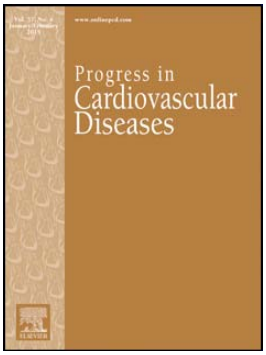

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Current Perspectives on Left Ventricular Geometry in Systemic Hypertension

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Abbreviations:

HTN: Hypertension or hypertensive

CVD: Cardiovascular disease

BP: Blood pressure

LV: Left ventricular or left ventricle

DM: Diabetes mellitus

LVM: Left ventricular mass

RWT: Relative wall thickness

CR: Concentric remodeling

LVH: Left ventricular hypertrophy

HHD: Hypertensive heart disease

2D: Two-dimensional

3D: Three-dimensional

CMR: Cardiac magnetic resonance

MI: Myocardial infarction

CKD: Chronic kidney disease

MetS: Metabolic syndrome

OSA: Obstructive sleep apnea

CHD: Coronary heart disease

RAAS: Renin-angiotensin-aldosterone-system

HF: Heart failure

SCD: Sudden cardiac death

FHS: Framingham Heart Study

LVEF: Left ventricular ejection fraction

RCT: Randomized controlled trial

LIFE: Losartan Intervention for Endpoint Reduction (study)

AF: Atrial fibrillation

BB: Beta blocker

CCB: Calcium channel blocker

ACEI: Angiotensin converting enzyme inhibitor

ARB: Angiotensin receptor blocker

Abstract

Hypertension (HTN) is a global health problem and a leading risk factor for cardiovascular disease (CVD) morbidity and mortality. The hemodynamic overload from HTN causes left ventricular (LV) remodeling, which usually manifests as distinct alterations in LV geometry, such as concentric remodeling or concentric and eccentric LV hypertrophy (LVH). In addition to being a common target organ response to HTN, LV geometric abnormalities are well-known independent risk factors for CVD. Because of their prognostic implications and quantifiable nature, changes in LV geometric parameters have commonly been included as an outcome in anti-HTN drug trials. The purpose of this paper is to review the relationship between HTN and LV geometric changes with a focus on (1) diagnostic approach, (2) epidemiology, (3) pathophysiology, (4) prognostic effect and (5) LV response to anti-HTN therapy and its impact on CVD risk reduction.

Hypertension (HTN) is one of the most common modifiable risk factors for cardiovascular disease (CVD), estimated to affect 32.6% of the adults in the US. Despite advances in medical treatment options for HTN, uncontrolled blood pressure (BP) remains as a public health problem.[1] The left ventricle (LV) is one of the main target organs of HTN and hemodynamic overload imposed by high BP can lead to remodeling and structural changes in the LV. In addition to hemodynamic parameters, several non-hemodynamic factors, such as gender, ethnicity, obesity, diabetes mellitus (DM), salt intake, and genetic and neurohumoral factors play important roles in LV remodeling. The complex interaction between these numerous variables leads to distinct LV structural alterations observed with HTN. LV mass (LVM) and relative wall thickness (RWT) are the main determinants of LV geometry. Based on these parameters, four distinct LV geometric patterns have been identified; normal LV geometry (normal LVM and RWT), concentric remodeling (CR; normal LVM with increased RWT), concentric LV hypertrophy (LVH; increased LVM and RWT) and eccentric LVH (increased LVM with normal RWT) **(Figure 1)**.[2, 3] Traditionally, LVH has been considered a beneficial adaptive response since increase in LVM and wall thickness may normalize LV wall stress. However, epidemiological studies have confirmed that, in the long term, LV geometric changes can be detrimental and increase the risk for CVD morbidity and mortality.[4] Prevention or regression of LV geometric changes with BP control is an effective way of decreasing future adverse CVD outcomes in patients with HTN.

Here we review the current concepts on the relationship between systemic HTN and LV geometric changes, including the epidemiology, pathophysiology, prognostic implications and imaging of LV geometric changes. We also discuss the impact of management of HTN on LV geometry and prognostic impact of LVH regression.

Assessment of LV Geometry

LV morphological changes, left atrial enlargement and diastolic dysfunction are the most commonly observed findings of hypertensive heart disease (HHD). Transthoracic echocardiography is a valuable and practical modality to assess changes in LV function and structure in patients with HTN. The

European Society of Cardiology / European Society of Hypertension guidelines on management of HTN recommend (class IIa) use of echocardiography for CVD risk assessment in asymptomatic patients with HTN if there is suspicion for concomitant CVD.[5] Appropriate use criteria also lists transthoracic echocardiography as 'appropriate' when evaluating patients with suspected HHD. However, it is not recommended for routine evaluation of HTN patients without signs or symptoms of HHD.[6]

Several formulas exist for calculation of LVM by M-mode and two-dimensional (2D) echocardiography. These formulas rely on the same concept that LV myocardial volume is calculated initially by subtracting the LV cavity volume from the volume enclosed within the LV epicardium. Then, this volume is multiplied by the specific gravity of myocardium (1.05 g/mL) to obtain LVM. However, LVM calculation by M-mode and 2D echocardiography has some limitations. For example, major distortions in LV geometry (e.g. apical aneurysm, septal hypertrophy, etc.) may lead to inaccurate calculations and any errors in the primary measurements may be magnified because of the cubing in the formula.[7] Three-dimensional (3D) echocardiography mostly eliminates these limitations of the linear method, since it directly measures LV volume. This particularly makes 3D echocardiography useful for evaluation of LV with irregular shape.[8] However, the feasibility, practical use and prognostic value of 3D echocardiography have not been well-validated. Moreover, normal reference values of LVM determined by 3D echocardiography have not been established.[9] Therefore, 3D echocardiography is still not routinely used for determining LVM.

Normal values for LVM varies depending on gender, ethnicity, age, height and weight. In order to allow for comparison between individuals with different body sizes, LV volume indexing (most commonly by body surface area) is preferred. Men usually have higher LVM compared to women independent of body size (normal: men $\leq$115 g/m^2 and women $\leq$95 g/m^2).[9]

Determination of RWT by echocardiography is essential for appropriate categorization of LV geometric patterns. RWT is calculated with the following formula: (2 x posterior wall thickness) / (LV internal diameter end-diastole). RWT of 0.42 is considered as the upper limit of normal and used to

distinguish concentric LVH from eccentric LVH and CR from normal LV geometry (**Figure 1**).[9] Use of posterior wall thickness as a determinant of RWT helps avoid the confounding effects of septal bulge and technical difficulties in defining the boundaries of 'true' LV septum. However, it should also be noted that RWT does not take into account the thickness of other walls and therefore does not accurately reflect the pattern of LV geometry in the presence of asymmetric LVH.[7]

Large cohort studies have shown that LV geometric abnormalities detected by echocardiography may show improvement as a response to treatment of HTN. However, echocardiographic measurements have limited reproducibility on an individual patient basis. Therefore, routine follow-up echocardiography to examine treatment response in subjects with HTN is not recommended unless there are changes in symptoms.[7] Because of insufficient data to support its benefit, periodic echocardiographic evaluation in patients with known HHD (without a change in clinical status or cardiac examination) received a score of 4 (maybe appropriate) from the Appropriate Use Task Force.[6]

Cardiac magnetic resonance (CMR) is considered more accurate for estimation of LVM compared to echocardiography. However, it is less commonly used for assessment of LV geometric changes because it has higher cost and is less feasible and available compared to echocardiography. Thus, LV geometry assessment by CMR is reserved for research purposes and clinical conditions requiring higher reproducibility and accuracy.[10] Although a strong correlation has been shown between LVM values obtained by echocardiography and CMR, LVM estimated by these two modalities cannot be used interchangeably. Beyond LVM and LV geometry, CMR is valuable in evaluating structural changes at tissue level. For example, CMR with late gadolinium enhancement can detect and quantify myocardial fibrosis.[2, 11] CMR has also been shown to quantify cardiomyocyte hypertrophy.[12] Prognostic implications of myocardial fibrosis and cardiomyocyte hypertrophy still remain unknown.

Epidemiology of LV Geometric Changes in Relation to HTN

LV geometric abnormalities are commonly seen in the general population. Our studies on a large clinical population who were referred for echocardiography (n=35602 patients) demonstrated that

abnormal LV geometry is very common (46%) in adult patients with preserved LV ejection fraction (LVEF). CR was identified in 35% of the patients and the frequencies of concentric and eccentric LVH were 6% and 5%, respectively.[13] We also found that the frequency of abnormal LV geometry is even higher (59%) in the elderly population (>70 years) with preserved LVEF and the distribution of abnormalities was as follows: CR 43%, concentric LVH 8.5%, eccentric LVH 7.4%.[14] It should be noted that LVM and RWT cut-off values used to define LV geometric patterns in our studies were slightly different from those recommended by the current guidelines.

Epidemiological studies have shown significant variability of the frequency of LV geometric abnormalities in patients with HTN. This variability is mainly driven by the population studied and use of different imaging modalities or LV geometric pattern definitions. LV remodeling appears to be influenced by gender. For instance, analysis from the Framingham Heart Study (FHS) revealed that, in the setting of isolated systolic HTN, men are more likely to develop eccentric LVH and women concentric LVH.[15]

Prevalence of LVH correlates significantly with severity, duration and treatment status of HTN. A meta-analysis of studies including individuals with HTN (n=37700) reported the prevalence of LVH as 10%-19% in the general population. However, LVH frequency was reported to be much higher (58-77%) in high risk HTN patients group which consisted of those with severe HTN, previous CVD events and ECG evidence of LVH.[16] Contrary to the general belief, this study demonstrated significantly higher prevalence of eccentric LVH (20.3%-23%) than concentric LVH (14.8%-15.8%) in patients with HTN.

Ethnicity shows significant impact on LVM. In fact, a population based study utilizing CMR demonstrated that compared to whites, blacks have 2- to 3-fold increased risk for development of LVH. And the ethnic disparity in LVM was shown to decrease but persist even after adjustment for traditional risk factors for LVH.[17]

Frequency and pattern of LV geometric abnormalities are also influenced by several other risk factors, including but not limited to DM,[18,19] prior myocardial infarction (MI), hypercholesterolemia,[20]

aortic stenosis and regurgitant valve disease **(Table 1)**.[21] Obesity is a well-known risk factor for HTN and an independent strong predictor for abnormal LV geometry. We have previously demonstrated that obese individuals are more likely to have abnormal LV geometry (CR being the most predominant pattern) when compared to leaner individuals.[22] In some other epidemiologic studies, obesity was shown to increase the risk of eccentric LVH more so than concentric LVH.[23] Conversely, DM has been shown to be associated with concentric rather than eccentric LVH.[24] Chronic kidney disease (CKD) and metabolic syndrome (MetS) are also other well-known predictors of development of LVH. A prospective epidemiologic study on HTN subjects with a mean follow-up period of 4.8 years showed that CKD and MetS are both independently associated with 1.5-fold increased risk of LVH. The presence of CKD and MetS show additive effect and presence of both conditions in the same patient was found to increase LVH development risk by 2.5 folds.[25] LVH is a very common finding in patients with obstructive sleep apnea (OSA). It appears that this relationship mainly derives from shared CVD risk factors or adverse outcomes such as HTN and DM. However, some epidemiological studies have shown an independent association between OSA and LVH, even after adjustment for BP.[26, 27]

There exists a complex relationship between exercise and LV geometry. Typically, endurance exercise with isotonic physiology is characterized by eccentric LV remodeling, whereas isometric exercise usually results in concentric LV remodeling.[28] Also exercise is well known to have beneficial effects on HTN. Several epidemiological studies have shown significant reductions in both systolic and diastolic BP with exercise and this effect usually persists for 24-hours post-exercise.[29] Interestingly, exercise has been shown to have favorable effects on the cardiac structure and function in HTN patients. In a prospective study including young adults (n=454) with stage 1 HTN, during a median follow-up of 8.3 years, sedentary lifestyle was found to increase risk of new onset LVH while routine physical activity prevented development of LVH, even after adjustment for other confounders.[30] A similar favorable effect of physical activity on LV mass was also demonstrated in older adults (age 55-80 years) with HTN.[31]

Excess dietary sodium intake is associated with elevated BP. However significant variation exists in BP response to sodium intake. Based on salt-intake response, BP can be categorized into two groups: salt-resistant and salt-sensitive. The link between dietary sodium intake and elevated BP forms a basis for the relationship between sodium intake and LVH. But independent of elevated BP, high dietary sodium intake may lead to increased LVM or LV wall thickness.[32] Consistently, dietary sodium restriction has been shown to result in regression of LVH. A randomized controlled study of 76 adults with mild-moderate HTN showed significant regression of LVH in the dietary sodium restriction arm after treatment of 12 months. The regression in LVH was attributed mainly to decrease in BP levels.[33]

LV Remodeling in HTN

According to the conventional concept, hemodynamic overload leads to two basic patterns of LVH: concentric and eccentric. Chronic pressure overload (i.e. HTN), at earlier stages, causes diastolic dysfunction and increased left sided filling pressures. Persistent elevation in filling pressures usually results in CR characterized by increased wall thickness and later, concentric LVH characterized by increased LVM and LV wall thickness.[7] In the short term, an increase in LVM and wall thickness may provide benefit by decreasing LV wall stress and preventing potential hemodynamic compromise. However, if pressure overload is left untreated, this adaptive remodeling may deteriorate and lead to chamber dilatation and systolic dysfunction. On the other hand, eccentric LVH, which is characterized by increased chamber radius and LVM with normal or minimally increased wall thickness, has been considered as an adaptive response to increased preload states (obesity, valvular regurgitation, chronic volume overload, etc.) rather than pressure overload.[21]

However, these assumptions have been challenged by the following new lines of evidence.[2] 1) It was recently shown that systolic BP (SBP) has a continuous relationship with adverse LV remodeling even in healthy normotensive adults.[34] 2) LV geometric changes that are considered compensatory may be related to abnormalities in myocardial mechanics even at the early stages of remodeling, which contradicts the assumption that these changes are adaptive.[35] The Multiethnic Study of Atherosclerosis

revealed high prevalence of myocardial strain abnormalities (evaluated by myocardial tagged magnetic resonance imaging) in asymptomatic patients with CR[36] and LVH.[37] 3) Contrary to common belief, data from some epidemiologic studies have suggested that eccentric LVH is actually more common than concentric LVH in patients with HTN.[16] 4) Also the transition from concentric LVH to depressed LVEF and chamber dilatation have not been demonstrated across epidemiologic studies, especially in the absence of coronary heart disease (CHD).

LV remodeling due to HTN is more closely related to persistence of increased afterload represented by 24-hour BP averages rather than office BP measurements. Indeed, a meta-analysis of fourteen studies demonstrated that home and ambulatory BP values more strongly correlate with LVH than office BP.[38] Also, a recent prospective study in patients with uncomplicated HTN demonstrated that changes in mean BP level is a stronger predictor of changes in LVM index than BP variability.[39] Furthermore, LVM shows more significant correlation with central aortic BP than peripherally measured BP. A recent meta-analysis of cross-sectional studies showed that LVM index is more closely associated with central SBP than brachial SBP.[40]

Recent studies utilizing high-resolution 3D CMR demonstrated that BP has distinct remodeling effects on different regions of the LV.[34] For instance, increased BP was found to be associated with concentric remodeling in the septum and eccentric remodeling in the lateral wall. It should be noted that such regional variations in LV remodeling challenge the current classification of LV geometric patterns. LV geometric changes have been shown to affect LV cavity shape as well. For instance, eccentric LVH is usually associated with a spherical LV cavity and concentric remodeling with an elliptical LV cavity.[2]

The majority of studies evaluating the relationship between HTN and LVH have focused on the concept of HTN as a risk factor for LVH. However, it should be kept in mind that HTN and LVH share several risk factors, such as DM, obesity, CKD, etc. Therefore, the coexistence of HTN and LVH in the same individual can also be explained by pathophysiologic mechanisms that play roles in the development of both conditions independently. For example, inappropriate activation of renin-

angiotensin-aldosterone system (RAAS) -a well-known cause of HTN- is also implicated in myocardial fibrosis and LVH independent of BP.[41]

Histopathological Background of LVH

In basic terms, concentric LVH is explained by an increase in cross-sectional area of individual myocytes by addition of new sarcomere units in parallel. In contrast, eccentric LVH is characterized by an increase in myocyte length by addition of new sarcomere units in series.[7] However, recent studies have demonstrated that LV remodeling in the setting of HTN is caused by more complex structural and functional changes at intra- and extra-cellular levels. For instance, at the cellular level, myocyte hypertrophy is associated with abnormalities in contractile cycle, energy metabolism and autocrine functions.[2] In rats with thoracic aortic banding (which causes a sustained increase in LV afterload), significant remodeling was detected in myocyte t-tubules and this remodeling was associated with the severity of LVH.[42] Similarly Shah et al. showed several alterations in myocyte cytoskeleton and calcium metabolism in spontaneously HTN rat models.[43]

HHD is also characterized by myocardial fibrosis and changes in the extracellular matrix. For example, HTN has been associated with fibroblast proliferation, increase in synthesis of myocardial type I collagen and decrease in myocardial collagen turnover.[44,45] Additionally, HTN causes remodeling of the 3D framework of myocardial collagen and thickening or fusion of the perimysial and endocardial collagen network.[45] These changes eventually lead to myocardial fibrosis. In a recent observational study, CMR was utilized for comprehensive characterization of myocardium and aortic function in patients with HTN.[46] The study revealed significant variability in interstitial fibrosis across LV geometric patterns. For instance, patients with eccentric LVH were found to have the highest level of intracellular and interstitial myocardial expansion. The study also identified significant impairment in systolic and diastolic strain in patients with both concentric and eccentric LVH.

Inflammation plays an important role in the development of cardiac remodeling. For instance, in mice models with transverse aortic constriction, toll-like receptor 2-mediated non-infectious inflammation was shown to be essential for cardiac remodeling due to pressure overload.[47]

Recent studies in animal models have shed some light on the pathophysiology of further increased risk of LV remodeling in the coexistence of HTN and DM. It was recently found that mice models with type-2 DM are more prone to hypertrophic remodeling of LV when compared to the models without DM.[48]

Prognostic Effect of LV Geometric Changes

LV geometric abnormalities, particularly LVH, have traditionally been considered as both a target organ response to chronic HTN or other CVD disorders and an independent risk factor for CVD, such as CHD, heart failure (HF), stroke, sudden cardiac death (SCD) and CVD mortality.[21] American College of Cardiology/American Heart Association guidelines of HF management consider HTN as stage A HF and structural CVD, including LVH as stage B HF.[49] This classification represents the progressive nature of development of HF and stresses the importance of prevention of progression from HTN and LVH to symptomatic (stage C) HF.

Numerous epidemiological studies have demonstrated that LV geometric changes in patients with HTN predispose them to increased risk of adverse CVD outcomes. Analysis on the FHS participants revealed the relationship between electrocardiographic LVH and CVD mortality more than 4 decades ago.[50,51] Similarly, another analysis from FHS confirmed the strong correlation between echocardiographically detected LVM and CVD morbidity and mortality.[52] A recent report from the Oregon Sudden Unexpected Death Study showed that abnormal LV geometric patterns (concentric and eccentric LVH and CR) are associated with increased risk of SCD in individuals with normal or borderline low LVEF.[53]

The relationship between LVM and CVD risk in HTN appears to be continuous with a stepwise increase in the risk from lowest quartile to highest quartile of LVM above the threshold of LVH.[54] The increased risk of adverse CVD outcomes appears to be true for both genders and across different races. In the Atherosclerosis Risk in Communities study, LVH was found to be a strong predictor of CVD in African-Americans and the LVH-related CVD risk was similar in both genders.[55] Similarly, in the Hispanic participants of a population-based cohort study, LVM was found to correlate with CVD events and combined cardiac event frequency increased with every 15 g increase in LVM.[56]

Our studies in the general clinical population have demonstrated a strong correlation between abnormal LV geometry and all-cause mortality in patients with preserved LVEF. When compared to patients with normal LV geometry, all-cause mortality risk was 2 times higher in patients with CR or LVH over a mean follow up period of 3.2 ± 1.4 years **(Figure 2)**.[13] In this population, 3616 patients with CR underwent a repeat echocardiogram and after a mean follow up period of 2.5 ± 1.5 years 45% of them continued to have CR, 43% regressed to normal LV geometry and 12% progressed to frank LVH. Mortality rate was significantly lower in patients who changed from CR to normal LV geometry and was significantly higher in patients who transitioned to LVH from CR. A similar strong correlation between LV geometric abnormalities and mortality was observed in elderly patients (>70 years) as well. Interestingly, in this elderly population, patients with CR had similar risk of mortality to those with concentric LVH but a higher risk of mortality than those with eccentric LVH.[14]

LVH also predicts worse outcomes in non-CVD. For example, in the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan trial, electrocardiographic LVH was found to be a predictor of progression of CKD in patients with type-2 DM and nephropathy.[57]

Presence of LVH has been shown to correlate with increased risk of cardiac arrhythmias as well. A report from the LIFE (Losartan Intervention for Endpoint Reduction) study, including patients with HTN demonstrated that ECG diagnosed LVH is a predictor of future atrial fibrillation (AF), although the effect was smaller compared to other predictors of AF, such as age, male gender and SBP. In this study,

when compared to atenolol, losartan was found to provide greater decline in risk of AF and stroke despite similar BP reduction. This decline in the risk was mainly attributed to improvement in left atrial enlargement and LVH with losartan. A recent meta-analysis of 10 studies with a total of 27,141 patients demonstrated that when compared to individuals without LVH, those with LVH had 3.4 and 2.8 times greater risk of supraventricular tachycardia and ventricular tachycardia, respectively.[58]

Novel Classification of LVH and Prognosis

Recently a new classification for LVH was proposed based on LV dilatation and concentricity.[59] The prognostic predictive value of this new classification was evaluated in HTN patients (n=939) enrolled in the LIFE echocardiography sub-study, which had a mean follow up of 5 years.[60] Patients with LVH were divided into 4-groups: concentric non-dilated, concentric dilated, eccentric non-dilated and eccentric dilated **(Figure 3).** The investigators found that eccentric non-dilated LVH is not associated with poor outcomes while all the other sub-groups had increased risk for all-cause and CVD mortality and a composite end-point of CVD events. Another recent study evaluated the association between this 4-tier LVH classification and CVD outcomes in participants of the Dallas Heart Study, a multiethnic, population-based cohort study.[61] Participants who underwent CMR and had normal LV systolic function and no history of HF were enrolled. Compared to the classic 2-tier classification, the 4-tier classification system was found to be a better prediction model of adverse CVD outcomes. Similar to the previous study, patients in all subgroups except the non-dilated eccentric LVH (indeterminate hypertrophy) had increased risk of HF or CVD death compared to participants without LVH.

Dynamic Nature of LV Geometric Changes

Despite extensive research, our understanding of the natural progression of LV geometric changes is still limited. A recent analysis of FHS participants (n=2604) evaluated the pattern, clinical correlates and prognostic significance of changes in LV geometry over 4 years.[62] It was observed that LV geometric patterns are more dynamic than is usually assumed. For instance, in this community based cohort of middle-aged to older adults, one third of participants with normal LV geometry at baseline

developed an abnormal LV geometric pattern (20% CR, 8% eccentric LVH and 4% concentric LVH) after 4 years of follow up. During the same follow up period, the progression rate from CR to eccentric LVH was 6% and to concentric LVH was 7%. The main clinical correlates of adverse changes in LV geometry were older age, male sex, and higher BP and body mass index. As expected, development of an abnormal LV geometric pattern was a significant predictor of adverse CVD outcomes such as HF, MI and CVD death after a median follow up of 12 years.

Progression from LVH to clinical HF and systolic dysfunction appear to be due to several mechanisms. History of CHD at baseline and interval history of MI, pulmonary edema on chest X-ray and presence of extensive myocardial fibrosis have been shown to predict development of depressed LVEF.[63] Our studies on a cohort of subjects with concentric LVH and normal LVEF evaluated the frequency and predictors of progression to systolic dysfunction.[64] We observed that after an average of 3 years of follow-up, 13% of subjects developed systolic dysfunction. Predictors of worsening systolic function were interval MI, conduction system disturbance (represented by prolonged QRS complex) and elevated follow-up arterial impedance, which is a measure of the LV afterload and was approximated by SBP/stroke volume index ratio. Moreover, hemodynamic stress and myocardial injury appear to play a role in transition from LVH to clinical HF. This was recently evaluated by a study on participants in the Dallas Heart Study without clinical HF or LV dysfunction. It was shown that elevated circulating levels of cardiac troponin T (a marker of myocardial injury) and N-terminal pro–B-type natriuretic peptide (a marker of hemodynamic stress) are strong predictors of progression to clinical HF and CVD death.[65]

Anti-HTN Therapy and LV Geometric Changes

HTN is the most common risk factor for CVD. Therefore, the primary goal of management of HTN is prevention of end-organ damage and reduction of CVD morbidity and mortality. Because of their easily measurable nature and predictive value for future CVD outcomes, LVM and LV geometric abnormalities have been studied extensively in the anti-HTN drug trials. There have been numerous studies showing significant reduction in LVM and prevention or regression of LV geometric

abnormalities with anti-HTN therapy.[66, 67] In the LIFE study, after 1 year of treatment with losartan or atenolol, the frequency of concentric LVH decreased from 24% to 6%, eccentric LVH from 46% to 37% and CR from 10% to 6%.[68] Interestingly, 34% of patients with concentric LVH switched to eccentric LVH, while only 3% of eccentric LVH patients transitioned to concentric LVH after 1 year. Other reports from the LIFE study demonstrated that LVM reduction with anti-HTN therapy is associated with significant improvement in diastolic filling parameters, systolic LV performance and stroke volume, independent of BP reduction.[68, 69]

There are several predictors of the extent of LVH regression with treatment of HTN. A recent meta-analysis of 28 randomized controlled trials (RCTs) consisting of a 2403 patients evaluated the influence of obesity and overweight on LVH regression in patients with HTN.[70] The authors found that compared to normal weight patients, obese or overweight ones had more significant regression with less reduction in SBP. They also reported that, in overweight and obese patients, RAAS blocking agents were the most effective anti-HTN drugs in regressing LVH and they were followed by beta-blockers (BBs), calcium channel blockers (CCBs) and diuretics.

Consistent with the epidemiologic data, regression of LVH with anti-HTN treatment correlates more closely with improvement in ambulatory BP levels compared to office BP. For instance, in a prospective trial including HTN patients with LVH, reduction in ambulatory BP was found to be superior to office BP for predicting LVH regression.[71]

There exists significant variability in the effects of anti-HTN therapy on LVH. A meta-analysis that included 39 RCTs conducted in the 1980s and early 1990s compared the efficacy of specific anti-HTN agents in LVH regression.[72] LVM reduction ratio was found to be 13.3% with angiotensin converting enzyme inhibitors (ACEI), 9.3% with CCBs, 6.8% for diuretics, and 5.5% for BBs. In the PRESERVE (Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement) study, enalapril (ACEI) and long-acting nifedipine (CCB) lead to similar degrees of reduction in LVM.[73] In the echocardiographic sub-study of the LIFE study, the losartan (angiotensin

receptor blocker [ARB]) based regimen was found to be superior to the atenolol (β_1 selective BB) based regimen in reduction of LVM index (-21.7 g/m^2 vs. -17.7 g/m^2, *P*=0.027).[74] In another longitudinal study, telmisartan (ARB) was found to be superior to carvedilol (α- and non-selective BB) in reduction of LVM index assessed by CMR or 3D echocardiography.[75] The potential benefit of RAAS blockage on LVH was supported by another prospective trial that compared eplerenone (aldosterone antagonist), enalapril (ACEI) and the combination of eplerenone and enalapril. The study consisted of 202 patients with HTN, and change in LV geometry was assessed with CMR. After a 9-month period of treatment, eplerenone and enalapril were associated with similar degrees of reduction in LVM. However, the combination of eplerenone and enalapril was found to be more effective in LVM reduction when compared to eplerenone alone.[76]

Because of the heterogeneity of clinic trials and inconsistency of results, current guidelines on management of HTN do not use target organ damage, such as LVH, to guide selection of initial or intensity of anti-HTN therapy. However, based on overall scientific evidence, we believe that ACEI, ARBs and/or CCBs should initially be preferred in patients with or at risk for LV geometric abnormalities.

Prognostic Impact of LVH Regression

Anti-HTN therapy induced LVH regression has been associated with improvement in CVD outcomes in several studies,[77, 78] but not in all.[79] In a meta-analysis of 5 studies consisting of a pooled population of 3149 HTN patients, LVH regression with anti-HTN therapy was shown to reduce risk of future CVD events, even after adjustment for other variables.[80] Some studies have even suggested that, compared to the changes in clinical BP, regression of LVH during anti-HTN therapy is a better predictor of lower risk of CVD events.[81] LVH regression appears to decrease risk of developing cardiac arrhythmias as well. Okin et al. found that improvement in electrocardiographic LVH with treatment of HTN is associated with lower risk of future AF, independent of the treatment modality or BP reduction.[82]

Regression of LVH was shown to lead to significant reduction in risk of future cerebrovascular events as well.[83]

Resolution of LVH appears to be associated with potential benefits in non-CVD outcomes as well. Okin et al. evaluated the risk of incident DM in a large-cohort of ~8000 HTN non-DM patients with LVH by electrocardiography.[84] The authors found that after a mean follow up of 4.6 years, resolution or continued absence of electrocardiographic LVH was associated with a 26% lower risk of incident DM after adjustment of other DM risk factors. The same group also reported that regression of electrocardiographic LVH during anti-HTN therapy is a predictor of a decreased rate of incident HF and hospitalizations for HF.[85]

Management of Co-morbidities

Lifestyle modification and non-pharmacological measures appear to have a favorable impact on LVM and LV geometry. Overweight and obesity are well-known risk factors for both HTN and LVH.[86] Multiple studies have confirmed the association between weight loss and decrease in BP and regression of LVH. A prospective study that was conducted more than 3 decades ago compared the effects of weight loss, anti-HTN therapy (with metoprolol) and placebo in a small group (n=41) of patients with HTN and overweight.[87] The investigators found that even modest weight loss (8 kg) results in more significant reduction in BP, LVM and LV wall thickness when compared to metoprolol or placebo. More recently, a meta-analysis of 23 studies consisting of a population of 1022 obese individuals with preserved systolic function demonstrated that bariatric surgeries result in significant decrease in LVM, RWT and left atrium diameter and improvement in LV diastolic function.[88]

Several epidemiological studies have shown a significant association between DM and LVH.[18, 19] It is also well-known that coexistence of HTN and DM dramatically increases risk of CVD morbidity and mortality.[89] Improved glycemic control in type 2 DM patients was recently shown to lead to improvement in LV systolic (measured by LV global longitudinal strain) and diastolic function (measured by septal e' velocities).[90] However, it has not been well established to what extent glycemic control affects LVH.

Therefore, BP control remains as the main strategy to prevent or treat LV geometric abnormalities in patients with HTN and DM. It was suggested by some studies that DM and MetS may blunt LVH regression expected from anti-HTN therapy. For example, in the LIFE study, subjects with DM or MetS resembling phenotypes were found to have less regression in LVH in response of anti-HTN therapy when compared to subjects without either condition.[91, 92]

Emerging Agents for LVH Regression

Allopurinol, a xanthine oxidase inhibitor, typically used to lower serum uric acid levels, has been the first 'non-anti-HTN agent' shown to induce LVH regression. Allopurinol was initially found to regress LVH in animal models.[93] Recent clinical trials in humans have demonstrated that high dose allopurinol can lower LVM in patients with CHD,[94] CKD[95] or DM without any impact on BP.[96] It is believed that allopurinol exerts its LVH regression effect mainly by reducing tissue oxidative stress, which is an important mediator of LVH.[97, 98] It should be noted that long-term prognostic impact of allopurinol-induced LVH regression is yet to be proven. Therefore, allopurinol has not been recommended by any guidelines for the treatment of LVH.

Conclusions

The LV is one of the major target organs for HTN and the hemodynamic overload due to HTN leads to LV remodeling. Increase in LVM and/or wall thickness constitute the key features of LV geometric abnormalities observed in HTN patients. Traditionally, LV geometric changes have been considered adaptive responses to pressure and/or volume overload. However, growing evidence now suggests that LV geometric abnormalities, even at earlier stages, are associated with impairment in LV function and impose significantly increased risk for CVD morbidity and mortality. Novel classification algorithms have improved prognostic predictability in LVH. LV geometric changes appear to have a dynamic natural course, which is an important feature from a treatment standpoint. BP control is the single most-important strategy for regression of LVH in HTN patients and this has been associated with favorable outcomes. Management of co-morbidities such as obesity, DM, and OSA might have

significant impact on regression of LVH. Improvements in our understanding of the pathophysiologic background, advances in the diagnostic modalities and evidence from clinical trials give hope for better identification and more effective prevention and treatment of LV geometric abnormalities in patients with HTN.

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FIGURE/TABLE LEGENDS

Figure 1:

Title: Left ventricular geometric patterns

Caption: Left ventricular geometric patterns determined by relative wall thickness and left ventricular mass index based on linear measurements. LVH, left ventricular hypertrophy. Adapted from Konstam et al.[3]

Table 1:

Title: Risk factors for abnormal left ventricular geometry

Figure 2:

Caption: Cumulative hazard plot for survival time based on left ventricular geometric patterns. (A) Normal left ventricular (LV) geometry, concentric remodeling (CR) and frank left ventricular hypertrophy (LVH). (B) Normal LV geometry, CR, eccentric hypertrophy (EH), concentric hypertrophy (CH). Adapted from Milani et al.[13]

Figure 3:

Title: 4-tier classification of left ventricular hypertrophy

Caption: LVH, left ventricular hypertrophy; LVM, left ventricular mass; BSA, body-surface area; LV, left ventricular; EDV, end-diastolic volume. Adapted from Bang et al.[60]

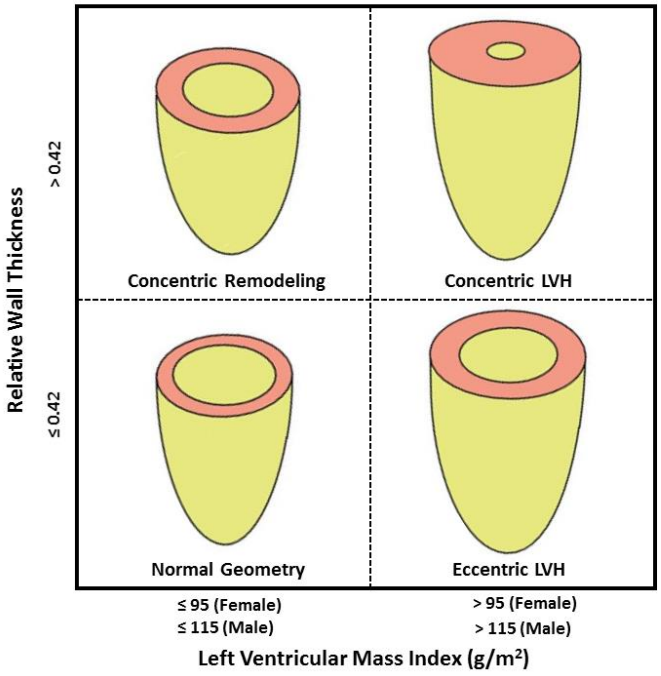


Fig. 1

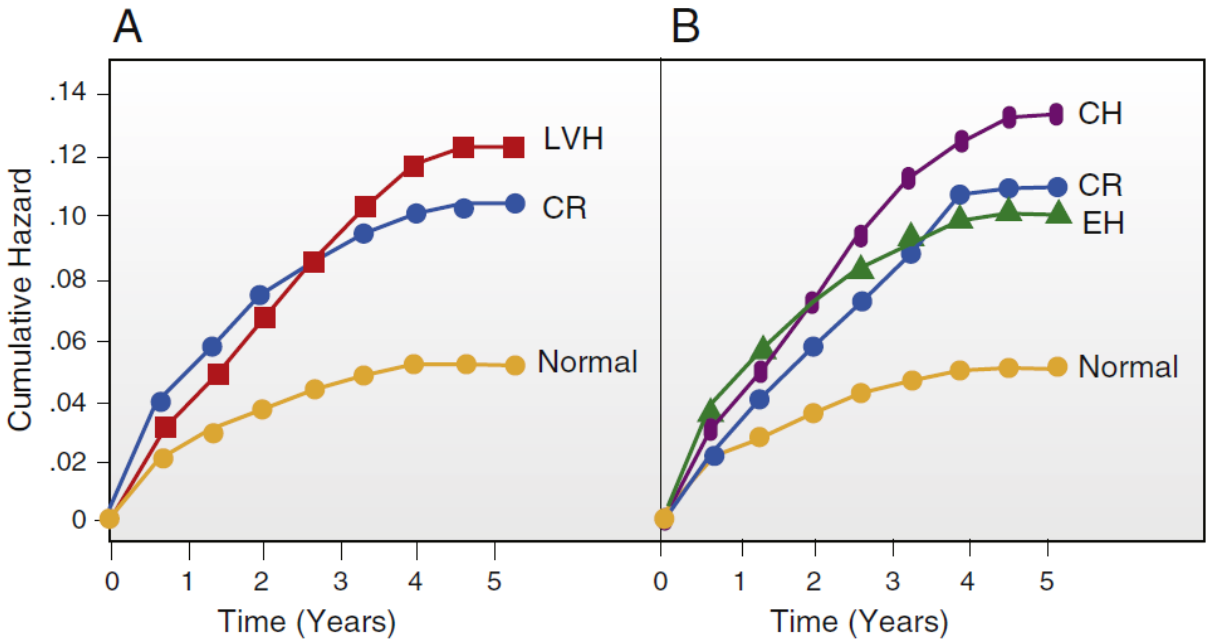
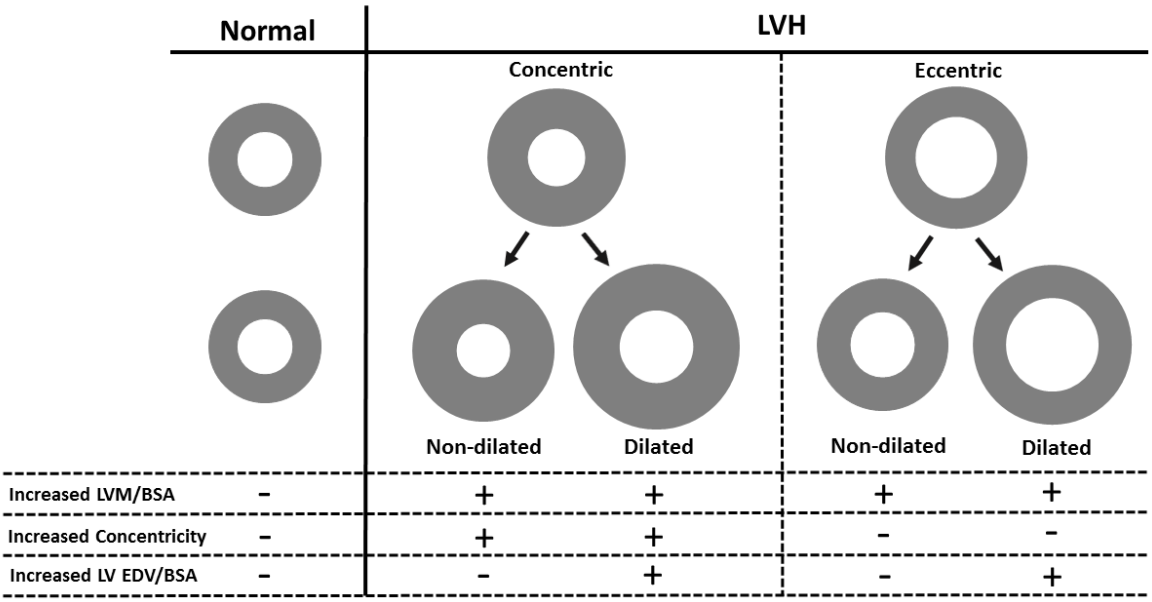


Fig. 2



Increased LVM/BSA	–	+	+	+	+
Increased Concentricity	–	+	+	–	–
Increased LV EDV/BSA	–	–	+	–	+

Fig. 3

Table 1: Risk factors for abnormal left ventricular geometry

Age
Hypertension
Coronary heart disease
Aortic stenosis or regurgitant valvular heart disease
Race (higher in African Americans)
Family history
Increased body mass index
Diabetes mellitus
Chronic kidney disease
Obstructive sleep apnea
Metabolic syndrome
Excess dietary sodium intake
Dyslipidemia
Primary hyperaldosteronism
Job strain
Sedentary lifestyle