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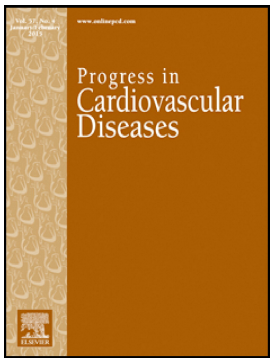

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Prognostic Implications of Left Ventricular Hypertrophy

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Abstract

Left ventricular hypertrophy (LVH) was one of the earliest studied echocardiographic characteristics of the left ventricle. As the myriad of measurable metrics has multiplied over recent years, this reliable and relevant variable can often be overlooked. In this paper, we discuss appropriate techniques for accurate analysis, underlying pathophysiology, and the contributions from various risk factors. The prognostic implications of LVH on stroke, serious arrhythmias, and sudden cardiac death are reviewed. Finally, we examine the effect of therapy to reduce LVH and the resultant clinical outcomes.

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Keywords: left ventricular hypertrophy, left ventricular mass, left ventricular geometry, left ventricle, hypertension, echocardiography, cardiovascular disease

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Abbreviations:
ACE - angiotensin converting enzyme
AF - atrial fibrillation
Ang II - angiotensin II
ARB - angiotensin receptor blocker
ASE - American Society of Echocardiography
BMI - body mass index
BP - blood pressure
BSA - body surface area
CAD - coronary artery disease
CCBs - calcium channel blockers
CI - confidence interval
CKD - chronic kidney disease
CMR – cardiovascular magnetic resonance
CR - concentric remodeling
CV – cardiovascular
CVD – cardiovascular disease
DBP – diastolic blood pressure
DM - diabetes mellitus
EACVI - European Association of Cardiovascular Imaging
Echo – echocardiography
ET-1 - endothelin-1
FHS – Framingham Heart Study
HF - heart failure
HTN - hypertension
HR - hazard ratio
LV - left ventricle
LVEF – left ventricular ejection fraction
LVH – left ventricular hypertrophy
LVM – left ventricular mass
MI – Myocardial Infarction

MMPs - matrix-metalloproteinases
OR - odds ratio
OSA - obstructive sleep apnea
RWT - relative wall thickness
RV - right ventricle
SBP - systolic blood pressure
SCD - sudden cardiac death
T-tubule - transverse-tubule
TGF-B1 - tissue growth factor-B1
TIMPs - tissue inhibitors of metalloproteinases
VEA - ventricular ectopic activity

Introduction

The left ventricle (LV) of the human heart can increase in size and undergo geometric changes in response to a wide array of pathophysiological stressors. These morphological transformations often closely follow disease progression, and provide valuable prognostic information about clinical outcomes. As such the study of LV hypertrophy (LVH) and its associated disease processes, implications, and treatments is of tremendous value. LVH and remodeling can be easily measured using a variety of non-invasive techniques, chief of among these being echocardiography. In this review, we discuss the current state of quantification of LVH, broad pathophysiology, associated disease states, prognosis, and effect of treatment.

LV Mass (LVM) Quantification and Definition

LVH was first studied non-invasively with electrocardiography and angiography, but with growth of echocardiography (echo) in the 1970s this quickly became the preferred technique.[1] The earliest echo studies recognized the value of this modality in accurately measuring wall thickness, end-diastolic diameter, and septal to posterior wall ratios to differentiate between types of LVH.[2] Devereux and Reichek conducted the first anatomic validation of LVM by echo in

1977 when they compared values on 34 patients with post-mortem LVM.[3] The original ellipsoid model they developed was based on short axis linear measurements taken of the LV from parasternal views using M-mode echo. They further refined this method in the 1980s with post-mortem analyses, and a variation of the cube formula they developed *(LVM = 0.8 {1.04[(LVIDd + PW + IVSd)^3 (LVIDd)^3]} + 0.6 g)* is still in use today.[4,5] With the improvement of 2D echo in the 1980s, these images were first used to ensure accurate linear measurement but then also to develop new models. The area-length and truncated ellipsoid formulas are 2D techniques based on tracings of the LV in short axis and length parameters from apical views.[6] These formulas are significantly more complicated but also validated against autopsy data.[5,7] The main benefit to a 2D LV quantification is improved accuracy in the setting of abnormal LV geometry, however, this method is subject to other errors such as LV foreshortening.[6] Despite these newer techniques, there has been a tremendous amount of prognostic data published about LVM calculated with linear measurements, giving intrinsic value to comparison by this method.[8,9] The most recent American Society of Echocardiography (ASE)/European Association of Cardiovascular Imaging (EACVI) guidelines recommend either technique for LVM quantification in a normal shaped LV.[10] The significance of technique becomes apparent, as the upper limit of normal for LVM varies based on the method of quantification; 95g/m^2 and 115g/m^2 for women and men respectively using a linear measurement, versus 88g/m^2 and 102g/m^2 using a 2D measurement.[10] The newest 3D techniques measure LVM directly without relying upon a model, accounting for abnormal LV geometry without the pitfalls or foreshortening.[11] Normal values for 3D have been published, however, given the lack of long-term prognostic information

and the evolution with changing technology, this is not yet the recommended first line technique for LV quantification.[10]

An important consideration in the quantification of LVM is appropriate indexing. LVM is known to increase with height and weight, thus reference values must be normalized to these variables in order to define a threshold for any particular individual's body size. Currently the ASE/EACVI recommend indexing LVM to body surface area (BSA) in m^2, a calculated value which includes a patient's weight and height.[10,12] Controversy arises when considering what degree of LVH is physiologic vs. pathologic for obese individuals, and alternative indexing has been proposed. De Simone et al. evaluated 611 normotensive individuals and found LVM was related to height to the 2.7 power and BSA to the 1.5 power. They also found that 14% of obese individuals with normal LVM by BSA had LVH when LVM was indexed to height$^{2.7}$.[13] A later study of 2400 patients, including those with hypertension (HTN), found a prevalence of LVH at 20-28% when indexed to height$^{2.7}$ vs. 7-11% when indexed to BSA. The population attributable risk of cardiovascular (CV) disease (CVD) was 1.8 times greater in the group indexed to height alone.[14] A review of 7,528 patients combined from the Askleipos study and the Multiethnic Study of Atherosclerosis found that indexing LVM to height$^{1.7}$ fared better at predicting CVD events than indexes of height$^{2.7}$ or BSA.[15] All these results suggest but do not definitively demonstrate that some pathologic LVH is underestimated in obese patients indexed with BSA.

Similar to the concerns with the evolution of 3D imaging technology and comparator validity, 2D echocardiography has changed significantly in the past 20 years. Harmonic imaging was developed for echo in the late 1990s, which took advantage of the acoustic properties of ultrasound waves to emit a low frequency signal for better tissue penetration and then receive

a reflected signal at a higher harmonic frequency for better resolution.[16] In a study from 2003 in 30 patients, the average measured LVM was 26% greater with harmonic versus fundamental imaging.[17] In vitro analysis with porcine hearts showed that harmonic imaging over measures tissue wall thickness and under measures LV internal diameters.[18] Another small study from 2002 reported larger LVM measurements with harmonic imaging (93+/-25g/m^2 vs. 79g/m^2, $p<0.001$), results mirrored in a study from the same year of 50 patients showing significant differences in LVM with harmonic imaging (185+/-74g vs. 166 +/-68g $p<0.0001$).[19,20] As improved techniques for LVM quantification such as 3D become more readily available these differences will be less significant, but as long as linear measurements are used for prognostic comparison the differences in technique should be noted.[21]

Pathophysiology

LVH as a singular clinical entity encompasses a broad group of diagnoses and pathologies, including infiltrative, hypertrophic, and familial dilated cardiomyopathies. From a population standpoint, however, the vast majority of LVH is related to chronic pressure and volume overload, as well as ischemic disease, with the caveat that other common comorbidities may play a synergistic and potentially independent role. The complicated role of hemodynamics in LVH was explored by Ganau et al. in 100 patients with and without HTN. They found that LV wall thickness and mass increased with blood pressure (BP) as expected, but statistically followed end diastolic volume more closely. This implies that stroke work, a combination of BP and stroke volume, was a better predictor of the compensatory increase in size than BP alone.[22] An increase in LV size, both by an increase in wall thickness and an overall increase in LV

diameter, is thought to be an adaptive response to increase in hemodynamic stressors; increased myocardial mass works to decrease wall strain and allow the myocyte to function at its prior level. Traditionally an increase in LV end diastolic diameter was thought to be a result of increased volume, such as in mitral regurgitation, and an increase in LV thickness was the result of increased afterload as with aortic stenosis. Recently, however , this has been called into question, as large studies have shown the correlation between BP and LVM to only account for a fraction of the variability.[23,24] In closely controlled animal studies with aortic banding, there is significant heterogeneity of LVH in response to an identical increase in hemodynamic stress.[25]

There appears to be a genetic component, as LVH was shown to have the highest correlation among first degree relatives in the Framingham Heart Study (FHS), and also shown to be linked in twin studies.[26,27] Specific genes and polymorphisms have been identified which are associated with LVH among siblings and in large population studies, giving weight to the heritability argument.[28,29]

At the cellular level, a hallmark of LVH is fibrosis and an alteration of the extracellular matrix. In several human studies of HTN and LVH, transvenous endomyocardial biopsies have found increased myocardial collagen in comparison with normotensive patients.[30,31] This collagen has further been associated with progressive systolic dysfunction. Collagen deposits in two distinct places in the HTN heart – both around the vessels, in what is termed perivascular fibrosis, and in the interstitial space, known as the endomysium and perimysium.[32] This collagen is deposited by myofibroblasts – termed as such because they exist within the muscle cells but deposit collagen similar to fibroblasts. They are morphologically distinct from

fibroblasts, however, and this transformation from fibroblast to myofibroblast is mediated by Angiotensin II (Ang II), Endothelin-1 (ET-1) and Tissue growth Factor-B1 (TGF-B1).[33] Ang II appears to play a central role, as it is secreted by activated macrophages in the setting of apoptosis and hemodynamic distress. The myofibroblasts which develop as a result of these increased cytokines alter the extra-cellular matrix and upregulate matrix-metalloproteinases (MMPs) and down-regulate tissue inhibitors of metalloproteinases (TIMPs). This MMP/TIMP imbalance has been extensively implicated in fibrosis and development of heart failure (HF).[34] Many of these changes have been considered a necessary adaptive response to increased hemodynamic load to prevent myocardial collapse, but MMP-deficient animal models have shown decreased hypertrophy and decreased fibrosis in response to sustained afterload without hemodynamic collapse.[35] MMP inhibitors have also been shown to prevent the onset of HF in spontaneously hypertensive rats.[36]

Giving further weight to the argument for a maladaptive neurohormonal milieu independent of hemodynamic stress, LVH in humans has been associated with increased circulating angiotensin II, epinephrine, and aldosterone, independent of BP.[37] Increased hormones, such as aldosterone from adipose tissue in metabolic syndrome have been associated with LVH in obesity.[38] A systemic response can be argued when chambers that are not directly affected by hemodynamic stressors, such as the right ventricle (RV), have been found to be hypertrophied in spontaneously hypertensive rats.[39] Correspondingly treatment with aldosterone receptor antagonists, such as eplerenone , has been shown to reduce RV fibrosis in spontaneously hypertensive rats without significant effect on BP.[40] Treatment with

losartan, an angiotensin receptor blocker (ARB), has also been associated with decreased myocardial fibrosis in humans with HTN.[31]

Another theme in the pathophysiology of LVH is progressive structural disorganization. At the cellular level, as there is increased collagen turnover driven by myofibroblasts, the hastily deposited collagen is laid down in an orthogonal meshwork. This disarrayed collagen architecture is associated with systolic and diastolic dysfunction.[41] At the ultrastructural level there has been a recent investigation of the transverse-tubule (t-tubule) in the progression of LVH. The t-tubule system is an organized series of membranes which function to conduct the membrane depolarization rapidly to many myocytes simultaneously for a coordinated myocardial contraction.[42] Wei et al. showed in 2010 a gradual disorganization of t-tubule architecture in a rat model of LVH.[43] Subsequent studies showed these changes in t-tubule disorganization were associated with strain abnormalities, and even preceded fibrosis or systolic dysfunction.[44] T-tubule ultrastructural remodeling has been shown to correlate down to a regional level of dysfunction.[45] In a recent analysis of myocardial specimens taken during LV assist device placement, a novel sheet-like remodeling of the t-tubule system was described, which predicted functional recovery after LV unloading.[46] All this is notable as there are several anchoring proteins between t-tubules and sarcolemma which could be target for potential therapy.[47]

Another issue in LVH is impaired coronary flow reserve. As the LV thickens, both as product of the perivascular collagen deposition and due to increased wall thickness, the minimum coronary vascular resistance increases and thus the maximum coronary flow reserve decreases.[48,49] This means that in the setting of exertion, decreased coronary flow reserve leads

to sub-endocardial ischemia, which could be associated with diastolic dysfunction as well as angina.[50]

Risk factors for LVH

Given the pathophysiologic complexity of LVH, multiple comorbidities have been identified which can play an independent or synergistic role in the phenotype of disease. (Table 1) However with the inter-related nature of the various comorbidities, the definitive proportional contribution can remain elusive.

Early echo results from the FHS clearly showed a relationship between BP and LVH in a large population of patients.[51] Devereux et al. conducted a more focused analysis in 1,935 patients from the Strong Heart study of between 1993 and 1995. They confirmed a relationship between both systolic BP(SBP) and diastolic BP(DBP) and LVM, but the correlation was weaker than expected (r=.22 and r=0.20 for SBP and DBP, respectively). When other hemodynamic factors, such as stroke volume, were considered in the multivariate analysis , they were able to increase the hemodynamic prediction of LVM (r=-.51), but ultimately concluded that half of all LVM variability was due to non-hemodynamic factors.[24]

The role of diabetes mellitus (DM) in LVH was seen in an analysis of 1,950 patients in the HypenGEN study, 20% of whom had DM. As expected those with DM had an increased incidence of risk factors known to effect LV size. However, even after adjusting for covariates, such as body mass index (BMI), SBP, age, and sex, there was still an increased likelihood of LVH in DM patients (38% vs. 26%, p=0.03).[52] Another large trial of 1,932 patients from the Northern Manhattan Study included 23% of patients with DM. Again, even after adjusting for age,

gender, BMI, race, coronary artery disease (CAD), and SBP, they still found an increased risk of LVH with DM (adjusted OR 1.46, 95% CI 1.13 to 1.88).[53] Animal models of isolated DM have not been associated with LVH, however, when exposed to similar HTN stimuli, such as AngII, DM mice had significantly more LVH when compared with non-DM mice.[54] This suggests that it is a multi-factorial process, and while single risk factors can be isolated they also need to be viewed in aggregate. Indeed, in patients randomized to treatment in the Losartan Intervention For Endpoint reduction in hypertension (LIFE) study, reduction of LVH was associated with a decreased incidence of new onset DM (Hazard Radio (HR) 0.62, 95% confidence interval (CI) 0.50 to 0.78).[55] Nonetheless, in the same study, losartan was found to be more effective in the reduction of LVH in those without DM than those with DM.[56] In addition to LVH, DM has also been shown to be related to abnormal LV geometry. A recent CV magnetic resonance (CMR) evaluation of the Multi-Ethnic Study of Atherosclerosis (MESA) showed that DM was associated with concentric remodeling (CR).[57]

Obesity is a well-recognized risk factor for LVH, however, the contribution of obesity and relative risk has been somewhat of a moving target as the definition of LVH is indexed to the same variable of body mass. De Simone et. al showed in a healthy normotensive population, 20% of obese individuals would have LVH if their LVM was indexed to an ideal weight BSA.[13] By definition, metrics of LVM indexed to height alone will have the greatest incidence of LVH in this population, and those which include body mass in allometric scaling will downplay its significance. Nonetheless across all studies, regardless of measure of index, the relationship between obesity and LVH persists. Levy et al. found a 9-fold to 10-fold increase in LVH from their leanest to most obese group in 4,976 patients from the FHS.[51] Obesity has been

associated with an increase in cardiac output and increased total blood volume, which likely plays a role in the pathophysiology of this relationship.[50,58] Lavie et al. studied a very large population of 30,920 patients, including 11,792 patients with obesity (BMI≥30). They found an increased incidence of abnormal LV geometry in obese patients indexed to BSA (49% vs. 44%, p<0.001), including increased CR (34 vs. 32%), eccentric LVH (7% vs. 6%), and concentric LVH (8% vs. 6%), all p<0.0001. Interestingly overall mortality was lower in the obese compared with the non-obese population (3.9% vs. 6.5%, p<0.0001), but abnormal LV geometry still portended increased mortality in both groups.[59] (Figure 1) Other studies have mirrored these results of increased frequency of abnormal LV geometry in obesity, but conversely lower mortality.[60] A recent large study out of Italy in 2017 found a higher incidence of LVH in obesity when compared with normal weight individuals (58.5 vs. 21%, p,0.001).[61] Interestingly the incidence of LVH was considerably higher than Lavie et al. (12%-15%) likely because LVM was indexed to $m^{2.7}$ and not BSA; unfortunately, no mortality data was available. Another recent large study from Italy evaluated 4920 patients with treated HTN and no LVH at baseline, and found that baseline obesity status predicted development of incident LVH at 48 month follow up.[62]

Following the myriad of known CV complications, smoking is also related with LVH. In the large MESA study mentioned previously, of 4,869 patients evaluated by CMR, current smokers had an average increase in LVM of 7.7g over non-smokers.[23] In the 4,850 patients from the Atherosclerosis Risk in the Community (ARIC) study, smokers had a higher prevalence of LVH compared with non-smokers (15% vs. 9%, p=0.008). In the ARIC study LVH was indexed by BSA, and the relationship remained even after adjusting for co-variates such as BP and CAD.

Unique to this study, they were able to demonstrate a linear relationship between pack-years of smoking and LVM index.[63]

Obstructive sleep apnea (OSA) and sleep disordered breathing have been associated with CVD for many years, LVH being no exclusion. Night-time hypoxia and frequent awakenings have been associated with an increase in sympathetic activity and elevated BP. In an analysis of patients from the Sleep Heart Health (SHH) study, even after adjusting for BP, DM, smoking, alcohol, and CAD, severe sleep apnea was still associated with an increase in LVM index compared to those without, adjusted odds ratio 1.78 (95% CI 1.14-2.79).[64] A later analysis combining some patients from the SHH study and patients from the ARIC study found the independent relationship between OSA and LVH only held up in women not men, however, this study was observational with additional inclusion criteria.[65]

Chronic kidney disease (CKD) and end stage renal disease are often seen in the setting of LVH, and pose another epidemiological challenge as they are intrinsically linked to other risk factors, such as HTN and DM. In a study of 1,160 HTN patients in Japan, of whom 40% had CKD (glomerular filtration rate (GFR) <60ml/min/1.72m^2), multivariate analysis showed CKD to be an independent risk factor for LVH (adjusted OR 1.52, 95% CI 1.18-1.96).[66] In a recent study of young patients (mean age 40+/-4 years) as part of the Coronary Artery Risk Development in Young Adults (CARDIA) study, even a mild decrease in renal function (GFR 60-75ml/min/1.72m^2) was associated with a greater LVM index on follow up.[67]

As discussed, only a fraction of the variability within LVH can be attributable to BP, however, an isolated BP reading used for many studies only represents a fraction of the hemodynamic load imposed upon the LV.[22] Clearly, BP still remains an important risk factor

down to the subclinical level, in fact increases in "normal" BP have been associated with progressive increases in LVM, suggesting that it is a continuous variable with pre-clinical implications.[68,69] Some of the variability within the BP contribution to LVH is due to the variability within BP itself. In a meta-analysis of 13 studies on "masked HTN," elevated ambulatory BP with normal office readings was associated with a 29% prevalence of LVH compared with 9% of normotensive patients ($p<0.01$).[70] Other studies have confirmed this closer relationship of ambulatory BP to LVH in comparison with office BP readings.[71] This makes empiric sense as LVH can be thought of as an averaged product of many continuous variables in the 24-hour period. Indeed, LVM correlates to ambulatory BP better than other known target organs damaged by HTN, and may serve as a better surrogate marker of cumulative effect.[72]

Other subtleties of BP itself are worth noting, BP trends throughout the day have been studied, with a typical dip at nighttime and increase during the day. In the Jackson Heart Study those with "reverse dipping" sign, that is a relative BP increase at night, had an increased LVM index of 8.3+/-2.1g/m2 compared to those with a normal dipping pattern ($p<0.001$).[73] The propagation of BP as it moves through the body is affected significantly by vascular stiffness, often creating disparities between central and peripheral BP; central BP can now be measured peripherally through the extrapolation of an arterial Doppler wave profile.[74] A recent meta-analysis of 12 studies over the past 15 years showed that central BP was more closely related to LVM index than peripheral BP ($r=0.30$ vs. $r=0.26$, $p<0.01$).[75] This is likely related to central BP more accurately reflecting the hemodynamic load experienced by the LV. A recent trial from Austria combined both of these concepts and measured 24-hour ambulatory central BP and compared these values with office brachial measurements in 289 patients. They found that

central ambulatory BP was more closely related to LVH than office peripheral BP (r=0.47 vs. r=0.29, p=0.003). [76]

LV Geometry

LVH was originally thought to exist in two forms: concentric whereby LV walls increased in thickness at the expense of internal diameter, and eccentric where LVM was gained by progressive dilation of the internal diameter. In 1992 Ganau et al. coined the term "concentric remodeling (CR)" when they described a third type of abnormal LV geometry whereby the LV walls were increased relative to the internal diameter, but absolute mass did not exceed the upper limit of normal.[77] Calculation of relative wall thickness (RWT) has not changed since it was first described; posterior wall thickness is multiplied by 2 and divided by the end diastolic diameter. Ganau et al. used a cutoff of 0.41 to describe the 95th percentile, and the most recent ASE/ESCVI guidelines recommend a cutoff of 0.42.[10,77] The posterior wall is used preferentially to the septum to mitigate the impact of abnormal septal geometry in the normal population.

The traditional paradigm was that concentric LVH (with CR as a precursor) was a response to increased afterload, and that eccentric LVH was either the result of increased pre-load states of decompensated concentric LVH. This is now known to be oversimplified as there is significant overlap between sub-types, and a single population can develop any of the abnormal LV geometries in response to an identical pathophysiologic condition.[78] (Figure 2)

The prevalence of abnormal LV geometry varies according to the population studied. In a large single institution study of 35,602 patients with normal LV ejection fraction (LVEF) referred for echocardiography, 46% of people were found to have abnormal LV geometry, 35%

with CR, 5% with eccentric LVH, and 6% with concentric LVH.[9] (Figure 3) A large meta-analysis from 2012 of 30 studies and 37,700 patients found similar rates of LVH in population studies (10-19%), but the prevalence rates increased in HTN cohorts (19-48%), and was highest in those with severe HTN and CVD (58-77%).[79] LV geometry also seems to be affected by age, as a study of 9,771 people over the age of 70 found CR in 43%, followed by concentric LVH (8.5%), and eccentric LVH (7.4%).[8]

HTN, while universally recognized as a risk factor for LVH, has been variably associated with either eccentric or concentric LVH in different studies.[9,80,81] This is likely due to differences in baseline population characteristics and co-morbidities. These include DM, a frequent covariate, which has been associated with CR and concentric LVH.[81] Obesity has traditionally been associated with eccentric LVH in the high output model, however, even this has been challenged as other studies report increased concentric LVH with obesity.[59,82] CAD, likely due to myocardial damage and remodeling, is associated with eccentric LVH.[83]

There are surprisingly few studies which examine the natural progression of abnormal LV geometry. Milani et al. took 3,616 patients with CR at baseline and re-evaluated them at a mean follow up time of 2.5 +/- 1.2 years. 45% of these patients had no change, 43% reverted to normal geometry, and 12% progressed to LVH.[9] In 2014 Lieb et al. analyzed 2,605 patients from the FHS and followed them over two screenings for a period of 4 years, demonstrating significant fluidity between LV geometries. Of those with normal LV geometry at baseline, 20% developed CR, 8% eccentric LVH, and 4% concentric LVH. A large number (53%) of those with CR at baseline reverted to normal LV geometry, with 6% and 7% progressing to eccentric and concentric LVH, respectively. Concentric LVH did have some regression as well (29%), but a

larger number progressed to eccentric LVH (19%) than those with normal LV geometry or CR.[84] (Figure 2)

LVH and Systolic Function

Systolic dysfunction is a well-recognized risk factor for mortality and adverse CVD events. Studies of LVH variably include and exclude patients with systolic dysfunction, given that it is a potential confounder, but the relationship between LVH and systolic dysfunction cannot be ignored.[9,85] Many of the same risk factors which predispose patients to LVH are also risk factors of systolic dysfunction, and LVH itself is a risk factor for systolic dysfunction. The Cardiovascular Health Study evaluated 3,042 patients with a baseline normal LVEF, stratified them by quartiles of LVM and followed them for a mean of 4.9+/-0.14 years. Those in the lowest quartile of LVM had a 4.8% risk of depressed LVEF on follow up, compared with 14.1% in the highest quartile ($p<0.001$).[86] These results were independent of the presence of CAD, however, there were more CAD events in the group with LVH at baseline compared to those without (8.6% vs. 4.6%, $p<0.001$). CAD was a factor again in another small study from 2004 of 159 patients with LVH, of whom 18% progressed to depressed LVEF over 4 years. Interim myocardial infarction (MI) was the single biggest predictor of depressed LVEF (41% vs. 8%, $p<0.001$).[87] In the MESA study of 4,869 patients who had a CMR exam, the presence of CAD was not specifically evaluated but patients with a smoking history and DM (both risk factors for coronary artery disease) were found to have lower LVEF.[23] Milani et al. analyzed 1,024 patients with concentric LVH and normal LVEF and followed up at a mean of 33+/-24 months, and found that 13% developed systolic dysfunction. The most common variable among those who

developed a depressed LVEF was interval MI.[85] Krishamoorthy et al. found similar results in a population of concentric LVH, with 20% developing depressed LVEF at 7.5 years, again with interval MI as the most common risk factor. Interestingly , the most common phenotype among those who developed depressed LVEF was still concentric LVH.[88]

Prognosis

Beyond tying together a diverse group of CVD risk factors, the true value in measuring LVH is its ability to predict a variety of clinical outcomes. (Table 2) This was studied early in 3,220 patients from the FHS with echo data, free from CVD at baseline, and followed for 4 years. Baseline LVM predicted incident CVD, death from CVD, as well as all-cause mortality, even after adjusting for age, smoking, obesity, DM, BP, and cholesterol.[89]

Within subtypes of LV geometry, there is disagreement between studies as to which pattern is the most predictive of mortality. This is likely due to differences in population characteristics between studies. In an early study of a thousand patients from Cook County Hospital in Chicago, patients referred for angiogram with an echo were followed for 9 years. Patients with concentric LVH were found to have the highest all cause as well as CVD mortality, followed by eccentric LVH, and then CR, regardless of CAD status.[90] In a larger population of older individuals referred for echo for routine clinical indications, Lavie et al. also found concentric LVH had the highest rate of mortality on a three year follow up. In contrast to the prior study though, they found that CR actually had a slightly higher mortality rate than eccentric LVH.[59] In a larger study (n=35,602), Milani et al. also found concentric LVH to have the highest mortality with less difference between CR and eccentric LVH (10.4%, 8.7%, and 8.4%

respectively).[9] (Figure 4) When the transition from one subtype of abnormal LV geometry was studied, those who progress to frank LVH from CR have universally worse prognosis than those who normalize.[9,84]

Two studies out of Italy in the early 2000s showed a continuous relationship between LVM and CVD events. The first of 1,925 men with LVM were stratified into quintiles and followed for 4 years. They found a continuously increased risk between each quintile, with those in the highest quintile having a relative risk (RR) of 3.5 (95% CI 1.8-6.8) for CVD events compared with those in the lowest quintile.[91] The second study was multi-institutional and showed a 40% increase in CVD risk for every 39g/m^2 of increase in LVM.[92] This continuous relationship between LVM and CVD events has been prospectively validated.[93] Conversely when LV regression has been studied, there was a RR 0.66 (95% CI 0.44-0.88) of CVD events for every standard deviation reduction in LVM.[94] Despite this strong association with CVD risk, LVH is not routinely considered in risk stratification assessments. [95]

Stroke and Atrial Fibrillation (AF)

LVH was an early recognized risk factor for stroke in the FHS, with an elderly 8 year follow up showing an 18.4% incidence of stroke in the highest quartile of LVM index vs. 5.2% in the lowest quartile (adjusted HR 2.72, 95% CI 1.39-5.36).[96] In a large CMR analysis, LVM was weakly correlated with stroke (HR 1.2 per 10% increase in LV mass), but more specifically LVM/volume ratio, or concentricity, had a very strong association (HR 4.2 per g/ml mass increase).[97] What is not known is whether these strokes are related to concomitant vascular disease or AF. Verdecchia et al. found that for every standard deviation increase in LVM, the

risk of AF was increased by 1.2 (95% CI 1.07-1.34) in a 5 year follow up.[98] A 2014 meta-analysis of 27,141 patients in 10 studies showed an 11.1% risk of supraventricular tachycardia (including AF) in those with LVH vs. 1.1% risk in those without ($p<0.001$).[99] In a recent study from Japan, this LVH-AF link was found to be strongest in those with eccentric and concentric LVH, less so in CR.[100] Accordingly, those with LVH regression by EKG in the LIFE study had a 12% lower rate of new onset AF for every standard deviation reduction in Cornell EKG product.[101] This decreased rate of LVH and new onset AF corresponded with a decreased rate of stroke in the losartan treated arm of this study, further solidifying the relationship between changes in LVM, AF, and stroke.[102]

Sudden Cardiac Death (SCD)/Ventricular Ectopic Activity(VEA)

One of the mechanisms of CVD mortality associated with LVH is through ventricular arrhythmias and SCD. LVH was one of the early identified risk factors of SCD in the FHS, which found a 5- to 9- fold increase in SCD among patients with EKG evidence of LVH and intraventricular conduction delay. Notably this risk was comparable to those with established symptomatic CAD.[103] A later echocardiographic analysis from the same study found a linear relationship, with an adjusted hazard ratio (HR) of SCD of 1.45 (95% CI 1.22-3.88) for every 50g/m increase in LVM.[104] The pathophysiology of ventricular arrhythmia in LVH has several potential mechanisms. Decreased coronary flow reserve in LVH induces subendocardial ischemia increasing VEA. Indeed multiple studies have found increased ectopy in LVH.[105,106] In animal models of LVH, the LV was also more susceptible to fibrillation from programmed stimulation. This was found to be related to a dispersion of refractory and repolarization

periods with the increase in LVM– effectively increasing the vulnerable periods of the QRS cycle.[107] The relationship between abnormalities of depolarization and SCD was seen in the LIFE study evaluating losartan in HTN patients. In an multivariate risk adjusted analysis, they found both baseline QRS duration and QT-peak interval were significantly associated with all-cause and CVD-mortality.[108] Accordingly, regression of EKG criteria for LVH was associated with a reduction in SCD independent of BP in separate studies of both ramipril and losartan.[109,110] Most recently an analysis out of Oregon from the Sudden Unexpected Death Study analyzed all types of LV geometry and found increased risk of SCD in concentric LVH, eccentric LVH, and even CR (Odds Ratio (OR) 3.20, 2.47, and 1.76 respectively, $p<0.007$).[111]

Therapy to Reduce LVH

With LVH being easily measurable and closely related to prognosis across a wide variety of CVD processes, it has been used extensively as a surrogate marker of treatment benefit. (Table 3) The most representative example of this is the LIFE study, which randomized 9193 people with HTN and LVH to either losartan or atenolol and followed them for a mean time of 4.8+/- 0.9 years. There was no difference in mean BP at the end of the study, but the losartan group showed significant reductions in LVH criteria by EKG, as well as a lower composite endpoint of death, stroke, or MI.[112] A sub-study of LIFE included 960 patients with echo at baseline and yearly through 5 years. Losartan was associated with a significant reduction in LVM index independent of BP (-21.7g/m^2 vs. -17g/m^2, $p=0.021$).[113] This reduction in LVH by echo was also associated with a reduction in the composite primary end point (HR 0.78 per -25g/m^2 in mass reduction, 95% CI 0.65-0.94).[114] Larger analyses of the study including those

with EKG criteria for LVH found a significant relationship between LVH and all of the individual outcome criteria: CVD-mortality, MI, stroke, and all-cause mortality.[115] Changes in LVH were also associated with improved parameters of diastolic function, and decreased recurrent hospitalizations for HF.[116,117]

A recent study from 2017 involving LVH and losartan found results comparable to that of the LIFE study, and studies of different ARBs have shown comparable benefit over beta adrenergic blockers.[118,119] When used in populations with diabetes and CKD, losartan was shown to decrease LVH and improve renal outcomes. Remarkably it was able to decrease CVD risk in patients with LVH to levels similar of those without LVH, likely due to the added benefits of angiotensin receptor blockade in this population.[120]

Other commonly used anti-hypertensives have been studied, however, none as thoroughly as losartan. The Action in Diabetes and Vascular Disease (ADVANCE) study evaluated perindopril-indapamide vs. placebo in patients with DM, and found a reduction in major adverse CVD events as well as a reduction in LVM index, but it also reduced BP in the treatment arm, thus confounding these results.[121] When compared with atenolol, perindopril-indapamide showed improved reduction in LVM index, but also an improved central BP reduction over the beta adrenergic-blockers – a theme that is seen in other studies.[122] A recent study of amlodipine+/-perindopril vs. atenolol+/-bendroflumethiazide found more significant reduction in LVM with the former.[123] When compared head to head angiotensin converting enzyme (ACE) inhibitors have shown no difference in reduction of LVM when compared with calcium channel blockers (CCBs).[124] A meta-analysis of 80 trials and 3,767 patients found a

reduction in LVM index of 13% with ARBs, follow by 11% with CCBs, 10% with ACE inhibitors, 8% with diuretics, and 6% with b-blockers.[125]

Exercise has consequences on LVM with disparate effects depending on the population in which it is studied. In young otherwise healthy individuals, endurance training results in increased LVM with concordant increases in LV diameter and improvement of diastolic metrics.[126] In slightly older individuals, regular physical exercise has been shown to reasonably prevent the development of LVH in comparison with sedentary individuals (OR 0.24 CI 0.07-0.85).[127]

Obesity is a known risk factor for LVH, and can be dramatically improved with bariatric surgery. In a longitudinal study of 43 patients having bariatric surgery, LVM index was found to decrease by 6.3g/$m^{2.7}$ at 9 months following surgery.[128] A meta-analysis from 2014 of 1,066 patients undergoing bariatric surgery showed a standardized mean difference of -0.46 in LVM index for individuals before and after bariatric surgery ($p<0.001$).[129]

Other less commonly considered but studied medications in the regression of LVH include spironolactone, allopurinol, direct renin inhibitors, and sacubitril/valsartan. With the re-emergence of spironolactone as a preferred anti-HTN therapy, it has been studied with LVM in two recent small studies. Spironolactone was found to decrease LVM, and when studied against non-spironolactone therapy, it improved diastolic parameters and reduced the risk of new onset symptomatic congestive HF.[130,131] Allopurinol inhibits xanthine oxidase, which in addition to uric acid metabolism also plays a role in generating reactive oxygen species which contribute to myocardial remodeling. In post MI animal studies allopurinol was found to reduce LVH and decrease interstitial fibrosis.[132] In a small randomized study of patients with CKD, allopurinol

was found to significantly reduce LVH (p=0.036).[133] In another small randomized study of 66 patients with CAD, allopurinol was again found to improve LVM after 9 months of therapy.[134] Aliskiren, the direct renin inhibitor, was studied in a randomized trial against losartan, and shown to be equally effective at lowering BP as well as decreasing LVM with a similar side effect profile.[135] Most recently the neprilysin inhibitor/ARB combination, sacubitril/valsartan, was studied against olmesartan in a randomized trial of 114 patients over 52 weeks. Despite a modest decrease in SBP, but not DBP, in the sacubitril/valsartan arm, they did find significant reductions in LVM index (-6.83 vs. -3.55 g/m2, p<0.029).[136] In contrast to these positive results, recent studies of alternative therapies such as renal denervation or long acting nitrates have shown no benefit in the reduction of LVH.[137,138]

Conclusion

LVH has been one of the most well studied clinical variables over the past 50 years of CVD research. As a measurable outcome, it exists both as a metric of the combined influence of many external and internal factors, as well as a prognostic marker for events to come. It is diverse in its phenotypes along a continuum of concentricity and LV dilation. LVH has been used as a surrogate marker of therapeutic success while awaiting clinical results, and a hard endpoint for individualized therapy. Despite its ubiquity, it is not routinely used in risk stratification, and the clinical implication when measured on echo often goes overlooked. Through a greater understanding of their significance, abnormal LV geometry and LVH can be included more often in the routine assessment of CVD.

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Table 1. Risk factors for LVH
Hypertension
Diabetes mellitus
Obesity
Obstructive sleep apnea
Chronic kidney disease
Tobacco use
Sodium Intake

Table 2. LVH prognostic associations
All-cause mortality
Atrial fibrillation
Congestive heart failure
Diastolic dysfunction
Myocardial infarction
Reduced coronary flow reserve
Stroke
Sudden cardiac death
Ventricular ectopic activity

Table 3. Therapy shown to reduce LVH
Angiotensin converting enzyme inhibitors
Angiotensin receptor blockers
Aldosterone receptor antagonist
Allopurinol
Calcium channel blockers
Direct renin inhibitors
Exercise
Sacubitril/valsartan
Weight reduction

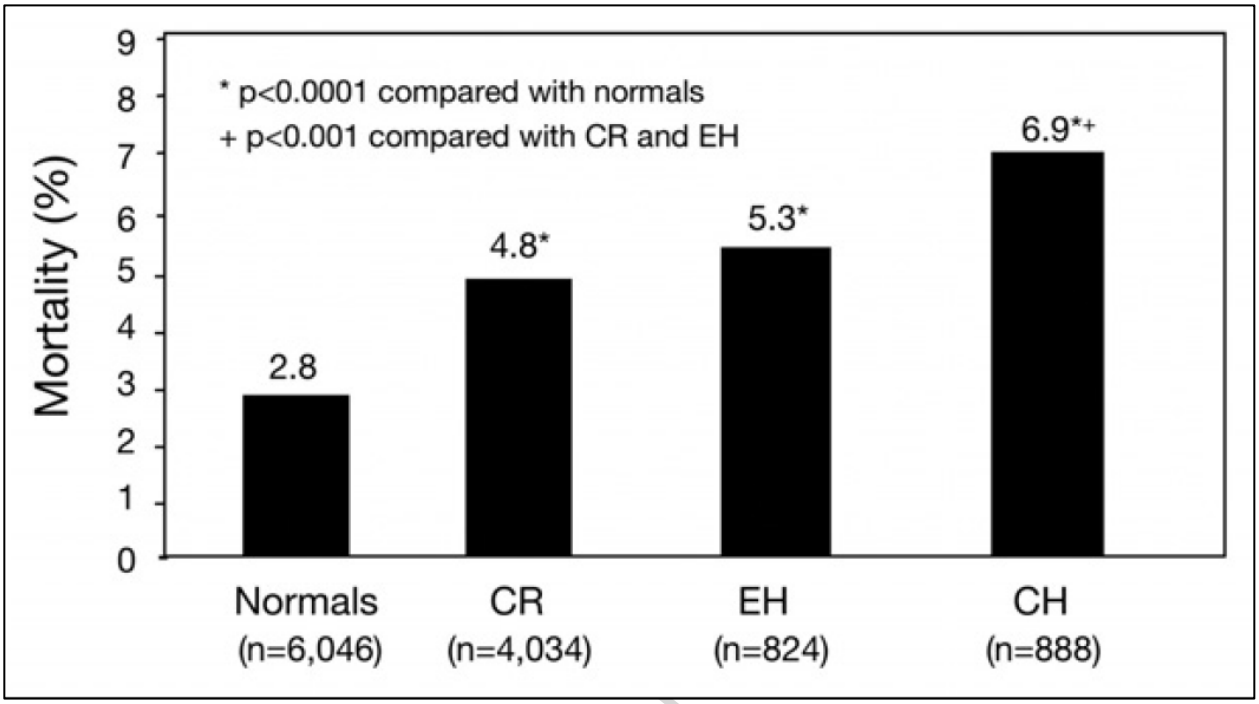

Figure 1. Mortality by left ventricular geometry in 11,792 obese patients with preserved ejection fraction followed for 3.2+/-1.4 years. Concentric remodeling (CR), eccentric hypertrophy (EH), concentric hypertrophy (CH). (reproduced with permission from Lavie et al.[59])

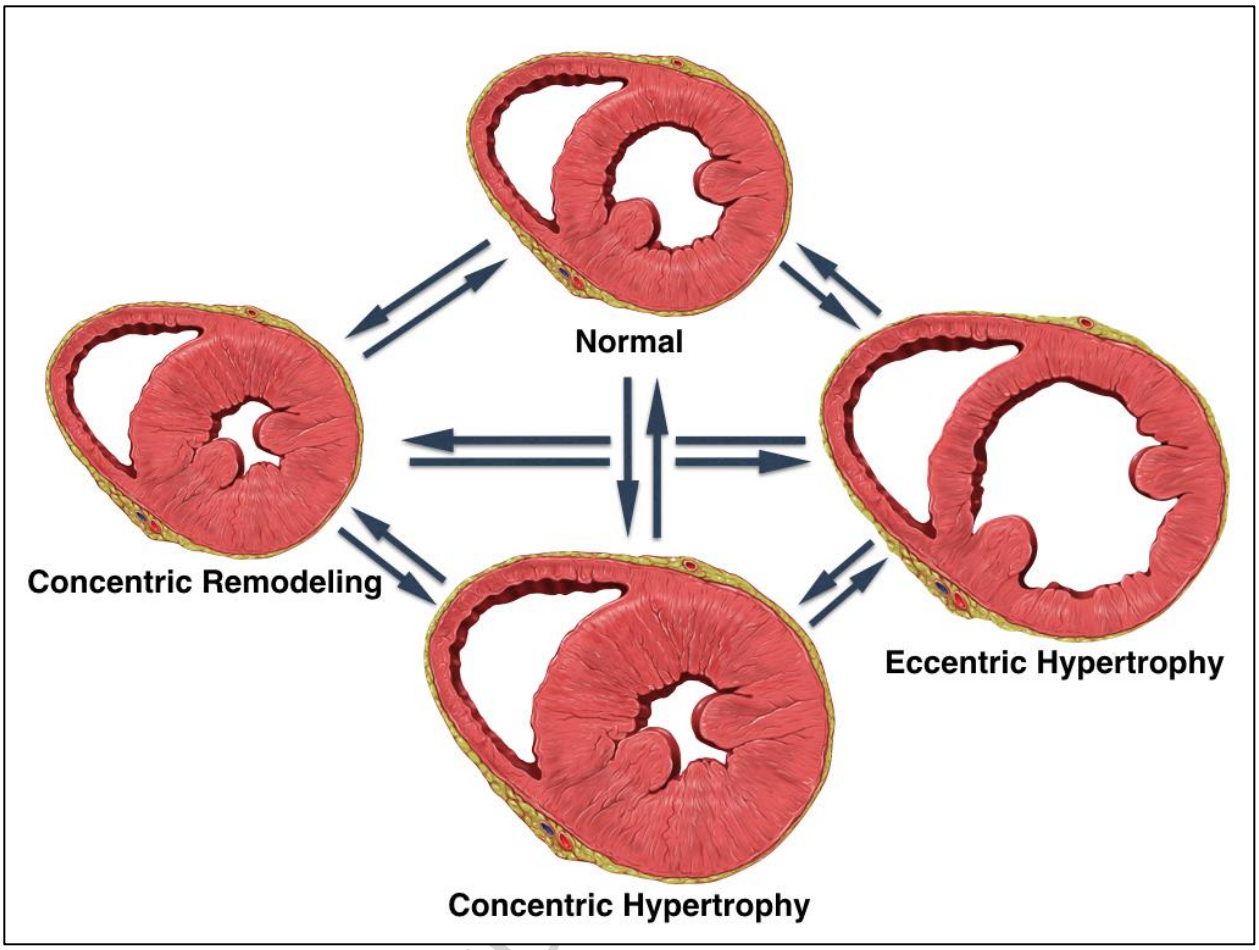

Figure 2. Adverse left ventricular (LV) remodeling includes concentric remodeling (increased relative wall thickness (RWT) without increase in LV mass), eccentric hypertrophy (increase LV mass without increased RWT), and concentric hypertrophy (increase in LV mass as well as increased RWT). The progression between subtypes is more fluid that once thought and a transition between any two types of abnormal LV geometry is possible. (images adapted with permission from Patrick J. Lynch, medical illustrator; C. Carl Jaffe MD, cardiologist. Creative Commons Attribution 2.5 License 2006)

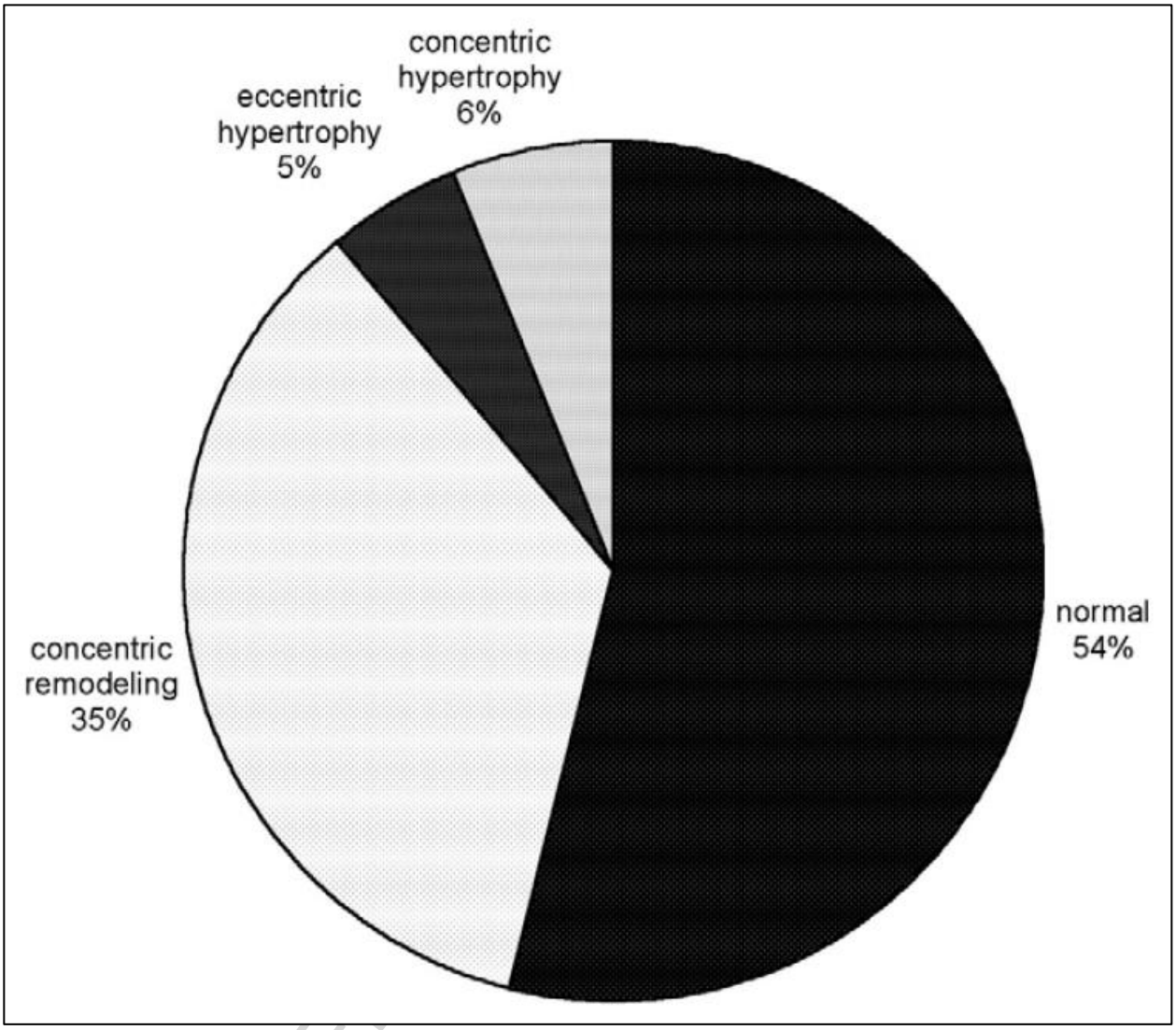

Figure 3. Frequency of left ventricular (LV) geometry subtype in a population of 35,602 patients with normal LV ejection fraction. (reproduced with permission from Milani et al.[9])

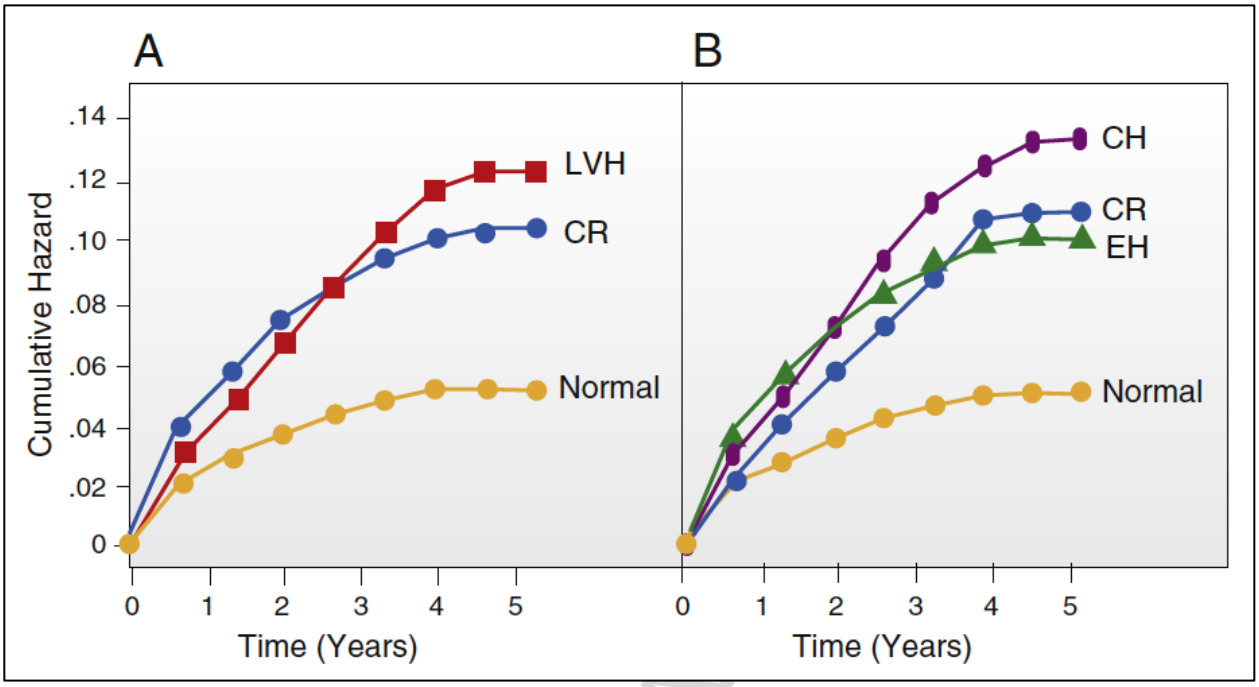

Figure 4. Plot of cumulative hazard over time for survival stratified by left ventricular geometry. A. Normal structure, concentric remodeling (CR), and left ventricular hypertrophy (LVH). B. Concentric hypertrophy (CH), CR, eccentric hypertrophy (EH), and normal structure. (reproduced with permission from Milani et al.[9])