «one-size-fits-all» approach that has worked relatively well for chronic HFrEF. However, in the context of HFpEF patients management, this approach needs to be revised in the light of current views on HFpEF phenotypic diversity. In general, virtually all HF syndromes, regardless of LV EF,

benefit from more tailored, personalized (individualized) therapy, which is obviously true for HFpEF as well. An example is the efficacy of renin-angiotensin-aldosterone inhibitors to improve adverse LV remodeling, which differs significantly in HFpEF patients depending on the severity of myocardial hypertrophy, fibrosis and capillary rarefaction. Finally, the deepening of understanding the etiologic, pathophysiologic and phenotypic heterogeneity of HFpEF/HFmrEF syndromes may favour more targeted and successful HFpEF/HFmrEF clinical trials and result in improvement of patient-tailored therapeutic strategies [1, 19].

CONCLUSION

In the light of current progress in fundamental sciences, the spectrum of LV (adverse) remodeling pathomechanisms goes far beyond its anatomical aspects, and is characterized by a number of adaptive and maladaptive molecular changes in response to damaging factor(s) impact, affecting all levels of the myocardial structural and functional organization, involving into the process all the chambers of the heart, and subsequently leading to the alterations in myocardial performance and HF development and progression.

The distinction of two fundamental patterns of LV dysfunction, particular systolic and diastolic ones, although being traditional and generally accepted in clinical practice, is very relative from a pathophysiological point of view, since any patient with HF has a combination of impaired contractility and diastolic properties of the myocardium, which are presented to a different extent and can be verified by the use of modern deep diagnostic techniques.

The broadening, deepening, structurizing and summarizing one`s knowledge of various pathomechanisms of LV remodeling and related myocardial dysfunction in HF patients, along with proper HF characterization and phenotyping, are important prerequisites for a better understanding of non-successful clinical trials, finding the cases where recent successes in clinical trials do not fit existing pathophysiological models, identifying new perspectives on further fundamental research, and, while translation their results «from bench to bedside», more rational designing of future interventional trials for novel treatment targets by facilitating appropriate enrollment criteria.

FUTURE PERSPECTIVES

Among the perspectives on future research in the field of HF development and progression, it is worth highlighting the integral (systems biology) approach to the analysis and interpretation of available and emerging data on various pathomechanisms of adverse LV remodeling and related myocardial dysfunction, as well as working out new conceptual pathophysiological models of HF, focusing, in particular, on better understanding of myocardial remodeling/HF phenotypic heterogeneity and a switch to personalized patients` management.

CONFLICTS OF INTEREST

Nothing to declare.

ETHICAL APPROVAL

Not applicable (no animals or human subjects were used in this study).

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Резюме

РЕМОДЕЛЮВАННЯ ЛІВОГО ШЛУНОЧКА ПРИ СЕРЦЕВІЙ НЕДОСТАТНОСТІ (ЧАСТИНА І): СУЧАСНІ УЯВЛЕННЯ ПРО ПАТОМЕХАНІЗМИ ТА АСОЦІЙОВАНУ ДИСФУНКЦІЮ МІОКАРДА

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Мета: здійснити огляд сучасних літературних даних щодо провідних патомеханізмів ремоделювання лівого шлуночка (ЛШ) у пацієнтів з серцевою недостатністю (СН), а також їхньої ролі у виникненні і прогресуванні дисфункції міокарда. Нинішня стаття є першою частиною огляду, присвяченого сучасним уявленням про патофізіологію ремоделювання ЛШ при СН.

Матеріал і методи. Тематичні наукові праці, опубліковані впродовж останнього десятиліття, були використані як матеріал для дослідження. Методологія дослідження передбачала застосування бібліосемантичного методу та структурно-логічного аналізу.

Результати та обговорення. Ремоделювання ЛШ формується внаслідок складних порушень на молекулярному, клітинному і тканинному рівнях, що призводять до змін маси, геометрії та функціонального стану міокарда, і, зрештою, виникнення та прогресування СН. Відомі численні патофізіологічні механізми, що створюють підґрунтя для систолічної дисфункції ЛШ, зокрема такі: дефекти функціонування саркомерів, порушення спряження збудження/скорочення, кальцієвого гомеостазу та роботи іонних каналів, мітохондріальна дисфункція та метаболічні порушення, пригнічення сигнальних шляхів, відповідальних за виживання кардіоміоцитів, прооксидантний стан, запалення і неналежний васкулогенез. Під діастолічною дисфункцією ЛШ розуміють порушення діастолічного розтягнення, наповнення та релаксації міокарда, незалежно від стану його (глобальної) систолічної функції, а також безвідносно до наявності клінічних проявів СН. Сучасна патофізіологічна парадигма СН з діастолічною дисфункцією та збереженою (глобальною) систолічною функцією ЛШ розглядає системне запалення як ключовий патомеханізм структурно-функіональних змін міокарда, що виникає на тлі різноманітних кардіоваскулярних та естракардіальних станів. У свою чергу, системне запалення ініціює ендотеліальну дисфункцію, яка чинить внесок у виникнення множинних уражень органів-мішеней.

Висновок. Поглиблення уявлень про різноманітні патомеханізми ремоделювання ЛШ, а також їхню роль у виникненні і прогресуванні дисфункції міокарда у пацієнтів з СН, є важливою передумовою для визначення перспективних напрямів подальшого фундаментального наукового пошуку та удосконалення дизайну майбутніх клінічних досліджень.

Ключові слова: **лівий шлуночок, ремоделювання, серцева недостатність, патофізіологія, патомеханізм, міокард, дисфункція**