How to estimate left ventricular hypertrophy in hypertensive patients

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ABSTRACT

Left ventricular hypertrophy (LVH) is a structural remodeling of the heart developing as a response to volume and/or pressure overload. Previous studies have shown that hypertension is not an independent factor in the development of LVH and occurrence does not depend on the length and severity of hypertension, but the role played by other comorbidities such as triglycerides, age, gender, genetics, insulin resistance, obesity, physical inactivity, increased salt intake and chronic stress. LVH develops through three phases: adaptive, compensatory, and pathological phase. Contractile dysfunction is reversible in the first two phases and irreversible in the third. According to the Framingham study, LVH develops in 15-20% of patients with mild arterial hypertension, and in 50% of patients with severe hypertension. The pathophysiology of LVH includes hypertrophy of cardiomyocytes, interstitial and perivascular fibrosis, coronary microangiopathy and macroangiopathy. Individuals with LVH have 2-4 times higher risk of having adverse CV events compared to patients without LVH. *(Anadolu Kardiyol Derg 2014; 14: 389-95)*
Key words: arterial hypertension, left ventricular hypertrophy, pathophysiology, cardiovascular events

Introduction

Arterial hypertension is a major cause of organ damage including the heart and left ventricular hypertrophy (LVH) is a consequence of systemic hypertension characterized by a structural remodeling of the heart. In hypertension, LVH is initially a transition phase and a compensatory process, but ultimately should be considered a condition preceding the overt disease (1).

LVH is an important factor in the occurrence of adverse cardiovascular events, among other things, is an independent predictor of sudden cardiac death. In relation to LVH the prevention, early detection and treatment are of active large clinical and practical importance in the treatment of patients with arterial hypertension (2).

General review of LVH

Anatomical studies have shown that the upper limit of normal cardiac mass is 450 grams for men and 400 grams for women. These values must be corrected according to epicardium thickness, body weight and age (3). The number of cardiomyocytes is similar in men and women at birth. Cardiomyocytes do not replicate during the first years of life and heart size increases concurrently with the increase of body size in both genders. From puberty on, the growth rate of the heart is higher in men than in women, implying that men and women have specific cardiac growth curves. This may explain why women develop LVH less frequently than men, despite having a similar number of adult cardiomyocytes (4, 5).

Using body weight and height, we can calculate body surface area. By dividing LVM with body surface area we can determine left ventricular mass index (LVMI). The latest ESH guidelines for hypertension management suggest that LVMI above 115 g/m^2 for men, and 95 g/m^2 for women determine LVH (6).

The increase in ventricular mass is due to the hypertrophy of existing myocytes and the increase of intracellular elements as the number of sarcomeres, the channels, the receptors, the Golgi complex etc. rather than hyperplasia and increase in the number of myocytes. The strain of left chamber is decrease, but at a very high value, because LVH is a pathological process. As consequence of morphological changes, end-diastolic stress of left ventricle is reduced in patients with concentric remodeling or hypertrophy, while mantaing the normal limits in patients with excentric hypertrophy, despite elevated blood pressure and work load (2). When a mechanism of hypertrophy is no longer sufficient to compensate for ventricular wall stress, then occur

heart failure (6). The development of LVH could be divided into three phases of which the first two are adaptive and compensatory. In these phases, left ventricle is not overloaded with filling and wall stress, accompanied by reversible contractile dysfunction. The third phase is a pathological stage and contractile function becomes abnormal. In this phase, the contractile dysfunction is irreversible and the removal of overload does not lead to physiological contractile function of left ventricle (2).

Prevalence of left ventricular hypertrophy

A recent analysis of 30 echocardiography studies in the last decade (1 January 2000-1 December 2010), including 37.000 hypertensive patients, showed that the prevalence of LVH ranged from 36% (conservative criteria) to 41% (less conservative criteria) in the pooled population. LVH prevalence was not statistically different between women and men (range 37.9-46.2 versus 36.0-43.5%, respectively) (7).

The exact prevalence of LVH in the hypertensive population varies widely and part of this variability depends on the applied diagnostic criteria, the method chosen to detect LVH and the ethnicity of hypertensive patients. Among patients with arterial hypertension, the proportion of LVH ranged from 48% (if diagnosed by ultrasound), to 22% (if determined by electrocardiography) and 3% (if determined by X-ray) (8).

The prevalence of LVH in the general population was low in the Framingham study, ranging up to 3% (established by electrocardiography). By echocardiography, the prevalence of LVH was about 5% for young adults (younger than 30 years), but up to 50% for those older than 70 years. In patients with mild hypertension, LVH was confirmed by echocardiography in 15-20%; however, in patients with severe hypertension, the prevalence was exceeding 50% (9). Other study showed that the incidence of LVH in mild hypertension was 15-30% (determined by echocardiography) (10).

Shu-xia et al. (11) in their original manuscript showed that the prevalence of LVH was 42.7% in 4270 hypertensive patients (37.4% in males and 45.4% in females). The prevalence of concentric remodeling, concentric and eccentric hypertrophy was 27.4%, 20.2% and 22.6%, respectively. In this paper female gender, age, body mass index, systolic blood pressure and serum triglyceride were also risk factors of LVH.

Previous studies have shown that hypertension is not an independent factor in the development of LVH and occurrence does not depend on the length and severity of hypertension, but the role played by other comorbidities such as triglycerides, age, gender, genetics, insulin resistance, obesity, physical inactivity, increased salt intake and chronic stress. Forward specify confirm the knowing that there are patients who are suffering many years from of arterial hypertension (AH) and do not have LVH and also patients with severe AH who besides high blood pressure have no other risk factors may not afflicted with LVH.

Pathophysiology of left ventricular hypertrophy

The remodeling process of LVH in arterial hypertension is not only based on a quantitative increase in left ventricular myo-

cardium, but also on changes in myocardial architecture, caused by the disproportionate growth of non-cardiac myocytes (12).

Ventricular myocardium can maintain cardiac output and face a hemodynamic burden for a long period besides the presence of any organic disease. In order to maintain cardiac output and reduce ventricular wall stress, it uses compensatory mechanisms, such as the increased activity of sympathetic nervous system, the Franck-Starling's law, and augment muscle mass. These mechanisms, compensatory adaptations to an increased chronic pressure load, are useful at the beginning but then lead to functional failure (13).

In the case of overload in aortic stenosis and hypertension, cardiac contraction is slower, but blood pumping is adequate due to an increased pressure inside the ventricle. An initial contractile force of the heart is not reduced in LVH, despite increase of stress in left ventricular wall, increase of end-diastolic pressure, and increase of LVM. Pressure-overload does not increase the diameter of the ventricle; but on the other hand, volume-overload increases ventricle's diameter, volume, and ventricular wall thickness. The ratio of wall thickness/chamber dimension remains as before the occurrence of LVH (14, 15).

The development of LVH may have three consequences in relation to intraventricular volume, wall thickness and wall mass (16). First, in the case of compensatory overload by pressure (such as in AH and aortic stenosis), the wall of the ventricle becomes thicker due to increase of myofibrils in parallel relationship. Thus, the end-diastolic volume remains normal or only slightly increased. This leads to an increase in the ratio between ventricular weight and volume, and to the development of concentric ventricular hypertrophy. In this situation, a ventricular response to pressure overload on its wall is appropriate.

Second, in cases of de-compensatory overload by volume, ventricular weight and volume are increased, and wall thickness is unchanged or only slightly increased. This is the result of a replication of myofibrils in series. This implies the development of dilatation rather than of wall thickness, which results in eccentric ventricular hypertrophy. A ventricular response in this situation is inadequate, because heart dilates without corresponding changes in wall thickness.

Third, LVH in hypertrophic obstructive cardiomyopathy is characterized by an excessive increase of wall thickness and muscle mass, with restriction of the intraventricular cavity. This leads to an increase in ventricular weight relative to volume. This type of hypertrophy is called inadequate hypertrophy with low wall stress, because systolic stress, oxygen consumption and the function of left ventricle are reduced.

The function of left ventricle is inversely correlated to systolic wall stress and end-diastolic volume. A ratio between LVM and chamber size can be used to assess the maintenance of wall stress. This ratio is increased in LVH caused by pressure overload, and normal in LVH caused by volume overload. Both forms of hypertrophy are associated with normal pressure on the ventricular wall. However, in patients with decompensate LVH, the cardiac wall stress was increased, and the ratio of

chamber dimension/wall thickness was decreased. This implies a disproportional enlargement of cardiac chambers in relation to wall thickness (17).

The development of LVH leads to some significant changes in morphology of myocytes. Cardiac cells have large volume, diameter, and may be elongated. Their function is isometric in order to adapt to pressure overload. The production of sarcomere is increased, thus increasing the contractile ability of myocytes. Some sub-cellular elements (sarcoleme and sarcoplazmatic reticulum) rearrange themselves inside the myocytes. Hypertrophic cells have irregular shape, with large Golgi complex, large nucleus, multiple nuclei, extended and/or twisted T tubules, or tubules arranged inside the nucleus (18). Hypertrophic cells have greater energy demand. The number of mitochondria is also increased. The balance between mitochondria and contractile elements, called mitochondrial/myofibril volume ratio, is of prime importance. An imbalance of this ratio may lead to disturbance of energy supply of the myocytes (19, 20).

The extracellular matrix proliferates in the hypertrophic myocardium by production of collagen, glycosaminoglycan and elastic fibers. This reactive interstitial fibrosis occupies the interstitial space, surrounds myocytes and interstitial coronary arteries, and makes large impact on ventricular remodeling. An invasion of inflammatory cells may further affect left ventricular remodeling by secretion of growth factors, proteases and cytokines. This leads to increased myocardial stiffness, disturbance of myocardial relaxation, and disturbance of diastolic function (21, 22). Degenerative changes in the myocardium occur in the last stages of heart failure. They include cell atrophy, isolation, and damage of intercellular connections, disturbance of cellular and myofibril organization, and proliferation of sarcoplasmatic reticulum. Normal sarcomere structure is impaired and myofibrils rupture (23, 24). Quantitative studies show that aging also leads to the reduction of the number of myocytes, and to reactive hypertrophy of the remaining ones. In men aged twenty, heart contains an average of 5.8 milliard myocytes in the left ventricle, and 2 milliard myocytes in the right ventricle. However, in men aged seventy, there is an average of 3.6 milliard myocytes in the left ventricle and 1 milliard in the right ventricle. According to this, an average loss of myocytes in both ventricles in fifty years ranges from 38 to 50%. In women, on the contrary, the number of mononuclear and binuclear myocytes in both ventricles is constant between the ages of 20 and 95. Loss of myocardial cells leads to progressive increase in volume of the remaining cells, thus maintaining a constant weight of the heart and even increasing the weight of the heart with age (14). Programmed cell death, in human and animal myocytes, can also explain the impact of aging on the heart (25, 26).

Coronary arteries are an important component that determines function of the hypertrophic myocardium. In hypertensive LVH, coronary component has some specific characteristics, which are rare in other heart diseases. Unlike LVH caused by aortic and mitral defects or congenital abnormalities, hypertensive LVH leads to increased coronary flow and higher oxygen consumption (MVO_2), despite a significant increase in coronary vascular resistance. Coronary vascular reserve (determined by pharmacological methods) is decreased to 72% in compensated patients (27, 28). Oxygen consumption per mass unit is proportional to systolic wall stress. Reduction of coronary reserve correlates to LVH, weight/volume ratio, end-diastolic volume, and peak systolic wall stress.

Functional impairments in coronary regulation may lead to an increase of coronary vascular resistance, because of the involvement of small intramural coronary arteries. There is no evidence of functional vasoconstriction of coronary arteries in AH, because small arteries and arterioles have thick walls, wall sclerosis, perivascular fibrosis, and narrowed lumen. Such histological changes lead to reduced elasticity of coronary blood vessels, and impair sub-endomyocardial auto-regulation. Maximal coronary flow after dipiridamol test was reduced by 30-50%. The implications of these findings refer to the use of antihypertensive therapy that may improve coronary circulation, in addition to regression of LVH (18, 29).

Impaired coronary flow in hypertensive LVH has high prognostic significance for the development of malignant arrhythmias and sudden death (30, 31).

Among 183 asymptomatic hypertensive patients, with no evidence of coronary disease, the incidence of ventricular arrhythmias was much larger in patients with reversible 201-Th scintigraphic defects, compared to patients without such changes (33% vs. 18%, p<0.02). Ventricular tachycardia was also significantly more common in patients with perfusion defects (14% vs. 4%, p<0.02) (31, 32).

All this indicates that hypertrophic myocardium is in a state of constant hypoperfusion, which in turn runs a variety of mechanisms that may further impair its anatomy and function. It contributes to increased risk of coronary heart disease, ventricular arrhythmias, left ventricular dysfunction, and ventricular dilatation. Finally, when the mechanism of hypertrophy is no longer sufficient to compensate for heart stress, heart failure occurs (7).

Hemodynamic and non-hemodynamic mechanisms play important role in patophysiology of LVH. Standard risk factors is determined by age, gender, body size, obesity, high blood pressure, physical inactivity, alcohol intake, smoking, diabetes, dyslipidemia, hypertrigliceridemia, high level of insulin, insulin resistance, salt intake (2). LVH adjusted for body weigh was 16% greater in obese compared to lean adolescents. Obese subjects have higher resting systolic blood pressure, higher fasting trigliceride and insulin levels, HDL-cholesterol levels is lower in the obese compared with the lean patients (31). However, the most important factors for the development of LVH are hemodynamic factors such as chronic pressure load, volume overload, arterial structure, contractility, and blood viscosity and non-hemodynamic presented by stimulation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, and genetic predisposition. Legdz et al. (33) in their study published in 2006 suggest that among typical metabolic

abnormalities of insulin resistance syndrome, plasma triglycerides and insulin resistance as well as degree of insulin resistance may contribute to cardiac hypertrophy and arterial stiffening independently of hemodynamic and humoral factors.

Diagnosis of left ventricular hypertrophy

Advances in imaging technology allow for the precise visualization of anatomy in vivo, including the LVH. The assessment of cardiac hypertrophy can be done with the help of classical techniques such as electrocardiography and echocardiography and new imaging methods such as cardiac magnetic resonance and three-dimensional echocardiography (34).

European Society of Hypertension and European Society of Cardiology proposed guidelines for assessing LV mass using electrocardiography and echocardiography (6). Electrocardiography is the most inexpensive and readily available method for LVH detection. Recommended criteria include Sokolow-Lyon index >3.5 mV, Cornell's voltage criteria >2436 mm-sec, and Romhilt-Estes score 5 or above. Some authors also showed that R wave voltage in aVL >1.1 mV correlates well with left ventricular mass index (35). The selection of appropriate ECG criteria for LVH detection should include the age factor according to a recent study (36, 37).

Using echocardiography, may measure interventricular septum (IVS) thickness, posterior wall thickness of left ventricle, and end-diastolic left ventricular diameter (EDD). These parameters can be used to calculate left ventricular mass index (LVMI). LVMI is calculated by dividing left ventricular mass with body surface area using a Penn convention formula (38). The latest ESH guidelines for hypertension management suggest that LVMI above 115 g/m^2 for men, and 95 g/m^2 for women determine LVH (6). These parameters determine concentric LVH, but are less valid for other types of left ventricular remodeling. An early experience indicates that LV volume measurement is more reliable and accurate with real time 3-D echocardiography. This may well become the standard mode of measuring LV volume and LVEF. Comparison of real time 3-D echocardiography measurement of LV parameters with M-mode and 2-D echocardiography and cardiovascular magnetic resonance (CMR) measurement showed that LV volume was underestimated by 2-D echocardiography but much improved by real time 3-D echocardiography. However, the LVEF obtained with CMR was similar to that obtained with 2-D and real time 3-D echocardiography. With 3-D echocardiography, a real time LV can be created and regional volume changes can be displayed (7).

It is also important to say that accept already mention techniques CMR can play crucial role in diagnosis of LVH. CMR is well validated for quantifying the volumes and mass of the ventricles and has become the clinical gold standard (39). Comparison with other techniques show wide variability in individual patients and are not greatly instructive. The accuracy and reproducibility of the measurements make CMR useful for the longitudinal follow-up of the patients and for the hemodynamic and remodeling researches (40). The accuracy of CMR for mea-

surement of global left ventricular volume is well established initially comparing CMR images of ex-vivo ventricles with the water displacement volume of casts of the ventricles. An important feature of CMR is the excellent inter-study reproducibility of volume and mass measurement. Other forms of reproducibility are often quoted for functional techniques, but they have little statistical import, whereas inter-study reproducibility can be used directly to quantify sample sizes with minimal clinical differences (40).

Electrocardiography is less specific and sensitive for the diagnosis of LVH in comparison to echocardiography. LVH, determined by Sokolow-Lyon index or Cornell voltage criteria, is a significant predictor of cardiovascular events (14). Exact evaluation involves calculating left ventricular mass by measuring intraventricular diameter and left ventricular wall thickness according to the recommendations of the ASA or Penn convention recommendations, and it was shown that such measures would be established with valid measurements obtained post mortem examination (1, 38).

Left ventricular hypertrophy and cardiovascular risk

Epidemiological evidence demonstrates that hypertensive patients with LVH associate with an increased risk of cardiovascular morbidity and mortality compared to patients without LVH; this risk increases proportionally with the degree of hypertrophy (6).

The prognostic role of LVH has been highlighted in the Framingham study. During a follow-up for ten years, patients with left ventricular mass index greater than 125 g/m^2 had significantly higher incidence of cardiovascular events (26% vs. 12%, p=0.006), and fatal cardiovascular events (14% vs. 1%, p<0001), when compared with patients who initially had not LVH (39).

In hypertensive patients, LVH is independent prognosticator of the composite end point of all-cause death and cardiovascular morbidity, a major predictor for stroke (41) as well as a determinant of renal outcome in patients with high cardiovascular risk (41).

A large number of studies demonstrate that the risk for cardiovascular events increase depending on the type of left ventricular hypertrophy (42-45).

Vakili et al. (14) showed that the risk of CV complications was significantly higher in patients with LVH. Patients with LVH have 2-4 times higher rate of multiple cardiovascular complications. They also showed that concentric hypertrophy, which is otherwise typical for AH, carries the greatest cardiovascular risk, while eccentric hypertrophy carries intermediate risk.

The origin of the risk of LVH for the development of CV diseases is a pathophysiological substrate of hypertensive LVH (Fig. 1). Thus, LVH is as a strong independent predictor of CV events including heart failure and all cases of mortality (Fig. 2) (7).

Frohlich et al. (20) have concluded that contrary to the physiological LV hypertrophy, pathological LV hypertrophy is accompanied by a poor prognosis.
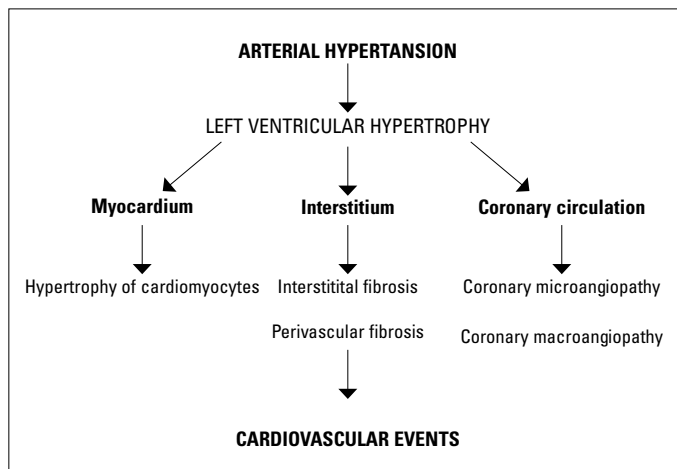
Figure 1. The pathophysiological pathway from arterial hypertension to left ventricular hypertrophy and cardiovascular events

Figure 2. Left ventricular hypertrophy and cardiovascular events
LVH - left ventricular hypertrophy

One of the main fields of research at the present is related to the effects of therapy on the possible regression of LVH. Several meta-analyses and the LIFE study reported a successful regression of LVH after treatment, particularly in patients under low CV risk. However, more research is needed on a prognostic significance of LV hypertrophy in patients with high CV risk (patients with diabetes, stroke or heart attack).

Focusing on hypertension, a recent study demonstrated that LVH, as LVMI, other than a surrogate marker of adverse CV outcome, was qualified as predictor of new-onset marker of target organ damage and particularly of new-onset microalbuminuria in hypertensive patients (45).

Geometric adaptation of left ventricle seems to have greater prognostic value independently of left ventricular mass. The development of concentric left ventricular hypertrophy has a greater risk for the development of CV events, independent of changes in left ventricular mass (46).
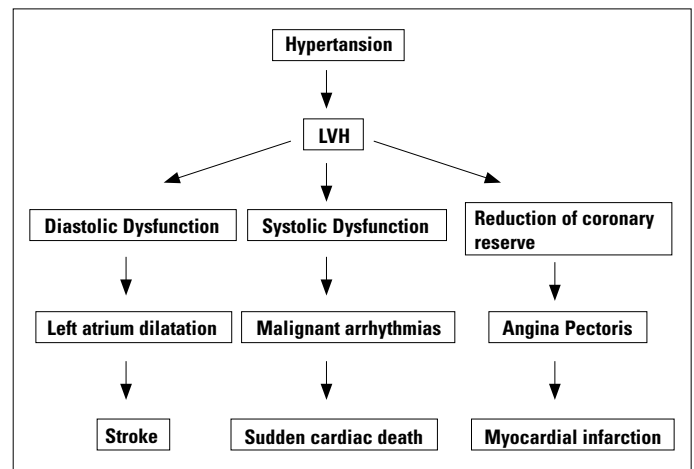
LIFE study has shown much greater prognostic relevance of changes in left ventricular geometry in addition to changes in left ventricular mass (1, 47).

Regression of LVH is associated with a reduction of risk of adverse CV events (1, 48). It leads to improvement of systolic and diastolic function, increase of coronary reserve, and reduction of cardiac arrhythmias.

Future studies should show whether the treatment of AH leads to clinical evidence of regression of LV mass, favorable changes in left ventricular geometry, and to structural improvement in the structure of myocardium (cardiomyocytes, interstitium, coronary arteries).

Pharmacologic strategies for prevention and regression of LVH

A large number of studies show that blood pressure-lowering therapy, using all classes of anti-hypertensive drugs, reduces left ventricular mass in patients with hypertension in comparison with placebo treatment. The latest ESH guidelines for hypertension management suggest the use of antagonists of rennin-angiotensin-aldosterone system and calcium antagonists to inhibit and reverse LVH (7). These anti-hypertensive agents are the most often recommended to prevent organ damage in hypertensive subjects. While, among different antihypertensive drugs the efficacy on LVH regression varies, renal sympathetic denervation, a new approach for patients with resistant hypertension, reduces LVH and improves cardiac function in patients with resistant hypertension (49).

Conclusion

Left ventricular hypertrophy is an independent predictor of serious CV events and sudden cardiac death.

Despite recent announcements of successful clinical regression of LVH in patients with arterial hypertension after treatment, there is still no evidence of structural improvement in myocardium. Prevention of LVH is at the same time the best form of prevention of adverse CV events. An early detection of patients with risk factors for the development of LVH, as well as their timely treatment would be the right choice for their protection from the occurrence of this serious condition.

Conflict of interest: None declared.

Peer-review: Partially external peer-reviewed.

Authorship contributions: Concept - S.E., D.L., A.B.Ç.; Design - S.E., D.L., A.B.Ç.; Supervision - S.E., D.L., A.B.Ç.; Resource - S.E., D.L., A.B.Ç.; Materials - S.E., D.L., A.B.Ç.; Data collection&/or processing - S.E., D.L., A.B.Ç.; Analysis &/or interpretation - S.E., D.L., A.B.Ç.; Literature search - S.E., D.L., A.B.Ç.; Writing - S.E., D.L., A.B.Ç.; Critical review - S.E., D.L., A.B.Ç.; Other - S.E., D.L., A.B.Ç.

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