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Review Article

Hypertension and Left Ventricular Hypertrophy

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Abstract

The left ventricular hypertrophy (LVH) in systemic hypertension (HTN) indicates target organ damage and is an independent risk factor for cardiovascular (CV) events. Among various modalities available for LVH assessment, cardiac magnetic resonance imaging has the highest sensitivity and specificity. M-mode echocardiography is the most widely method for LVH assessment currently due to its ease, availability, and reasonably good sensitivity and specificity. LVH is a risk factor for heart failure, stroke, coronary artery disease, and arrhythmias. Variable degree of LVH regression occurs with different antihypertensive medications. LVH regression with treatment has shown a reduction in the risk of CV events.

Key words: Cardiovascular, hypertension, left ventricular hypertrophy

Introduction

The left ventricular hypertrophy (LVH) is an adaptive response by the heart to chronic pressure overload. It indicates hypertension (HTN)-related target organ damage and also shown to be a predictor of heart failure (HF), coronary artery disease, and stroke.[1,2] The development of LVH varies with severity of HTN ranging from <20% in mild HTN to nearly 100% in severe, complicated HTN.[3] The risk of cardiovascular (CV) events increases with increase in the left ventricular (LV) mass.[4] LVH is a potentially reversible risk factor and the regression of LVH with antihypertensive treatment has shown to improve the CV risk, long-term prognosis.

Pathogenesis

Increase in LV mass is a compensatory response to pressure overload. The terminal differentiation of cardiomyocytes occurs soon after birth and hence the increase in mass is secondary to the hypertrophy of existing myocytes rather than hyperplasia.[5] In response to pressure overload, parallel addition of sarcomeres occurs that causes an increase in myocyte width, which leads to increase wall thickness. As a consequence of this remodeling, there is concentric hypertrophy (increase in cardiac mass at the expense of chamber volume). In contrast, predominant volume overload results in eccentric hypertrophy (increase in cardiac mass and chamber volume).[6] Myocyte growth to support an increased mechanical load is associated with increase in the surrounding architecture of connective tissue, ground substance, capillary, and nerve networks. The composition of connective tissue predominantly consists of collagen along with smaller amounts of laminin, elastin, and fibronectin. The complex collagen weave is predominantly responsible for the ventricle's diastolic stiffness.[5]

The inconsistent correlation between blood pressure (BP) and LV mass suggests that the development of LVH is mediated by the mechanical stress of pressure overload alone. Various neurohormonal factors have been implicated in the development of LVH by exerting trophic effect on myocytes and non-myocytes in the heart. Angiotensin II, aldosterone, and norepinephrine have shown to directly increase myocyte hypertrophy and matrix deposition independent of their effects on blood pressure.[7-9] Evidence suggesting a role of renin–angiotensin–aldosterone (RAA) system is also a reduction in LV mass and myocardial fibrosis that occurs by the treatment of BP with drugs that modify the actions of the RAA system.[9,10] Demographic factors such as age, sex, race, and body size also influence the development of LV hypertrophy.[11] Gene polymorphisms of

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various components of the RAA system have also shown to predict the response of LV mass to HTN treatment.[12] Thus, the development of LVH occurs by a combination of hemodynamic and non-hemodynamic factors with genetic and non-genetic influences [Figure 1].

Diagnosis and Measurement

The identification of LVH in hypertensive patients is important for clinical practice and research as it influences treatment and is also a risk factor for CV events. The diagnostic methods currently available are electrocardiogram (ECG), echocardiography, and cardiac magnetic resonance imaging (MRI).[13] The advantages and disadvantages of each are outlined in Table 1.

At present, in clinical practice, ECG is usually the first test performed to evaluate for LVH. Various validated criteria include Romhilt-Estes score, Sokolow–Lyon, Cornell voltage, Cornell voltage QRS duration product criteria, and the Gubner index.[14] ECG criteria have shown to have high specificities and low sensitivity. In the validation studies of LVH ECG criteria, the sensitivity has been reported to range from 6 to 52% and the median specificity ranges from 89 to 99%.[14,15] In view of low sensitivity, a normal ECG will not exclude LVH.

Transthoracic echocardiography is the most common diagnostic tool used for LVH assessment. The important parameters for the assessment of LVH severity by echocardiography are wall thickness, LV mass, and LV geometry. In clinical studies, LVH is often described in terms of LV mass which has shown to be a predictor of CV events. LV mass is indexed to body surface area to enable comparison of various body statures. At present, M-mode echocardiography is the standard clinical diagnostic method used which detects all but the mildest degrees of LVH. Two-dimensional (2-D) echocardiography has the advantage of being more accurate and reproducible than the M-mode method[16] as it takes into account the length of the LV as well as the myocardial wall thickness. However, its use is limited by the lower frame rate and resolution. 2-D echocardiography is less widely used to estimate the LV mass than M-mode echocardiography, in view of the difficulty in obtaining images of suitable quality and is also more time consuming. The upper limits of normal ranges of LV mass as per American Society of Echocardiography chamber quantification update are >95 g/m^2 in women and >115 g/m^2 in men.[17] Three-dimensional (3-D) echocardiography offers the advantage of obviating inaccurate geometric assumptions, inherent to 2-D echocardiography, which is more prominent in remodeled ventricles. The accuracy of 3-D echo is reportedly similar to cardiac MRI for measuring LV mass.[18] However, the limitations of 3-D echo involve difficulties in accurately tracing the LV epicardial border in poor acoustic windows and dilated ventricles resulting in under estimation of LV mass compared to cardiac MRI, but is more accurate than the alternate echocardiographic methods.[19]

LV mass evaluation by cardiac MRI has the advantage of a 3-D high-resolution modeling of the LV, which is free of geometric assumptions, contrast use, dependency on acoustic window, or ionizing radiation. LV mass determined by cardiac MRI is more accurate and precise than M-mode, 2-D echocardiography. It has also shown to have better interstudy reproducibility for normal, dilated, and hypertrophic cardiac chambers.[20] The two methods cannot be used interchangeably for the assessment of LV mass in view of inherent differences in the estimation. However, echocardiography being less expensive, has better versatility, acceptability, and availability compared with MRI making it the most widely used tool in clinical practice for the assessment of LV mass. The use of cardiac MRI at present is limited to areas of research.

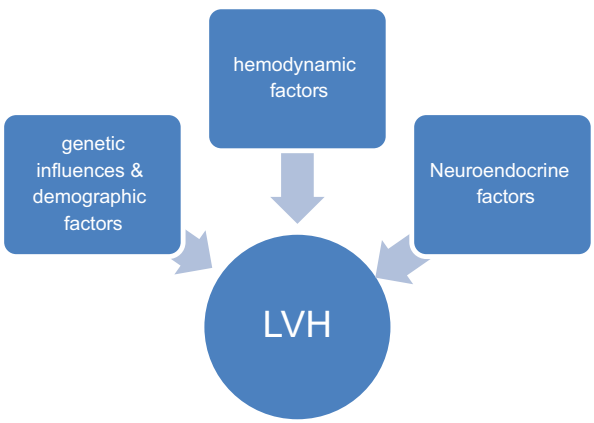

Figure 1: Multifactorial pathogenesis of the left ventricular hypertrophy in hypertension

Table 1: Advantages and disadvantages of various methods for the assessment of LVH

Parameter	ECG	M-mode	2-D echo	3-D echo	Cardiac MRI
Sensitivity	Low	Moderate	High	High	High
Specificity	High	High	High	High	High
Complexity	Low	Low	Moderate	Moderate	Moderate
Cost	Low	Moderate	Moderate	Moderate-High	High

ECG: Electrocardiogram, LVH: Left ventricular hypertrophy, 2-D: Two dimensional, 3-D: Three dimensional, MRI: Magnetic resonance imaging

LVH and Clinical Outcomes

LVH represents HTN-related target organ damage and is an intermediate unfavorable prognostic marker.[3] LVH (diagnosed by ECG or echo) has shown to be an independent risk factor for CV events in patients with HTN [Table 2].[2,21-25] The reason for this association may include a combination of anatomical changes, electrophysiological alterations, and increased activity of RAAS and sympathetic system.[26] The relationship between increasing LV mass and CV morbidity and mortality is linear.[4]

The first discernible manifestation of heart disease in most hypertensive patients is LV diastolic dysfunction.[6] When pressure overload remains sustained, filling of the hypertrophied remodeled LV decreases, diastolic dysfunction progresses,

Table 2: Studies in hypertensives showing the association between LVH and CV outcomes

Study	Study design/inclusion criteria	Key outcomes
Haider *et al.*[22] (1998)	Observational (*n*=3661) >40 years old subjects from Framingham Heart study with LVH followed up for 14 years	LVH independently associated with sudden cardiac death. (HR 1.45 for each 50 g/m^2 increase in LV mass)
Verdecchia *et al.*[23] (PIUMA, 2001)	Cohort (*n*=2363) HTN, mean age 51±12 years	Each 1 SD increase in LV mass (29 g/m^2) associated with an independent 31% increase in the risk for a cerebrovascular events
Verdecchia *et al.*[2] (MAVI, 2001)	Multicenter, prospective (*n*=1033) HTN, age ≥50 years	Each 1 SD increase in LV mass (39 g/m^2) associated with an independent 40% rise in the risk of major CV events
Vakili *et al.*[24] (2001)	Meta-analysis of 20 studies (*n*=48,545)	LVH associated with increased CV morbidity and all-cause mortality across all groups except ESRD
De Simone *et al.*[25] (Cohort derived from Strong Heart Study, 2005)	Cohort (*n*=1026) Inclusions: HTN, No CVD, 47–80 years	Increased LV mass was associated with higher fatal and non-fatal CV events (HR 1.68, *P*<0.05)

HTN: Hypertension, LV: Left ventricular, HR: Heart rate

and HF with preserved ejection fraction (HFpEF) ensues. The end stage of hypertensive heart disease consists of dilated cardiomyopathy with combined diastolic dysfunction and diminished ejection fraction. Hypertensive heart disease can be divided into four stages from a clinical standpoint.[6]

I: LV Diastolic dysfunction without LVH

II: LV Diastolic dysfunction with concentric LVH

III: HFpEF (clinical HF with dyspnea, pulmonary edema)

IV: Dilated cardiomyopathy with reduced EF and HF

The combination of LVH with elevated cardiac biomarkers such as high sensitivity cardiac troponin T, and N-terminal pro-B-type natriuretic peptide (N-T pro-BNP) represents patients with highest risk of developing symptomatic HF, particularly HFrEF.[6] Increased myocardial mass and interstitial fibrosis are associated with a reduced coronary flow reserve leading to an increased risk for myocardial ischemia. The presence of LVH has also shown to be an independent risk factor for the development of coronary events and stroke.[23,24]

LVH has been associated with the development of atrial fibrillation, supraventricular tachycardia (SVT), and ventricular arrhythmias (tachycardia and fibrillation). The exact mechanism of arrhythmogenicity in LVH is not fully understood. The non-uniform propagation of the action potential throughout the myocardium, slowing, and fractionation of ventricular conduction creates a milieu for arrhythmogenesis. Additional factors such as myocardial ischemia, scars, neuroendocrine factors, LV wall stress, and electrolyte imbalances may enhance the pro-arrhythmic risk of LVH.[26,27] In a large meta-analysis of LVH and arrhythmias, patients with LVH had 3.4-fold greater odds of developing SVT and 2.8-fold greater odds of developing ventricular tachycardia and fibrillation.[28] Regression of LVH with antihypertensive treatment has shown to improve CV outcomes.

Antihypertensive Treatment and LVH Regression

BP reduction has shown to reverse LVH. HTN-related LVH is more closely associated with 24 h BP readings than office recordings.[29] Although majority of antihypertensive drugs cause attenuation of LVH, the extent of LVH regression is different with each class. In a large meta-analysis of 80 randomized double-blind antihypertensive trials, the extent of LV mass reduction with various class of antihypertensives was analyzed.[30] The reduction in LV mass index was 13% with angiotensin receptor blockers (ARB), 11% with calcium channel blockers (CCB), 10% with angiotensin-converting enzyme inhibitors (ACEI), 8% with diuretics, and 6% with β-blockers. The reduction in LV mass was significantly more with ARBs, CCBs, and ACEIs compared to β-blockers. Similar findings were noted in a more recent meta-analysis evaluating the aforementioned drugs.[31]

Many studies have shown that LVH regression is associated with better CV outcomes and long-term prognosis [Table 3].[32-35] The Losartan intervention for endpoint reduction study showed that LVH regression (ECG determined) with antihypertension treatment improved prognosis, independent of BP.[28] A meta-analysis of studies reporting LV mass measured by echocardiography before and during HTN treatment, demonstrated that regression of LVH was associated with a significant (59%) reduction in CV events risk when compared to persistence or new development of LVH.[30]

In the real-world setting, there might be many problems in achieving LVH regression in spite of optimal BP control as shown in the subpopulation of Strong Heart Study.[37] Various factors associated with failure of LVH regression include older age, female sex, obesity, higher baseline LV mass index, established vascular disease, and cluster of metabolic abnormalities resembling phenotypic metabolic syndrome.[38-40] Non-pharmacological measures such as weight loss and dietary salt restriction have been linked to the reduction of LV mass independent of BP control.[38,39] However, a clear association is yet to be established. Early initiation of antihypertensive treatment, control of metabolic factors is important in addition to optimal BP control to prevent irreversible LVH.

Table 3: Studies showing improvement in CV outcomes with LVH regression

Study	Study design/inclusion criteria	Key outcomes
Levy *et al.*[32] (1994)	Observational (*n*=524) Subjects from Framingham Heart Study with LVH by ECG were followed.	Improvement in ECG features of LVH resulted in decrease CV risk
Verdecchia *et al.*[33] (2003)	Meta-analysis (*n*=1064) LVM determined by echo, before and during antihypertensive therapy	Regression of LVH was associated with a significant (59%) reduction in CV events risk when compared to persistence or new development of LVH.
Okin *et al.*[34] (LIFE, 2004)	Cohort (*n*=9193) HTN, ECG LVH, 55–80 years	After at least 4 years of follow-up, LVH regression documented by Cornell product associated with decreased MI, CV death, and all-cause mortality
Devereux *et al.*[35] (LIFE echocardiography substudy, 2004)	Cohort (*n*=941) HTN, ECG LVH, 55–80 years	At 1 year follow-up, each 1 SD decrease in LV mass associated with lower CV death, MI, and all-cause mortality independent of baseline LV mass and BP reduction
Verdecchia *et al.*[36] (PIUMIA, 2006)	Cohort (*n*=880) HT, mean age 48 years	Risk of cerebrovascular events was 2.8 times higher in those with lack of LVH regression or new development of LVH

LIFE: Losartan intervention for endpoint, HTN: Hypertension, ECG: Electrocardiogram, LVH: Left ventricular hypertrophy

Conclusions

Assessment of LVH is an important aspect in the management of HTN. It indicates target organ damage, facilitates monitoring of BP control, and also is an independent marker of CV risk. For LVH assessment, ECG, though specific, lacks sensitivity and currently M-mode and 2-D echo are the most widely used tools for LVH assessment with 3-D echo and MRI limited to research purposes. Optimal choice of antihypertensive drugs is essential for achieving LVH regression and also reduces CV events.

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