Review Paper

Is Left Ventricular Hypertrophy Regression Important? Does the Tool Used to Detect It Matter?

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Left ventricular hypertrophy (LVH) has been demonstrated to define an adverse cardiovascular prognosis. However, due to poor noninvasive tools in which to accurately define LVH, the clinical manifestations dictate an inexact manner in which to either initiate therapy or to gauge the success of LVH regression. Herein, the authors define the current state of imaging modalities available to interrogate LVH and its regression, but concentrating chiefly on the "gold standard" of cardiovascular magnetic resonance imaging (CMR). The authors review the data demonstrating the importance of LVH regression. Additionally, they highlight the strengths and weaknesses of CMR via several pinnacle studies that demonstrate the ease, efficiency, and accuracy of this new noninvasive reproducible and available tool to relatively inexpensively delineate LVH. Finally, upon pharmacologic administration of an antihypertensive regimen, the authors, for the first time, define a goal of left ventricular mass reduction (in grams) for echocardiography and CMR based in part on Framingham data aiming at improving cardiovascular risk. J Clin Hypertens (Greenwich). *2009;11:441–447.* ©*2009 Wiley Periodicals, Inc.*

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Over the past 4 decades there has been growing recognition of the importance of left ventricular hypertrophy (LVH), as numerous studies have documented a strong relationship between LVH and increased mortality and morbidity several times above and beyond the absolute risk of hypertension alone.[1–8] Furthermore, recent studies have showed that regression of LVH was associated with improved outcome independent of blood pressure (BP) control.[9–11] In this context, considerable attention has been devoted to determine whether different forms of antihypertensive therapy might differ in their ability to regress LVH. Initial studies showed conflicting data that supported this notion,[12,13] while others did not.[14] However, recent studies[15,16] using a more accurate tool to detect and follow LVH, namely cardiovascular magnetic resonance imaging (CMR), have showed significant differences between antihypertensive therapies in regard to their ability to regress LVH-quantifying LV mass (LVM).

In this review article, we highlight studies that answer the question of whether LVH regression does matter. Also, we will show that the choice of antihypertensive therapy plays a significant role. Our chief goal, however, is to define the role that CMR plays in detecting small but clinically significant reductions in 3-dimensional (3D) quantified LVM in short periods after initiating antihypertensive treatment. Finally, we will unveil a manageable clinical goal for LVH regression to

accomplish when considering instituting antihypertensive therapy.

LVH DETECTION

Many tools are currently available for the assessment of LVH; however, the various techniques differ in cost, availability, sensitivity, and specificity. Electrocardiography (ECG) is easy to perform, widely available, and inexpensive. However, the sensitivity of ECG ranges from 7% to 35% for mild LVH to 30% to 60% for moderate to severe LVH. The specificity is high (80%–90%) in severe LVH.[17]

LVM as measured by M-mode echocardiography was used as the reference standard in most of the ECG-LVH validation studies.[18] However, it is neither accurate nor reproducible. It relies typically on 1-dimensional (1D) left ventricular (LV) wall thickness measurements entered into a mathematic formula with geometric assumptions about the shape of the LV for the calculation of a 3D structure. In some studies, echocardiography underestimates the prevalence of LVH in hypertensive cohorts.[19] In other studies, M-mode echocardiography consistently overestimated the LVM in the presence of LVH.[20] Finally, the accuracy and reproducibility of LVM as measured by M-mode echocardiography have been shown to be poor as compared with direct measurement by 3D CMR.[21]

During the past 2 decades, CMR has been established as the gold standard for the quantitation of LVM. It provides a spatially defined 3D data set at multiple contiguous levels throughout the heart; hence, the measurement of LVM does not require geometric assumptions about the left ventricle. The inherent accuracy of CMR measurements of LVM has been validated using post-mortem hearts, imaged ex vivo for humans,[22] or in vivo for animal studies.[23] CMR was demonstrated to be more accurate and reproducible, as well as having much less variability than M-mode and 2-dimensional (2D) echocardiography.[24,25] There is good agreement between the CMR-obtained and true LVMs, with a standard deviation of the difference of approximately 8 g (95% confidence interval [CI], ≈15 g) in humans and 10 g (95% CI, ≈19g) in canine studies. The greater accuracy and reproducibility of CMR has important implications for clinical practice and research. Much smaller sample sizes can be used to detect the same change in LVM. Alternatively, using the same sample size, smaller degrees of changes can be identified. For instance, the landmark paper by Bottini and colleagues[25]demonstrated that to detect a 10-g LVM regression with a power of 0.8 at the P=.05 level required 550 patients by echocardiography, while only 17 patients were required by CMR. The impact of this finding on society is enormous. Specifically, in the Eplerenone, Enalapril, and Eplerenone/Enalapril Combination Therapy in Patients With Left Ventricular Hypertrophy (4E) trial,[15] for which our center served as the CMR core laboratory, the ability to detect a similar degree of LVM regression as was seen in the 5-year Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial was performed in 9 months by CMR. CMR used approximately 100 patients, while the LIFE echocardiography substudy[11] used more than 500 patients. Moreover, using a cost comparison between CMR and echocardiography, there was a 92% savings via the CMR, despite the fact that the CMR was upfront the more costly tool. Thus, long-term, it can be seen that the cheaper imaging tool might be counterproductive. Importantly, if one estimated the average amount of money a pharmaceutical company lost on patent expiration at over $1 million/day, the impact of getting a drug to market after 4 years would be over a billion dollars. The impact to society is immeasurable when receiving Food and Drug Administration regulatory approval in years, not decades. Thus, this concept has been rapidly adopted by leading pharmaceutical companies because they recognize that there are higher long-term costs associated with older, albeit more established, imaging tools.

CLINICAL IMPLICATIONS OF LVH

Overall, the importance of LVH in medicine is still not widely appreciated despite decades of research. This understanding has been hampered by the relatively recent capability to recognize LVH in a meaningful manner. As detected by ECG or echocardiography, it is well documented that LVH is associated with an increased risk of mortality and morbidity several times above and beyond the risk of hypertension alone. LVH has been associated with an increase in the incidence of heart failure, ventricular arrhythmias, myocardial infarction (MI), decreased LV ejection fraction, sudden cardiac death, aortic root dilation, carotid atherosclerosis, and cerebrovascular events.[1–8] This was independent of the presence of coronary artery disease or hypertension.[5]

PROGNOSTIC SIGNIFICANCE OF LVH REGRESSION

There is a well-documented association between LVH and increased mortality and morbidity

independent of the presence of hypertension. The observation that, despite substantial benefits from lowering blood pressure (BP), conventional treatment does not normalize the risk of major cardiovascular events in patients with hypertension.[26–28] These findings have raised many questions: does LVH regression confer further reduction in mortality and morbidity, beyond lowering BP? Does the choice of antihypertensive medication matter in regression of LVH? Do we need to target our treatment goals to BP control, LVH regression, or both? Why is there no recommended threshold of LVH in g/m^2 that could serve as a pharmacologic goal for adequate change in order to institute a clinically meaningful impact relating to LVH regression? Should there be?

Uncertainty persists concerning the relationship between lower LVM and improved outcome during treatment of hypertension, because some studies have supported this concept[9,29–31] while others have not.[32,33] However, more recently there has been growing evidence that regression of LVH is associated with decreased morbidity and mortality independent of other risk factors. This has been supported, in part, by the following trials:

The Heart Outcomes Prevention Evaluation (HOPE) trial[9] evaluated the benefit of the angiotensin-converting enzyme (ACE) inhibitor ramipril in high-risk patients. Ramipril decreases the development and causes regression of ECG-LVH independent of BP reduction, and these changes were associated with reduced risk of death, MI, stroke, and congestive heart failure. A much smaller HOPE substudy of 38 patients did suggest that office BP measurement might belie the true extent of the antihypertensive effects as nocturnal ambulatory BP reduction averaged 17/8 mm Hg. However, this smaller cohort may have not completely represented the larger HOPE population since they had significant peripheral vascular disease.[34]

In the LIFE trial, 2 reports have studied the relationship between regression of LVH and prognosis. The first trial[10] included 9193 patients with ECG LVH who were randomly assigned to a losartan- or atenolol-based treatment regimen, with follow-up assessments for at least 4 years (mean 4.8 years). The second trial[11] included a total of 941 patients with ECG LVH (enrolled in the first trial) who had their LVM measured by echocardiography at enrollment and thereafter were followed up annually for a mean of 4.8 years for cardiovascular events. In the 2 trials, regression of LVH by both ECG and echocardiographic criteria was significantly correlated with reduction in the incidence of the primary end point (cardiovascular death, MI, and stroke). This correlation was independent of treatment method and BP reduction.

Other trials have demonstrated that regression of LVH is associated with a reduced number of ventricular premature beats,[35] decreased vulnerability to inducible ventricular fibrillation,[36] and less hospitalization for heart failure in hypertensive patients.[37] Furthermore, regression of LVH was associated with improvement of midwall myocardial shortening (MWS),[38] which is a favorable outcome. A reduced midwall shortening is associated with lower exercise performance and has been shown to be an independent predictor of an adverse outcome in hypertensive patients, particularly in patients with LVH. Here, it is worth mentioning that in addition to the accurate measurement of MWS, CMR provides more details about marked regional heterogeneity in hypertensive LVH patients when compared with 2D echocardiography. This was illustrated in a recently published study by our center.[39] This study is the first to compare findings from echocardiographic MWS and magnetic resonance imaging (MRI) tissue tagging in hypertensive LVH patients. Although global MWS by echocardiography and average MRI circumferential strain are similarly depressed in hypertensive LVH, MRI demonstrates severely depressed strain localized to the septum in the face of preserved chamber function, normal end-systolic stress, and similar wall thicknesses. Symmetric concentric LVH does not predict symmetric LV contraction. The observed abnormal strain patterns may represent a novel marker for early regional myocardial dysfunction in LVH patients with otherwise preserved chamber function.

CHOICE OF ANTIHYPERTENSIVE THERAPY

As mentioned above, regression of LVH is associated with a better outcome; therefore, this should be taken into consideration when choosing antihypertensive medications, in addition to other factors. In general, lowering BP, weight loss, and dietary sodium restriction decreases cardiac mass in patients with LVH,[40,41] with effects less prominent among patients with diabetes.[42] However, the regression of LVH during hypertension treatment is not explained entirely by BP control, indicating that the type of therapy plays a major role.

Initial studies showed inconsistent data regarding the differences between the ability of antihypertensive medications in regressing LVH. A detailed analyses of echocardiographic data from the Treatment of Mild Hypertension Study (TOMHS)[14]

assessed changes in LV structure by M-mode echocardiograms in a double-blind placebo-controlled clinical trial of 844 mildly hypertensive participants randomized to nutritional-hygienic (NH) intervention plus placebo or NH plus 1 of 5 classes of antihypertensive agents. The trial concluded that NH intervention with emphasis on weight loss and reduction of dietary sodium is as effective as NH intervention plus pharmacologic treatment in reducing echocardiographically determined LVM. Whereas, in the Department of Veterans Affairs Cooperative Study Group[13] the results of this study showed that in men with mild to moderate hypertension and a high prevalence of LVH, various classes of antihypertensive drugs have disparate effects on LVM. Moreover, at least some of the drug-related differences in reduction of LVM were independent of differences in factors known to affect LVM, such as the magnitude of systolic BP reduction, body weight, level of physical activity, race, and age. After adjustment for these covariates, baseline LVM influenced the results of the study such that, at 1 year, decreases in LVM were noted with hydrochlorothiazide, captopril, and atenolol in the highest tertile, whereas increases were noted with prazosin, diltiazem, and clonidine in the lowest tertile.

The first meta-analysis[12] that included only double-blind, randomized, controlled clinical studies (39 clinical trials), showed that ACE inhibitors seemed to be more potent than β-blockers and diuretics in the reduction of LVM index; calcium channel blockers were intermediate. More recently, this was illustrated in both the Heart Outcomes Prevention Evaluation (HOPE)[9] and the Losartan Intervention For Endpoint Reduction in Hypertension (LIFE)[10,11] trials when LVH regression was achieved "independently" of BP control; a losartan-based regimen was superior to an atenolol-based regimen in reducing LVM. Other studies using more accurate methods to measure LVM, such as CMR and 3D echocardiography, also demonstrated the importance of various types of antihypertensive therapy in regressing LVH.

In the 4E trial (eplerenone, enalapril, and eplerenone plus enalapril),[15] patients with mild to moderate hypertension and echocardiographically determined LVH were randomized to eplerenone, enalapril, or the combination. The primary end point was the change in LVM over 9 months as determined by CMR. Eplerenone was as effective as enalapril in LVH regression and BP control. The combination of eplerenone and enalapril was more effective in reducing LVM and systolic BP than eplerenone alone. In the MRI cohort at the month 9 end point, all 3 treatment groups exhibited significant reductions from baseline in mean systolic BP and diastolic BP. These were statistically comparable, with the exception that systolic BP was reduced significantly more with eplerenone/enalapril than with eplerenone (P=.048). Overall, the rate at which systolic BP normalized occurred in the rank order eplerenone/enalapril >eplerenone >enalapril.

However, post hoc analyses demonstrated only a poor correlation between BP control and LVH regression in any treatment arm. These data suggest that there is no trend favoring greater changes in LVM with greater reductions in BP.

Another study assessed the effects of telmisartan compared with carvedilol on LVM regression.[16] Using 3D echocardiography, telmisartan ($P<.001$) and carvedilol ($P<.001$) progressively reduced LVM index by 21.97±5.84 (15.7%) and 12.31±3.14 (9.1%)g/m^2, respectively. Similar magnitudes of reduction were observed using CMR (15.5% and 9.6%, respectively). Reductions in LVM index achieved with telmisartan were statistically superior to carvedilol ($P\leq.001$) despite similar reductions in blood pressure; a common emerging theme.

A more recent meta-analysis[38] involved a larger number of studies to evaluate the relative efficacy of different antihypertensive medications for their ability to reverse LVH in patients with hypertension. Eighty trials (TOMHS trial was not included) with 146 active treatment arms (n=3767) and 17 placebo arms (n=346) were identified. Adjusted for treatment duration and change in diastolic BP, there was a significant difference (P=.004) among medication classes: LVM index decreased by 13% with angiotensin receptor blockers (ARBs) (95% CI, 8%–18%), 10% with ACE inhibitors (95% CI, 8%–12%), 11% with calcium antagonists (95% CI, 9%–13%), 8% with diuretics (95% CI, 5%–10%), and 6% with β-blockers (95% CI, 3%–8%). In pairwise comparisons, ARBs, calcium antagonists, and ACE inhibitors were more effective in reducing LVM than were β-blockers ($P<.05$). The presumed mechanism is that angiotensin II promotes myocyte cell growth and aldosterone increases collagen content and stimulates development of myocardial fibrosis, making targeting the renin-angiotensin-aldosterone system very attractive, not only for BP control but also for better LVH regression.

AREAS OF UNCERTAINTY

Despite growing knowledge of the clinical importance of detecting and reversing LVH in order to achieve a better outcome, there is no definitive

threshold of LVH regression in g/m^2 to be the target of antihypertensive medications in order to institute a clinically meaningful impact on LVH regression. Also, since the most widely used method to detect LVH, ECG, has a low sensitivity (60% in severe LVH), what is the best way to detect LVH in asymptomatic patients with no evidence of LVH on ECG? Given the gold standard that CMR has been shown to be via a process of its high resolution, low variability, and ability to image completely the heart in 3D without geometric assumptions, it is reasonable to support CMR as the technique of choice. As stated above, the precision of this tool permits orders of magnitude less patients to detect statistically significant regression in LV mass (g/m^2) than echocardiography. It was recently shown that 3D echocardiography has an improved capability as compared with 1D and 2D echocardiography. For similar reasons, it would be reasonable to consider CMR the best method for serial follow-up for LVH regression after initiating appropriate treatment, since both M-mode and 2D echocardiography are not able to detect small changes in LVM, which may be clinically significant. This is already in practice at leading CMR centers, including ours, for judging effectiveness of pharmacologic and surgical therapies.

It is apparent that the penetration of the CMR technique may still represent an uncommon luxury in many settings. Nevertheless, the clinical ramifications of detecting and treating HTN have been obvious for decades, such that the cost to society pales in relation to the relatively low cost of accurate detection. For instance, the cost of a CMR in our institution (Allegheny General Hospital, Pittsburgh, PA) is $1200, but approximately $450 is reimbursed by Medicare (January 2009). This is considerably less than the cost of many antihypertensive medications for the next 12 months. Over the cost of a lifetime, this initial outlay to detect and initiate therapy when amortized over a lifetime is insignificant, especially when balanced against the reduction in the egregious morbidity and mortality.

SHOULD WE HAVE A TARGET FOR LVH REGRESSION?

Finally, scrutiny of the literature reveals a distinct absence of authors willing or able to suggest a suitable threshold for LVH regression. Yet, innumerable trials have demonstrated that regression of LVH is not only possible but that in so doing translates into a reduction in overt events, maintenance of systolic function, aborting of premature congestive heart failure, and reduced cerebrovascular accidents. Thus, this absence of such definable goals is intriguing. Should it be? Is there precedence in the literature for a clinical goal to be achieved upon institution of therapy? Indeed, innumerable examples paint the landscape of cardiovascular therapies such as National Cholesterol Education Program guidelines for cholesterol management, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines for BP reduction, and insulin therapy guided by glycated hemoglobin A_{1c}. Can there be any explanation for the conspicuous exclusion of a goal to be considered for LVH regression? It would appear that the primary reason for this is due to the perceived inability to sufficiently and accurately quantify LVH. As stated above, this issue is no longer a sufficient explanation to mitigate against advancing an achievable threshold since CMR is available. Under the notion that in the Framingham Heart Study cutoff for the upper limit of normal LVM was 125 g/m^2 and 110 g/m^2 in men and women, respectively, by echocardiography, and 72 g/m^2 and 62 g/m^2, respectively, for CMR, thresholding for quartiles of mortality suggests that there is an important incremental benefit achieved once a 15% regression in LVM has ensued. This would result in a goal of 106 g/m^2 and 94 g/m^2 using echocardiography, whereas 62 g/m^2 and 53 g/m^2 would be the goal via CMR in men and women, respectively. This target (Table) provides clinicians a suitable objective and worthwhile pursuit to accomplish, in addition to achieving BP goals.

SUMMARY

Hypertension is a major risk factor for cardiovascular and cerebrovascular adverse events. It affects every major organ in the human body, leading to devastating consequences such as stroke, MI, heart failure, renal failure, blindness, and sudden death. This, in turn, has an enormous clinical and socioeconomic impact. Moreover, hypertension is a mostly asymptomatic disease in initial stages and by the time it is diagnosed, evidence of end-organ damage will be present. In clinical practice, it is important to identify early damage to these organs, which, in turn, helps to predict the long-term prognosis and thus leads to timely preventive measures.

In conclusion, LVH represents generally an early preclinical, but a late recalcitrant, hypertensive lesion affecting the heart and cardiovascular system, associated with an increased risk of mortality and morbidity several-fold above the risk due to hypertension

Table. Representation of the Upper Limits of Normal for Men and Women by Echocardiography and Cardiovascular Magnetic Resonance Imaging, Along With Proposed Goals for Left Ventricular Hypertrophy Regression by Pharmacologic Intervention

	Men		Women	
	Upper Normal Limit	Goal of Reduction	Upper Normal Limit	Goal of Reduction
Echocardiography	125 g/m^2	≤106 g/m^2	110 g/m^2	≤94 g/m^2
Cardiovascular magnetic resonance imaging	72 g/m^2	≤62 g/m^2	62 g/m^2	≤53 g/m^2

Note: the overestimation of echocardiographic-determined left ventricular mass is well recognized and has been reported by many authors. The ability to resolve the endocardium and distinguish finite trabecular myocardium vs a coalescing of the trabeculations, as well as complete interrogation of 3-dimensional mass vs 2-dimensional estimations help to explain the generally lower quantitated mass by cardiovascular magnetic resonance imaging. Adapted from Nadour et al.[43]

alone. Therefore, early detection and initiation of appropriate treatment leads to improved outcomes with lower mortality and morbidity. CMR appears to provide the best technique to detect and track LVH, helping to facilitate institution of pharmacologic therapies aimed at reducing the growing morbidity and mortality of LVH. We propose that a secondary goal of BP control is to target a 15% regression in LVM to achieve further reductions in clinical events. To our knowledge, this is the first consideration advocating such a strategy. Incorporation of this approach into imminent JNC proclamations would not only underscore the need for more aggressive treatment of LVH but lead to individualized strategies based on objective findings not guided simply by BP. We believe this would translate into marked clinical benefit with far-reaching socioeconomic ramifications.

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