DEVELOPMENT OF LEFT VENTRICULAR HYPERTROPHY IN ARTERIAL HYPERTENSION: ANALYSIS OF SCIENTIFIC RESEARCH

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Abstract*. This article presents an analysis of scientific studies on the development of left ventricular hypertrophy in the context of arterial hypertension. Arterial hypertension is a risk factor for the development of various cardiovascular complications. Key points discussed in the article include analysing the relationship between arterial hypertension and left ventricular hypertrophy. The research data also covers the study of left ventricular mass and left ventricular mass index in patients with arterial hypertension. The analysis highlights the importance of blood pressure control in preventing the development of cardiovascular disease.*
Keywords*: arterial hypertension, left ventricular hypertrophy, chronic heart failure, left ventricular mass, left ventricular mass index.*

Arterial hypertension (AH) remains the leading cause of death worldwide, affecting 25% of the adult population. According to a study from Framingham, 90% of people aged 55-65 years already have or will soon have AH. The course of AH often leads to the development of left ventricular hypertrophy (LVH), which is detected in a significant proportion of patients, and in 30% of all patients with AH, and up to 90% if the disease is severe [31]. LVH is strongly associated with the development of heart failure, arrhythmias and myocardial infarction, as well as with an increased risk of serious complications and death. The presence of electrocardiographic criteria of LVH increases the risk of stroke and is chaemic attack by 79%, and echocardiographic criteria by 64% [23].

LVH can be divided into two forms: physiological and pathological, each involving different cellular signalling pathways. Physiological LVH is characterised by a slight (10-20%) increase in cardiac mass with an increase in cardiomyocyte size. Myocardial thickening can be observed in athletes and is not associated with cardiomyocyte death or other pathological processes.

Pathological LVH is characterised by moderate (20-40%) or severe (more than 40%) increase in myocardial and cardiomyocyte mass. In contrast to physiological LVH, pathological LVH is accompanied by loss of cardiomyocytes, widespread interstitial fibrosis and reactivation of fetal genetic programming of cardiomyocytes. Pathological LVH is subdivided into concentric and eccentric forms [8].

In chronic AH, the left ventricle can adapt to high afterload by uniform wall thickening (concentric hypertrophy), while the ventricular volume remains constant. Cardiomyocytes, subjected to constant pressure, also thicken. With prolonged volume overload (e.g., mitral regurgitation), cardiomyocytes elongate rather than thicken, resulting in eccentric hypertrophy and left ventricular dilation [31].

LVH is indeed widely recognized as initially forming in a concentric pattern, which is suggested to be a compensatory response aiming to normalize the systolic stress on the left

ventricular wall. It is interesting to note that a study involving 204 patients with asymptomatic LVH found no cases of eccentric ventricular remodeling. This highlights the significance of understanding the distinct patterns of ventricular remodeling and their implications in the context of LVH [24].

Patients with LVH have reduced exercise tolerance due to the development of diastolic dysfunction. LVH is the main cause of heart failure with preserved ejection fraction (or diastolic heart failure). The process of diastolic dysfunction development in myocardial hypertrophy is as follows:

The first disturbance is myocardial relaxation. The process of myocardial relaxation depends on the energetic mechanism, which is activated by the entry of calcium ions into the reticulum of cells during diastole. The rate of relaxation depends on the rate of decrease in the intracellular concentration of calcium ions, which, in turn, is determined by the ability of a special calcium ATP-ase on the surface of the sarcoplasmic reticulum to pump calcium ions from the cytosol of the cell inside the reticulum [1].

In myocardial hypertrophy, there are changes in the functioning of the nuclear apparatus of cells, resulting in the expression of genes that were important in embryonic development. One of the significant changes is a decrease in the density of calcium ATP-ase molecules on the sarcoplasmic reticulum membrane, which occurs at the stage of compensatory hypertrophy [4]. This process can be reversible with improvement of haemodynamic conditions and normalisation of calcium ion transfer from the cell cytosol to the sarcoplasmic reticulum.

The second disturbance is an increase in myocardial stiffness, which is a passive aspect of the myocardium determined mainly by the mechanisms of its structural components in the interstitial space. Hypertrophy causes significant connective tissue formation in the interstitial space of the myocardium in hypertensive heart patients, leading to increased left ventricular filling pressure and the development of heart failure.

Basic mechanisms of myocardial extracellular space transformation during prolonged course of AH:

In the compensatory stage, there is an equal increase in the muscular and interstitial components, but as the disease progresses, the interstitial component begins to grow faster [31]. Hypertrophy has an adaptive character with a proportional increase in both components; however, with further increase in the interstitial component, there is a transition to a pathological process with the development of diastolic and, subsequently, systolic heart failure [32].

The increase in myocardial mass during prolonged AH depends on the proliferative mechanisms of angiotensin II, which stimulates cell growth and the synthesis of growth factors [20]. Angiotensin II plays a dual role in the development of myocardial hypertrophy. Its positive properties include its proliferative effects, and its negative properties include its fibrotic effect, which also provides important evidence against the assumption of an exclusively adaptive and adaptive nature of hypertrophy. In patients with longstanding AH, LVH is associated with an unfavourable prognosis because of differences in the muscular and interstitial components. The discovery of right ventricular fibrosis in AH, independent of haemodynamic overload, indicates the importance of neurohumoral factors rather than haemodynamic, with special attention to angiotensin II and aldosterone, in this process [32]. Angiotensin II stimulates fibrosis growth both directly and indirectly through its effect on transforming growth factor-β, fibroblast growth factor and aldosterone. This hormone blocks the activity of matrix metalloproteases, mainly by

increasing the production of plasminogen activator inhibitor-1 by fibroblasts and tissue inhibitor of matrix metalloproteinases-1 by endothelial cells [19].

A factor in fibrogenesis is significantly aldosterone, which, like angiotensin II, promotes fibroblast growth and proliferation, as well as the synthesis of type I and type III collagen [31]. Aldosterone also increases the production of tissue inhibitor of matrix metalloproteinases-1 by endothelial cells and inhibitor of plasminogen activator-1 and transforming growth factor-β by fibroblasts [19,38]. Studies support the possibility of local synthesis of aldosterone in the heart of patients with heart failure, where cardiomyocytes express the aldosterone synthetase gene [31].

Multiple studies confirm the dense association between HLH and the risk of developing chronic heart failure (CHF) [18,17]. For example, with a systolic blood pressure of 160 mmHg in a 60-year-old man, the risk of CHF increases from 0.37% to 0.9% in the presence of LVH. Taking into account comorbidities such as coronary heart disease, valve disease or type 2 diabetes, the risk of CHF can be as high as 5.1% or 9.5%, respectively [41]. The MESA study found that increased left ventricular myocardial mass (LVM) correlates with the incidence of events associated with CHF, increasing the risk up to 8.6-fold with increasing LVM [9]. LVH is also a risk factor for the development of atrial fibrillation in patients with AH [5,13,14].

The ALLHAT and PROSPER studies show that the presence of LVH in patients at high risk of cardiovascular complications is associated with an increased risk of atrial fibrillation, stroke, CHF, myocardial infarction and mortality [16]. Similar results were obtained in the PROSPER project, where it was found that in addition to age, duration of PR and QTc intervals, and ECG repolarisation abnormalities, LVH was a key predictor of atrial fibrillation in elderly people at high risk of cardiovascular complications [26].

Several studies confirm the importance of LVH in the development of pathology in patients with AH. In one of the prospective studies conducted by E. Andrikou and colleagues found that LVH is a predictor of microalbuminuria in patients with AH, and an increase in LVMI of 23.3 g/m² is associated with a 15% increase in the risk of microalbuminuria [3]. In another study conducted by M. Ravera et al. on 39,525 patients with AH revealed that the presence of LVH is associated with a more than threefold increase in the risk of chronic renal failure, and also becomes a significant risk factor for chronic kidney disease and the need for dialysis [37].

It was found that prognosis in patients with AH is related to the level of LVH [21]. Different degrees of LVH have been defined: mild (LVMI 96-108 g/m2 in women and 116-131 g/m2 in men), moderate (LVMI 109-121 g/m2 in women and 132-148 g/m2 in men) and severe (LVMI more than 122 g/m2 in women and 149 g/m2 in men). A study by A. Barbieri and colleagues showed that an increase in LVMI increases the risk of adverse prognosis in patients with AH [7]. According to the results of this study, out of 2545 patients with AH, 15.4% had mild LVH, 12.1% had moderate LVH, and 9.6% had severe LVH.

Multivariate analysis showed that the risk of cardiovascular complications and death increased by 1.3 times for each degree of increase in LVMI. Other studies by the same authors have also shown that the risk of all-cause mortality depends on the severity of LVH, and this risk increases with increasing degree of LVH [6]. The echocardiographic index of LVMI was more informative in predicting unfavourable outcomes than interventricular septal thickness

The choice of diagnostic criteria is crucial to assess the prevalence of LVH. Three main methods are used in clinical practice: electrocardiography (ECG), echocardiography (ECHO) and magnetic resonance imaging (MRI) of the heart. The study conducted by D. Pewsner et al. found

that electrocardiographic criteria are not recommended for exclusion of LVH in AH patients [34]. According to C.L. Mazzaro et al. the low sensitivity of electrocardiographic criteria is confirmed even when they are modified for the diagnosis of LVH in AH patients [27].

Although electrocardiographic criteria are less informative for the diagnosis of LVH [34], their presence in patients with AH has a high prognostic value [43]. Due to the low sensitivity of electrocardiographic criteria in the detection of LVH, the preferred method of its diagnosis in patients with AH is ECHO [36]. This method also provides additional information about the structure and function of the heart, making it a preferred method over ECG [2].

At present, standard echocardiographic criteria for the assessment of LVH, such as LVM and LVMI, have been developed and implemented in practice. Echocardiographic determinants of LVH are considered to be the most important independent risk factors for cardiovascular disease and death [39]. However, there is discussion and controversy regarding the accuracy and prognostic value of echocardiographic criteria for the assessment of LVH [15,11].

MRI should be used to measure left ventricular mass and size only when ECHO cannot be performed or to obtain additional information about the heart [10,33].

In an analytical article by A.M. Maceira and R.H. Mohiaddin summarises the different types of LVH detected by cardiac MRI, depending on the cause of the disease [25]. Thus, in the practice of physicians in assessing the prevalence of LVH in hypertensive patients, significant differences may be related to the choice of diagnostic criteria - electrocardiographic or echocardiographic.

Clinical studies confirm that the regression of LVH in patients with AH is considered a favourable prognostic indicator. Meta-analysis conducted by P.Verdecchia et al. showed that the regression of LVH significantly reduces the risk of cardiovascular complications by more than 50% [42].

Data from the large multicentre LIFE trial suggest that a reduction in electrocardiogram parameters reflecting the degree of LVH as a result of antihypertensive therapy for approximately 4.8 years reduces the risk of cardiovascular events by 14% for every 1050 mm/ms reduction in the Cornell index and by 17% for every 10.5 mm reduction in the Sokolow-Lyon index voltages [28]. LVH regression depends on the degree of blood pressure reduction and is associated with the choice of antihypertensive therapy.

The study conducted by S.D. Pierdomenico et al. included 387 patients with AH, in whom LVH was confirmed by echocardiography. They evaluated the efficacy of antihypertensive therapy in achieving regression of LVH during 2 years of follow-up. The results of multivariate regression analysis adjusted for the dynamics of blood pressure reduction showed that the regression of LVH significantly reduced the risk of cardiovascular complications by 64% compared with no regression [35]. Reducing enlarged LVM in patients with AH on antihypertensive therapy not only reduces the risk of overall cardiovascular complications but also reduces the likelihood of new cases of atrial fibrillation, as shown by the LIFE study and a similar analysis by T. Okura and J. Higaki [29,30]. Also, the LIFE study found that regression of electrocardiographic parameters associated with LVH as a result of long-term antihypertensive therapy was associated with a reduced risk of new CHF events and associated hospitalisations [22].

Conclusion*:* Patients with AH have different degrees of severity of LVH and its geometry. These differences may be due not only to pressure, but also to the presence of comorbidities and the level of neurohormonal activation. It is also important to consider genetic factors. The classical

paradigm explains that in response to pressure, adaptive LVH occurs to maintain its pumping function. However, over time, the adaptive capacity of the left ventricle decreases and systolic dysfunction develops. Drug interventions, such as calcineurin inhibitors, may be effective in inhibiting the development of LVH. The prevalence, risk of LVH and its regression with antihypertensive therapy depend on multiple factors, including clinical, haemodynamic, neurohumoral, and genetic mechanisms, as well as the choice of assessment criteria and the drugs used. LVH is of significant importance in predicting cardiac, vascular, and renal complications in patients with AH. It is important to note that regression of LVH can improve the prognosis of patients with AH.

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