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THERAPY

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LEFT VENTRICULAR REMODELING IN HYPERTENSION: EVOLUTION OF THE APPROACH (review)

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Abstract: Left ventricular remodeling is one of the earliest complications of hypertension that has been proven to be an independent predictor of cardiovascular morbidity and mortality. In this article, the development of approaches to understanding its mechanics and prognostic value are briefly reviewed, with additional focus on patients with obesity and type 2 diabetes mellitus as frequent comorbid pathologies that significantly modify the typical morphological changes of the heart in hypertension. The main intacardiac mechanisms of decrease of left ventricular function constituing the direct pathophysiological and pathomorphological base for development of chronic heart failure are presented.

KeyWords: hypertension, left ventricle, remodeling, dysfunction, chronic heart failure.

Left ventricular (LV) remodeling is one of the earliest complications of hypertension that has been proven to be an independent predictor of cardiovascular morbidity and mortality [1]. In this article, the development of approaches to understanding its mechanics and prognostic value are briefly reviewed, with additional focus on patients with obesity as a frequent comorbid pathology that significantly modifies the typical morphological changes of the heart in hypertension [1-3].

Historically, the development of concentric hypertrophy of the LV was considered the most typical pattern of its structural and functional remodeling in hypertension [4, 5]. An increase in the LV wall thickness allowed the specific tension of the tissue to remain constant [6]. Dilatation of LV, on the other hand, was considered to be a marker of exhaustion of adaptive reserves of the cardiac muscle and a sign of heart failure [5].

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However, this concept was not able to explain the entire range of variations of the LV reaction to prolonged increase in blood pressure.In various studies, the cases of maladaptive (excess) hypertrophy [7], normal LV geometry as well as "paradoxical" findings in patients with eccentric LV hypertrophy in hypertension have been described: some patients of this group were characterized by an increase in cardiac output and minute volume of the heart despite the traditional notions of left ventricular dilatation as a marker of systolic dysfunction [8, 9]. A. Ganau, R.B. Devereux, M.J. Roman et al. should be considered the founders of the modern approach to the LV remodeling classification in hypertension [4, 10]. In 1992, they presented the results of an elegant study in which a comparative analysis of echocardiographic data was performed on 165 untreated patients with essential hypertension and 125 age- and sex-matched healthy subjects. The results obtained in the control group allowed the authors to suggest the relative wall thickness (RWT) of the LV of 0,44 as the upper limit of the normal range (these values were observed in 99% of healthy subjects, of which 98% had normal calculated LV mass). Approximating these results on the patients with essential hypertension, the authors proposed a classification of LV geometry based on the joint accounting of RWT and the presence of LV hypertrophy (Table 1) [4].

Table **1.**

Left ventricular geometry classification by A. Ganau et al. (1992)

LV geometry patterns	LV RWT	LV hypertrophy
Normal	< 0,45	No
Concentric remodeling (CR)	≥ 0,45	No
Concentric hypertrophy (CH)	≥ 0,45	Yes
Eccentric hypertrophy (EH)	< 0,45	Yes

Application of the obtained classification to the cohort of surveyed patients with hypertension has shown somewhat unexpected results. Thus, the presence of concentric hypertrophy of the LV, which was considered typical for patients with hypertension, was found only in 13 (7,9%) of the patients from main group; 21 (12,7%) patients had a concentric remodeling of LV without hypertrophy, 44 (26,7%) - eccentric hypertrophy and 87 (52,7%) - normal LV geometry.

In order to investigate the pathophysiological basis of the obtained results, the authors examined the features of hemodynamics that were typical for the described types of remodeling. It turned out that the patients with concentric patterns of remodeling (CR and CH) were characterized by an increase in the overall peripheral vascular resistance on the background of normal or slightly increased volume load, while patients with eccentric LVH, on the contrary, demonstrated an increase in the cardiac index and circulating blood volume on the background for normal values of peripheral vascular resistance [4, 10].

The study by A. Ganau et al. has caused a considerable interest of specialists in view of the revealed features of the LV structural adaptation among the hemodynamically heterogeneous population of patients with hypertension. In order to more closely investigate the phenomenon described, the studies were conducted to determine the distribution of types of LV remodeling in hypertensive patients with concomitant pathology.

Thus, in [11], a significantly more frequent development of LVH in patients with essential hypertension on the background of type 2 diabetes has been shown (97.0% vs. 63.1%, $p < 0.001$) due to significantly increased rate of patients with concentric hypertrophy (61.2% versus 26.1%, $p = 0.010$), while the share of EH of the LV in both groups was the same (35.8% vs 37.0%; $p > 0.05$). A similar distribution was identified in a study of 400 patients of a Japanese population [12]: the patients with type 2 diabetes had an increased incidence of LV CH (39,4% vs 26.8%, $p < 0.001$); the presence of diabetes mellitus was independently associated with an increase in the LV RWT of ≥ 0.45.

A number of studies have also investigated the features of LV remodeling when combined with obesity. Thus, in [13], a significantly higher incidence of LVH, primarily by concentric type (with an increase in both thickness of the walls and sizes of the LV cavity) in patients with hypertension on the background of abdominal obesity was observed. The author emphasizes the association of LV CH with abdominal obesity due to chronic hyperactivation of renin-angiotensin-aldosterone system (RAAS) and an increase in the level of insulinemia in metabolic syndrome, which results in an increased production of the extracellular matrix components, as well as hypertrophy of cardiomyocytes. The study performed on 1292 male patients has also demonstrated that the presence of obesity was associated with an increased detection of LV hypertrophy; as a note, although CH remained the most common variant of the left ventricular geometry in all groups, an increase in the body mass index (BMI) was clearly related to increased incidence of EH [3].

A number of prospective studies have also been devoted to estimating the prognostic value of LVH and different LV remodeling patterns. It should be noted that the mass and geometry of the LV indices occupy a special place in the definition of cardiovascular risk, being, on one hand, related to the generally accepted risk factors (such as the level of blood pressure, BMI), and on the other hand – having an independent predictive value. Thus, the presence of the LVH (defined by an electrocardiogram and echocardiographic method) was recognized as an independent risk factor for increased cardiovascular and cerebrovascular morbidity and mortality both in the general population and in patients with hypertension in a number of studies with

an odds ratio (OR) of 1.5 to 3.5, weighed OR of 2.3 for all studies [7, 10, 14].

H.M. Krumholz et al. have conducted a comparative analysis of clinical anamnestic data and ultrasound parameters of the LV in 3216 patients with hypertension – participants of the Framingham study [15]. It turned out that the rate of cardiovascular events during 8 years of observation was the highest in the group of patients with concentric hypertrophy, and the lowest – in those with normal LV geometry. This pattern was also maintained after standardizing the frequency of events by the presence of traditional risk factors. The OR of cardiovascular events and death from any cause was 2.1 (1.5-3.1) and 2.1 (1.3-3.4), respectively, for males, and 1.6 (1.0-2.6) and 1.5 (0.9-2.5) for females. An important point was the detection of the highest values of LV myocardial mass in the group of patients with CH; Standardizing the risk levels by myocardial mass significantly weakened the described relations: the mentioned OR were 1,3 (0,8-2,1) and 1,7 (0,8-3,5) for males, 1.2 (0.6-2.3) and 1.1 (0.5-2.3) for females, with no significant differences being revealed in the incidence of cardiovascular events and death for any reason.

The syndrome of chronic heart failure (CHF) is one of the typical complications of the natural current of hypertension. The problem of its diagnosis and treatment remains one of the most pressing in modern cardiology given the high mortality rates among patients with manifest CHF, especially its congestive form [16].

Pathogenetic basis of chronic heart failure is presented by an absolute or relative inability of the heart to supply the cardiac output adequate to needs of the body. At the initial stages of the CHF development, the altered neurohumoral regulation of cardiac activity and vascular tone causes a series of hemodynamic reactions aimed at supporting systemic blood circulation at an adequate level; with the further course of disease, the exhaustion of myocardial adaptation reserves results in the heart's inability to translate the venous pre-load increasing in physical activity to an adequate cardiac output, which is accompanied by clinical manifestations of heart failure. As the functional cardiac failure continues to worsen, the described condition offsets with less physical activity, and then at rest; clinically it is accompanied by the development of congestive heart failure that, along with myocardial infarction and cerebral stroke, classifies the patient to stage III (advanced) hypertension, due to the drastic deterioration in the quality of life and low five-year survival [16].

It should be noted that, similar to the vast majority of nosologies in the internal diseases clinic, CHF was first described as a clinical syndrome, with setting the relations between the characteristics of the objective manifestations of disease and morphological changes of the heart being only possible according to the results of autopsies [17]. This situation naturally contributed to the limitation of CHF syndrome understanding by its congestive form that, on one hand, allowed the physician to diagnose the clinical state, and on the other – was accompanied by the development of severe irreversible changes in the cardiac muscle (primarily, dilation of its cavities) being easily revealed post mortem.

The broad introduction of echocardiography, first to the scientific research and subsequently to the clinical practice, has allowed to confirm the association of severe CHF with the dilatation of the cavities of the heart, especially the LV. In addition, the study of calculated parameters of intracardiac hemodynamics has revealed a significant decrease in LV stroke volume in these patients [18, 19]. This condition was called systolic dysfunction; with the aim of standardizing the values of the stroke volume, the most recognition was obtained by its indexing by the LV end-diastolic volume. The new parameter was called LV ejection fraction (EF). At the same time, it was found that the deterioration of systolic function of the LV compared to healthy persons considerably anticipated the development of manifest CHF. This fact became the basis to the introduction of the concept of asymptomatic left ventricular dysfunction [17, 18].

The studies conducted in patients with hypertension have revealed that the development of latent and, subse-

quently, manifest systolic dysfunction is preceded by a long state of compensatory hyperfunction and LV hypertrophy [4, 10]. Moreover, in a number of studies it was shown that prolonged exposure to neurohumoral effects mediating remodeling of the cardiac muscle leads to a decrease in the LV contractility. These findings complement the concept of natural development of systolic heart failure following LV myocardial hypertrophy after prolonged natural course of hypertension [20-23].

Nevertheless, it did not explain the existence of a large number of patients with advanced clinical symptoms of CHF, in some cases even congestion, in whom the ultrasound examination of the heart revealed the systolic function of the LV to be normal or even elevated. After years of scientific debate, this phenomenon was recognized and a special form of clinical heart failure was defined - heart failure with preserved ejection fraction [16, 17].

Introduction of Doppler analysis of intracardiac blood flow to routine ultrasound examination, and in recent years – analysis of peak velocities of mitral annular motion in the tissue Doppler mode allowed to conduct a careful assessment not only of the systolic function of the ventricles but also state of their diastolic filling; thus, it became possible to directly assess both aspects of ventricular pumping function [16,17]. As a result, studies followed [24] which have revealed that, in the absence of valvular heart disease or tachyarrhythmias which can lead to inefficient hemodynamic, chronic heart failure with preserved ejection fraction of the LV in most cases is caused by impaired diastolic filling of the latter.

Studies conducted in hypertensive patients without systolic dysfunction revealed a strong association between the development of LV hypertrophy, especially its concentric pattern (see Table 1), and type I diastolic dysfunction (impaired relaxation), which did not contradict the concept of active, energy-consuming muscular relaxation mechanism [17]. With further course of disease, extracellular matrix remodeling with development of diffuse myocardial fibrosis leads to restrictive changes of LV diastolic blood filling, causing pseudo-normalization of transmitral blood flow velocities (type II diastolic dysfunction) due to decreased myocardial compliance causing impairment of atrial phase of ventricular filling [17, 24]. This process in separate cases was accompanied by initial manifestations of the LV cavity dilation and, accordingly, the development of its eccentric hypertrophy. Restrictive type of diastolic dysfunction in patients with essential hypertension was rarely observed.

Thus, the development of diastolic and /or systolic myocardial dysfunction in the chronic course of the underlying cardiovascular disease always precedes, and later, with the progression of functional disorders, accompanies clinical manifestation of CHF syndrome. At the same time, the deterioration of the pumping function of the heart may be, to varying degrees, due to decrease in ventricular contractility as well as impairment of their diastolic filling, which should not be considered independent processes in view of their frequent coexistence and, most importantly, common mechanisms of development.

Absolute or relative myocardial energy deficit in the hypertensive heart that may arise both as a result of increased need for oxygen and nutrients (an increase in the myocardial mass and power developed in hypertension) and their reduced delivery (concomitant coronary atherosclerosis) naturally leads to impairment of active relaxation of the LV. Chronic neurohumoral hyperactivation results in development of myocardial hypertrophy, in which an increase in the thickness of the myofibrillae is accompanied by enhanced synthesis of the extracellular matrix components with the development of diffuse fibrosis, resulting in restrictive disorders of LV filling. Both energy deficit and pathological remodeling of the ventricular wall contribute to the development of impaired contractility.

All three components contribute to a decrease in pumping function of the LV, with progression of disease at the later stages usually causing further deterioration of systolic function, which is accompanied by severe structural changes of the myocardium that are difficult and rarely subjected to reverse development even under the influence of adequate treatment [16, 17]. Thus, the possibly

earliest detection of diastolic dysfunction of the heart in patients with hypertension (optimally before the clinical manifestation of CHF) opens the prospects for timely correction of pathophysiological disturbances of circulation and patholigical cardiovascular remodeling, having the potential as the most effective measure for secondary prevention within the commonly recognized strategy of cardiovascular risk factors management.

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