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Is Left Ventricular Hypertrophy a Valid Therapeutic Target?

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Abstract

Purpose of Review The purpose of this review is to answer the question whether left ventricular hypertrophy (LVH) could be considered a therapeutic target in patients with hypertension. To fulfill this purpose, we briefly outline different methods of measuring LVH, then discuss the current evidence and unresolved controversies regarding the relationships among LVH, blood pressure (BP), and cardiovascular disease (CVD) outcomes.

Recent Findings The methods and criteria used for defining LVH in clinical studies lack consistency and are inherently different. Electrocardiogram (ECG) has been the most common method, but some studies used echocardiography, and recently, the cardiac magnetic resonance imaging was used by some studies as well. Regardless of the method, studies have shown that higher BP is a risk factor for LVH, regression of LVH is possible by successful BP lowering, and LVH is associated with CVD outcomes. Nevertheless, recent trials revealed that although intensive BP lowering (systolic BP target of < 120 mm of Hg) resulted in lower rates of developing new ECG-LVH and higher rates of regression of existing LVH, the benefit of intensive BP lowering on the risk of CV events was not meaningfully influenced by its favorable effect on ECG-LVH. These findings raise several critical questions about the mechanistic links between hypertension treatment, LVH regression, and reduction in CV events. Given these questions and findings, LVH improvement cannot yet be considered a reliable surrogate outcome measure for use in the context of hypertensive heart disease.

Summary LVH is a modifiable risk factor related to systolic BP and regression of LVH may reduce subsequent CV events. However, LVH may not be the "holy grail" in regard to therapeutic targets in hypertensive heart disease, but it could be considered one of the markers in the successful management of hypertension.

Keywords Systolic blood pressure · Left ventricular hypertrophy · Regression · Cardiovascular disease

Introduction

Hypertension remains a major public health problem associated with considerable morbidity and mortality [1]. An increase in left ventricular (LV) wall stress is the principal mechanical factor in the development of LV hypertrophy (LVH). In observational studies, LVH, measured as increased LV mass (LVM), is the strongest independent predictor of cardiovascular disease (CVD) events after age, with an average risk ratio of 2.5 for overall CV events, including myocardial infarction (MI), heart failure (HF), stroke, and death [2, 3]. Although the development of LVH has been related to a number of other conditions, including obesity and aortic stenosis, hypertension is the most well-known underlying condition [4–6]. In addition, studies have shown that LVH can precede the development of hypertension and that LVH associated with blood pressure (BP) in the normal range confers the same CV risk as established hypertension [7–11]. Despite the wealth of literature linking electrocardiographic and echocardiographic LVM to increased CV risk, LVH is not routinely screened for unlike other traditional risk factors. The purpose of this review is to answer the question whether LVH could be considered a therapeutic target in patients with hypertension. It briefly outlines the different ways of measuring LVH, and highlights the relationship of LVH to CV outcomes, recent advances, and some unresolved controversies.

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What Is LVH?

LVH, as defined by increased LVM, can occur either through ventricular dilation or wall thickening. However, the increase in LVM is not the only attribute that is changed in LVH [12]. LVH can be the result of diverse etiologies, and is characterized by pathological changes in myocardial tissue characteristics on the genetic, molecular, cellular, and tissue level beyond a simple increase in the number of otherwise normal cardiomyocytes [12]. The mechanisms responsible for progression to hypertrophy include not only a response to the mechanical stress from increased BP but also the influences of neurohormones and cytokines [13, 14]. In addition, there is a considerable interindividual variability in the LVH response to hypertension. For example, African Americans compared with Caucasians have increased LVM [14, 15]. Additionally, co-morbid conditions like obesity, diabetes mellitus, and coronary artery disease can also affect the pattern of LVH.

Measurement of LVH

LVH diagnosis and the criteria used for defining LVH in clinical studies lack consistency. In clinical practice, the electrocardiogram (ECG) is usually the first method used for assessing for the presence of LVH. Many different validated criteria are available. These ECG criteria generally have high specificities and low sensitivities; that is, a normal ECG does not exclude the presence of LVH. The principal ECG-derived diagnostic characteristics for LVH detection include an increased QRS complex amplitude and duration, a leftward shift of electrical axis of the QRS in the frontal plane, and ST segment deviation and T wave changes associated with left ventricular strain [15]. M-mode echocardiography is frequently used in clinical studies and detects all but the mildest degrees of LVH. However, M-mode echocardiography has substantial measurement variability and significant rates of non-evaluability (33% in the Cardiovascular Health Study resulting in assessment bias [9, 16]. Data from three-dimensional echo investigations are scarce and its reproducibility has been insufficiently studied.

Cardiac magnetic resonance imaging (CMRI) provides three-dimensional coverage of the LV without image quality limitations related to ultrasound transmission and is thus more accurate in estimating dimensions of the LV than echocardiography. CMR has been extensively compared to echocardiography for the assessment of LVM, specifically in patients with hypertension, and shown to have greater accuracy and reproducibility as well as much lower variability and rates of non-evaluability [17, 18•, 19]. This is true even with the newer harmonic and contrast echo techniques [20]. In studies of LVM regression, these features of CMR allow for sample sizes that are 10% of those needed for echocardiography, which more than offset the cost differential between these imaging modalities [18•]. For example, a study seeking to detect a 10-g reduction in LVM following a therapeutic intervention with 90% power and $P < 0.05$ would require a sample size of $n = 273$ by echocardiography, but only $n = 9$ by CMR [18•]. Thus, CMR is the in vivo reference standard for measuring LVM [21–23].

However, even considering the advantages of CMR estimates of LVM over echocardiography or ECG, discrepancies between ECG-LVH criteria and LVM persist. Since the hypertrophied myocardium is pathologically altered in more ways than just an increase in LVM, it is apparent that ECG-LVH has to move beyond estimation of LVM [12]. Importantly, both diffuse and focal slowed conduction velocities in the LV myocardium result either in an increased QRS voltage or in QRS patterns consistent with ECG findings in LVH despite an unchanged LVM [12]. Furthermore, changes in LVM can result from diverse etiologies, including number of and size of cardiomyocytes, edema, fatty infiltration, and ischemic cellular changes [24, 25]. These complex changes are not easily captured by a modality that depends on electrical activity such as ECG [24]. Taken together, LVH by ECG and LVH by imaging are likely to be two distinct but related phenotypes [24], as they measure diverse things.

LVH and Systolic Blood Pressure

Observational studies have demonstrated linear associations between higher systolic BP and LVH. LVH prevalence varies with severity of hypertension, ranging from < 20% in mild hypertension to almost 100% in severe or complicated hypertension [26]. The Framingham Heart Study showed that even mild increases in BP are associated with increased LVM [27]. There is evidence that hypertension-related LVH is more closely associated with 24-h BP averages and BP variation than with clinic BP readings [28–30]. Studies showed a strong association between higher levels of systolic BP and ECG-LVH. There was a dose-response relation between systolic BP and ECG-LVH; the prevalence of ECG-LVH almost doubled as the levels of systolic BP increased in severity from normal BP to elevated BP to stage-1 hypertension to more severe hypertension [31]. A similar dose-response relation between SBP and the prevalence of ECG-LVH has been reported in the Framingham Heart Study [4]. Similarly, studies in which LVH was ascertained by imaging (imaging-LVH) have shown a linear relation between increasing prevalence of LVH with higher levels of systolic BP [32–34]. The similarity between ECG-LVH and imaging-LVH in relation to SBP in these studies supports the current practice of using ECG-LVH in studies examining the impact of resting casual BP on LVH.

BP Lowering and LVH

Several prior reports showed that regression of LVH can occur in response to interventions aimed at lowering high BP; hence,

there is little debate about the favorable effect of lowering BP on LVH. However, these studies were not designed to examine whether lowering BP beyond a standard goal of < 140 mmHg is associated with greater reduction of the risk of LVH [35–37]. In addition, there are limited data from randomized trials examining the effect of BP lowering on LVM, and whether reducing LVM reduces risk of major CVD events independent of BP changes [38–41]. In a meta-analysis of randomized trials, regression of echocardiographic LVM was associated with BP lowering and multivariable meta-regression analysis showed regression of LVM was more pronounced with larger reductions in systolic BP [42]. However, all these studies compared the treatments between 2 different antihypertensive agents, without a placebo or usual care arm, and the final BPs in both treatment groups were similar. Furthermore, it is not known whether lowering BP beyond what is recommended would be associated with greater regression of LVH.

Intensive Systolic BP Lowering and LVH

In the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD) trial of patients with both hypertension and diabetes mellitus, intensive SBP lowering (< 120 mmHg) was associated with a 39% lower risk of electrocardiographic LVH compared to standard BP lowering (SBP < 140 mmHg) [43•]. Similar results were reported from a small clinical trial in which SBP lowering to < 130 mmHg was compared with a goal of < 140 mmHg in adults ≥ 55 years of age without diabetes mellitus [44]. In a recent report from the large landmark hypertension trial of patients without diabetes [Systolic BP Intervention Trial (SPRINT)], intensive BP lowering resulted in lower rates of developing new ECG-LVH and higher rates of regression of existing LVH [45•]. Hence, successful BP lowering is expected to reduce the prevalence of new occurrence of LVH and enhance regression of existing LVH. Currently, SPRINT-HEART is looking at the relationship between intensive BP lowering and the gold standard, LVM assessed by CMRI.

Antihypertensive Drug Classes and LVH Regression

There has been extensive recent debate regarding whether specific antihypertensive drug classes have greater effect on regression of LVH in patients with hypertension [46]. While some studies showed no difference among the four main antihypertensive classes (angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), beta blockers (BBs), calcium channel blockers (CCBs), and diuretics) in reducing LVH, others suggested ACEIs, and to a lesser extent CCBs, are more effective than BBs and diuretics [42, 47•]. The few studies that examined other classes of antihypertensive drugs suggest that vasodilators do not reduce LVH and may in fact worsen it [48]. Studies have also shown that LVH regression is not uniformly seen with BP reduction [49]. Further, patient characteristics such as older age, kidney disease, female sex, obesity, and metabolic syndrome can affect the LVM regression [50–52]. Overall, most current society guidelines indicate that successful lowering of BP is more important than the selection of individual antihypertensive classes in preventing or reversing LVH [REF]. However, some practice guidelines have included statements about considering a specific antihypertensive medication class for its potential benefit on LVH, e.g., ACEIs and/or excluding a class, e.g., direct vasodilators [53, 54].

LVH and Cardiovascular Outcomes

LVH by both ECG and imaging has been associated with worse CV outcomes [38, 55–59]. In the Framingham Heart Study, patients with no known CVD and severe ECG-LVH had three times the risk of composite CV outcomes compared to patients with no known CVD and mild ECG-LVH [55]. Similarly, hypertensive patients in the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study with severe ECG-LVH was 14% more likely to have a composite CV outcome compared to those with mild ECG-LVH [38]. Increased LVM versus normal LVM on echocardiography results in nearly two times the risk of both CV death and all-cause mortality. These findings hold up even after correction for systolic BP and ECG-LVH [2, 56]. Additionally, severe imaging-LVH versus mild imaging-LVH has been associated with close to three times the risk of stroke after controlling hypertension [57].

Impact on LVH Regression to Cardiovascular Disease Risk

The regression of LVH by both ECG and imaging has been associated with a reduced risk of CV events [38, 60]. In both studies, the reduction in LVM was predictive of a lower rate of events independent of the degree of BP reduction, as well as other potential confounders. Similarly, risk of composite CV outcomes was cut in half in males in the Framingham Heart Study who had decreasing serial ECG-LVH [55]. The rate of HF admissions after ~ 5 years of follow-up was also decreased in patients with serial regression of ECG-LVH [61]. However, a large meta-analysis that included 12,809 participants with 2259 events failed to show a significant relationship between LVH (both imaging and ECG-LVH) changes and clinical events [62•]. Supporting this, the recent results from SPRINT showed that the benefit of intensive BP lowering on the risk of CVD events was not meaningfully influenced by its favorable effect on ECG-LVH [45•]. This post hoc analysis of SPRINT found that adjusting for ECG-LVH as a time-varying covariate did not significantly affect the primary CV

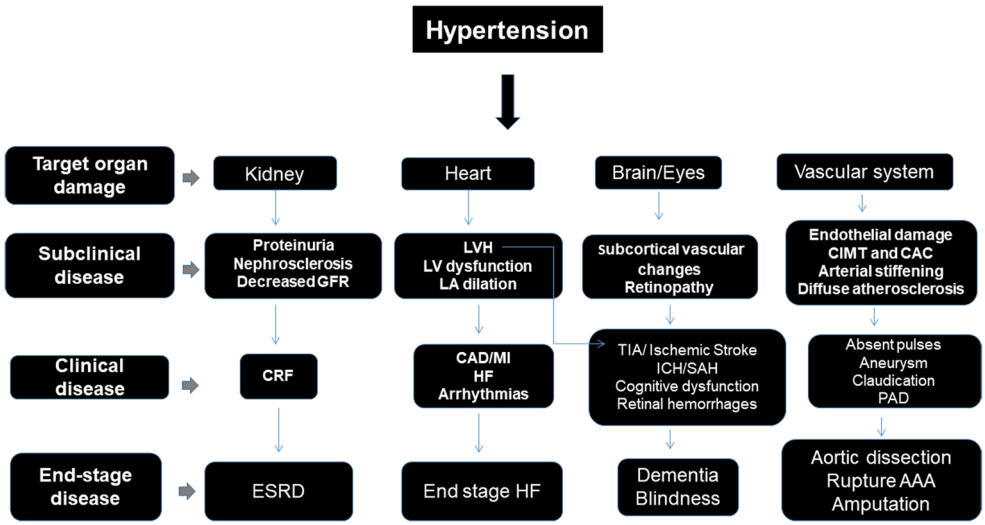

Fig. 1 Hypertensive heart disease: from hypertension to target organ damage. GFR, glomerular filtration rate; LVH, left ventricular hypertrophy; LV, left ventricle; LA, left atrium; CIMT, carotid intima-media thickness; CAC, coronary artery calcification; CRF, chronic renal failure; CAD, coronary artery disease; MI, myocardial infarction; HF, heart failure; TIA, transient ischemic attack; ICH, intracerebral hemorrhage; SAH, subarachnoid hemorrhage PAD; peripheral arterial disease; ESRD, end stage renal disease; AAA, abdominal aortic aneurysm

outcomes (HR 0.76 with 95% CI 0.64–0.9 vs HR 0.77 with 95% CI 0.65–0.91). Similarly Cao et al. showed that SBP partially explains the association of ECG-LVH with CVD mortality, but ECG-LVH virtually has no impact on the SBP associations [31]. In addition, prior studies have shown that a risk of HF persists even after LVH regressions, suggesting that hypertension-induced adverse myocardial changes are not limited to increased LVM alone [60]. This suggests that LVH is probably only one of many factors by which SBP exerts its impact on CVD. Another possible explanation is that LVH may mediate the effect of intensive BP lowering on certain CVD outcomes but not others. Hypertension can also cause diffuse endothelial dysfunction, vascular hypertrophy, atherosclerosis, increased platelet activation, prothrombotic, and proinflammatory states. Increased production of reactive oxygen species and decreased nitric oxide bioavailability have been suggested as a hallmark of endothelial dysfunction and a pathogenetic mechanism in atherosclerosis. For this reason, hypertension has also been called a vascular disease [63, 64]. All of these factors ultimately contribute to target organ damage. Likewise, neurohormonal activation, especially excess sympathetic activity and renin-angiotensin-aldosterone system activation, may drive myocardial changes independently of BP, and sympathetic neural mechanisms also have an arterial stiffening effect [65]. SPRINT-HEART results will assess the mechanistic link between LVM and CVD reduction with BP lowering.

Is Left Ventricular Hypertrophy a Valid Therapeutic Target?

The answer to this question is less certain. As discussed previously, several studies suggested that LVH is a modifiable risk factor related to SBP and that regression of LVH may reduce subsequent CV events and death. However, several critical questions must be answered before LVH can be used as a therapeutic target, primarily because the critical mechanistic links between hypertension treatment, LVH regression, and reduction in CV events are not well understood, especially in the lower BP range as tested in SPRINT. Given these considerations, LVH improvement cannot yet be considered a reliable surrogate outcome measure for use in the context of hypertensive heart disease. While LVH is not the "ultimate" therapeutic target, as shown in Fig. 1, LVH appears to be a biomarker that reflects the effect of long-term uncontrolled hypertension on a target organ in addition to the kidney, brain, and eyes. LVH is probably the best example of target organ damage that correlates with CV risk.

Conclusion

LVH is a modifiable risk factor related to SBP and regression of LVH may reduce subsequent CV events. However, mechanistic links between hypertension treatment, LVH regression, and reduction in CV events are not well understood, especially in the lower BP range. Overall, LVH is not the "holy grail" in regard to therapeutic targets in hypertensive heart disease, but could be considered an important biomarker in the successful management of hypertension.

Compliance with Ethical Standards

Conflict of Interest Jeremy Earl Brooks declares that he has no conflict of interest.

Elsayed Z. Soliman declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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