Regression of left ventricular hypertrophy: lessons from clinical trials

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Abstract

Introduction

Hypertension is an epidemic that affects more than 1 billion people worldwide annually. Left ventricular hypertrophy is the phenotypic expression of hypertensive heart disease, which depends on complex interactions among genetic makeup, environmental factors and lifestyle. Left ventricular hypertrophy has been shown to be independently associated with adverse cardiovascular morbidity and mortality. Targeting left ventricular hypertrophy with different pharmacological agents and lifestyle modifications has been associated with favourable results and results in improved outcome. Evidence shows that the drug targets rennin-angiotensin-aldosterone are more effective system in reducing left ventricular mass. Moving forward, the new frontier in this field will be to understand the genetic influences on left ventricular hypertrophy regression and progression and ways to intervene early and treat this public health burden.

Conclusion

Targeting left ventricular hypertrophy regression with various anti-hypertensive agents results in improved clinical outcomes. Therefore regression of LVH can be considered surrogate endpoint in the treatment of hypertensive heart disease.

Introduction

Hypertension affects approximately 1 billion of population worldwide and approximately 50 million in USA annually. Increase in blood pressure (BP) has been shown consistently to increase the risk of cardiovascular morbidity and mortality through end-organ dysfunction. This risk appears to be linear and independent of other cardiovascular risk factors.

Left ventricular hypertropy (LVH) is the phenotypic expression of hypertensive heart disease. In response to increased afterload in hypertensive patients, LV mass increases as an adaptive process to reduce LV wall stress. However, if the increase in the afterload persists, the adaptive response turns maladaptive. The data from Framingham cohort and work by other investigators demonstrate that this increase in LV mass independently predicts cardiovascular morbidity and mortality. There is good evidence supporting pharmacological therapies and lifestyle modifications targeting BP, during which LVH translates into improved clinical outcome. This paper discusses outcomes of clinical trials on regression of LVH.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Prognostic implication of left ventricular hypertrophy

There is robust data indicating association between LVH and increased cardiovascular morbidity and mortality (Table 1). Levy et al.¹ reported that LVH, quantified by echocardiography, independently predicts cardiovascular morbidity and mortality. A total of 3320 participants, aged more than 40 years and free of cardiovascular disease, were enrolled in the Framingham Heart Study for 4 years¹. There were total 208 cardiovascular events, 37 cardiovascular deaths and 124 all-cause deaths. The relative risk (RR) for developing cardiovascular disease was 1.49 in men and 1.57 in women for every 50 g/m² increase in the LV mass above normal. This increment was also associated with higher all-cause mortality (RR = 1.49 and 2.01 in men and women, respectively) and cardiovascular mortality (RR = 1.73 and 2.12 in men and women, respectively). Data from the same cohort also showed that LVH increased the risk of sudden cardiac death, more so in men than women⁴.

Hypertensive black adults tend to have higher LV mass odds ratio (OR) = 1.80; 95% CI: 1.29 – 2.51 and OR = 2.50; 95% CI: 1.58 – 3.96, LVH indexed to height and body surface area BSA, respectively) and relative wall thickness when compared with their Caucasian counterparts. In the black population, LVH portends greater cardiovascular risk as compared with other ethnic groups⁴ and women fare worse as compared with...
Current evidence suggests that LVH can be targeted through reducing BP by pharmacotherapy and lifestyle to concentric LVH phenotype, which has been independently associated with worse outcomes. Verdecchia et al. showed that for each 29 g/m² increase in LV mass, there is a significant independent increase in the risk of stroke (RR = 1.31; 95% CI: 1.09 – 1.58) in hypertensive patients. In a meta-analysis of 20 studies with 48,545 patients, Vakili et al. found that LVH consistently predicted worse cardiovascular morbidity and all-cause mortality across all groups and population except end stage renal disease (ESRD) patients. Mean adjusted risk rates for cardiovascular morbidity and all-cause mortality were 2.3 and 2.5, respectively.

**Critical appraisal of the validity of relevant articles**

**Left ventricular hypertrophy regression**

Current evidence suggests that LVH can be targeted through reducing BP by pharmacotherapy and lifestyle.

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All antihypertensive drugs appear to have some effect on LVH regression (Figure 1). While there is no consensus on the best pharmacological agent to regress LVH, the current evidence favours the drug-targeting renin–angiotensin–aldosterone system (RAAS). Data from bench research showed that activation of the RAAS system causes hypertrophy of cardiomyocyte, much akin to load-induced hypertrophy and fibrosis, both of which are mediated by angiotensin II via angiotension-1 (AT-1) receptor.16 It has been shown that manipulation of the RAAS system translates to LV regression and outcomes are improved clinically, angiotensin receptor blocker (ARB) seems to have additional class action on LVH regression, independent of BP control, as shown in numerous clinical trials.

The Losartan Intervention for Endpoint Reduction in a Hypertension (LIFE) study showed that losartan-based antihypertensive regimen resulted in a greater reduction in LV mass index from baseline as compared with atenolol-based regimen across all strata (−21.7 ± 21.8 vs. −17.7 ± 19.6 g/m², P = 0.021).11 This reduction was independent of the baseline LV mass index and BP. There was a change in LV geometry and reduced concentricity in both the arms and lesser increment in LV internal diameter with losartan-based treatment. Similar reduction in LV mass was documented using three-dimensional echocardiography and magnetic resonance imaging (MRI) among the hypertensive patients treated with telmisartan as compared with carvedilol.12 In a Heart Outcome Prevention (HOPE) Study, patients at high risk for CAD were randomly assigned to receive ramipril and placebo, and followed up prospectively for 4.5 years. The study patients treated with ramipril were protected against LVH and regression of LVH was independent of BP with ramipril treatment.13 The Left ventricular hypertrophy study, Indapamide Versus Enalapril (LIVE study) was a prospective, double-blind study that compared indapamide SR 1.5 mg and enalapril 20 mg in reducing LV mass index in hypertensive patients with LVH.14 At the end of 48 weeks, indapamide significantly reduced the LV mass index from the baseline (−8.4 ± 30.5 g/m² from baseline; P < 0.001); whereas enalapril did not (−1.9 ± 28.3 g/m²) despite the fact that both the drugs significantly reduced BP. Also, the change in LV mass index did not correlate with BP and indapamide progressively reduced the wall thickness throughout the study period. Similarly, the Prospective Randomised Enalapril Study Evaluating Reversal of Ventricular Enlargement (PRESERVE) study evaluated if antihypertensive treatment with enalapril induces greater LVH regression than nifedipine by > 10 g/m² despite equivalent BP reduction.15 A total of 303 patients were followed up for 1 year and there was no difference between the groups in terms of LVH regression from the baseline.

It is not clear whether dual blockade of RAAS with different pharmacological agents will incur incremental benefit in BP control and LV mass reduction. The 4E-Left Ventricular Study was a double-blind study, which studied LVH regression among groups treated with eplerenone, enalapril and eplerenone/enalapril.16 At the end of 9 months, changes in LV mass were assessed by MRI. The decrease in LVH mass from baseline was statistically significant in all three groups. The eplerenone/enalapril arm was most effective in terms of absolute reduction in LV mass. There was poor correlation between antihypertensive effect of the drug and reduction in the LV mass. However, the data from other studies suggest that there was no additional benefit with dual RAAS blockade. The combination of ramipril and telmisartan had a similar effect on LVH than ramipril alone among the patients at high vascular risk.17 A similar result was reported from Aliskiren in a Left Ventricular Hypertrophy (ALLAY) trial.18 A total of 465 patients with hypertension, increased ventricular wall thickness and body mass index > 25 kg/m² were randomised to receive aliskiren 300 mg, losartan 100 mg, or their combination daily for 9 months. Cardiac MRI was used to assess LV mass at the baseline and at completion of study. In all the three arms, LV mass regressed significantly from the baseline (−4.9, −4.8, and −5.8 g/m² reductions in the aliskiren, losartan, and combination arms, respectively; P < 0.0001 for all three arms). However, there was not much difference between monotherapy and combination therapy independent of BP. The Treatment of Mild Hypertension Study (TOMHS) compared the effects of both pharmacological and non-pharmacological approaches with the treatment of hypertension on LVH regression. It was a double-blind, placebo-controlled trial involving 844 patients with mild hypertension.19 The patients were advised weight loss and dietary salt reduction, nutrition-al-hygienic intervention (NH), or NH intervention and randomised to one of the five classes of antihypertensives: (1) chlorthalidone (a diuretic); (2) acebutolol (a β-blocker); (3) doxazosin (an α-antagonist); (4) amlopidine (a calcium channel antagonist); or (5) enalapril (an angiotensin-converting enzyme inhibitor). After a follow-up of 4 years, NH intervention was as effective as NH intervention and pharmacological intervention in reducing LV mass. Interestingly, there was a smaller decrease in BP in the

ACEI angiotensin converting enzyme inhibitor; BB beta-blocker.

Figure 1: LVH regression with antihypertensive treatment. LVH, left ventricular hypertrophy; ARB angiotensin-receptor blocker; CCB calcium channel blocker; ACEI angiotensin converting enzyme inhibitor; Diuretic; BB beta-blocker.

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NH intervention only arm (9 vs. 13 mmHg). All the groups showed a significant decrease in LV mass from baseline and addition of chlorthalidone had modest additional effect on reducing LV mass. Recent analysis of data from the Multiple Risk Factor Intervention Trial (MRFIT) showed that the chlorthalidone-treated cohort had greater LVH regression than the hydrochlorothiazide-treated and usual care groups. This effect was thought to be secondary to greater reduction in BP with chlorthalidone.

In a meta-analysis, Klingbeil et al. identified 80 trials with 146 treatment arms (3767 patients) and 17 placebo arms, and the data were adjusted for treatment duration and diastolic BP. They found a significant difference among different medication classes (P = 0.004). Overall, LV mass index was decreased by 1.3% with angiotensin II receptor antagonists (95% CI: 8 – 18), by 11% with calcium channel antagonists (95% CI: 9 – 13), by 10% with ACE inhibitors (95% CI: 8 – 12), by 8% with diuretics (95% CI: 5 – 10), and by 6% with β-blockers (95% CI: 3 – 8) (Figure 1).

Recently, the focus has been shifted to downstream pathways and oxidative stress in the pathogenesis of LVH. Previous studies have shown that allopurinol reduces oxidative stress. In a recent randomised, double-blind, placebo-controlled study, allopurinol 600 mg/day was shown to reduce absolute LV mass (~2.65 ± 5.91 vs. +1.21 ± 5.10 g in the placebo group, P = 0.012) and LV mass indexed to body surface area (~1.32 ± 2.84 g/m² vs. +0.65 ± 3.07 g/m² in the placebo group, P = 0.017) in patients with type II diabetes mellitus. Non-pharmacological intervention and lifestyle changes aimed at LVH regression involve weight loss, aerobic exercise and low-salt diet.

**Left ventricular hypertrophy regression and outcome**

LVH is an adaptive response by the human heart targeted to maintain cardiac output in the face of increased pressure and or volume overload. This compensatory response ultimately regresses into a maladaptive one causing heart failure. This transition is basically determined by the complex interplay of environmental, neurohormonal and genetic factors.

Over the last two decades, our understanding of the pathophysiology of LVH has greatly improved. As a result, attempts to stem or reverse this phenotypic response using pharmacological agents and lifestyle modifications have been fruitful and new novel approaches are being explored.

Regression of LVH is independently associated with improved cardiovascular outcome (Table 2). Levy et al. reported reduction in LVH using Cornell voltage criteria was associated with improved cardiovascular outcome in men and women (OR = 0.46, 95% CI: 0.26 – 0.84 and OR = 0.56, 95% CI: 0.30 – 1.04, respectively) after adjusting for age and baseline voltage; whereas worsening or no serial change conferred worse outcome. In the same study, the severity of LVH at baseline predicted the outcome in graded manner with the lower quartile associated with lower risk than the highest quartile. In the LVH regression sub-study of the HOPE Trial, LVH prevention/regression significantly reduced primary outcome of cardiovascular death, myocardial infarction and death (12.3% vs. 15.4%, P < 0.006) and congestive heart failure (9.3% vs. 15.4%, P < 0.0001) when compared with LVH persistence/progression. In both the studies LVH was defined by EKG criteria which is less sensitive to echocardiography in defining LVH. Regardless, this association holds even when echocardiography is used to define LV mass.

Verdecchia et al. followed 430 patients with serial echocardiography and 24-hour ambulatory BP monitoring from the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA) registry. Total duration of follow-up was 1217 patients/year. They showed a reduction in LV mass.
among the patients with essential hypertension, predicts lower cardiovascular risk [hazard ratio (HR) = 0.46, 95% CI: 0.22–0.99, P < 0.04] adjusted for baseline LVH. In the same study, the event rate was lower among the subset of patients with LV mass > 125 g/m² with LVH regression than the patients whose LV mass remained persistently elevated (1.58 vs. 6.27 events per 100 person-years; P = 0.002). In a meta-analysis, the same group showed association between LVH regression and lower cardiovascular decrease events²⁷. A total of 1064 hypertensive patients from four studies were included in the analysis and showed that LVH regression reduced the risk of subsequent cardiovascular disease (OR = 0.41, 95% CI: 0.21–0.78, P = 0.007) as compared with lack of

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PUIMA: Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (Italian Cardiovascular study) ; LVH, left ventricular hypertrophy; ECG-electrocardiogram, BP-blood pressure, CHF-congestive heart failure, MI-myocardial infarction, DM-diabetes mellitus.
regression or development of new LVH.

In the LIFE Echo Study, 941 patients aged between 55 and 80 years with essential hypertension and echocardiographic and echocardiographic evidence were followed for a mean of 4.8 for composite endpoint of cardiovascular death, fatal and nonfatal myocardial infarction and fatal or nonfatal stroke. The composite endpoint occurred in 11% of the patients and Cox regression analysis showed a strong association between LVH regression with treatment and composite endpoint [HR = 0.78 per 1-SD (25.3) decrease in LV mass index; 95% CI: 0.65 - 0.94; P = 0.009] independent of reduction in the BP and assigned treatment. There was a parallel independent association between LVH regression and lower cardiovascular mortality, all-cause mortality and myocardial infarction.

Interestingly, regression or absence of progression of LV mass has been reported to be associated with lower incidence of diabetes mellitus. In addition, LVH regression has been reported to improve LV systolic performance. A total of 679 hypertensive patients with electrocardiogram (ECG) evidence of LVH from the LIFE sub-study were followed with a yearly echocardiogram during 3 years of antihypertensive treatment. During this period, the mean BP reduction and LV mass regression were approximately 15% and 17%, respectively, and the stress-corrected mid-wall fractional shortening increased from 97 ± 13 to 105 ± 12% (P < 0.001). This improvement was independently inversely related to changes in LVM (β = −0.211) and relative wall thickness (RWT) (β = −0.334). Thus, LVH regression also improved LV systolic function.

**Conclusion**

LVH is a result of complex interaction among genetic makeup, lifestyle and environment factors. It represents the end organ dysfunction in HTN and other disease. Multiple studies have shown that LVH is an independent risk factor of increased cardiovascular morbidity and mortality and is of major public health burden. Evidence suggests that targeting LVH regression is possible and results in improved clinical outcomes. Therefore regression of LVH can be considered surrogate endpoint in the treatment of hypertensive heart disease. Among various drugs, the ones targeting RAAS, in particular ARBs, appear to have class actions in reducing LV mass independent of BP control. More recently, allopurinol, which reduces oxidative stress at tissue level, may reduce LV mass in type II diabetes mellitus. It remains unclear if this reduction in LV mass translates into improved outcome.

In the last two decades, there have been dramatic advances in personalised medicine and personalised risk prediction. However, attempts to understand and predict the risk associated with LVH through genomics have been a mixed bag of success. This is because the complex phenotype of LVH is not in its entirety and stems from our genetic constitution rather than its interaction between environment and our lifestyle. Moving forward, the new frontier in this field will be to understand the genetic architecture through new study design and genomic technologies and identify its impact on progression and/or regression of LVH.

**Clinical applicability**

LVH is phenotypic expression of end organ dysfunction associated with increased stroke work modulated by complex interplay of genetic make of an individual, life style and environment. As discussed above it is independently associated with increased cardiovascular morbidity and mortality. LVH regression through pharmacological intervention and life style modification has positive prognostic impact on cardiovascular morbidity and mortality independent of blood pressure reduction. Therefore, it can be used a surrogate marker assessing the treatment effect of antihypertensive treatment on prognosis. Tailoring of antihypertensive regimen to consist of various pharmacological agents that mechanistically act on different levels may be more effective in regressing LV mass and could translate into better clinical outcomes.

**Abbreviations list**

ALLAY, Alikiren in a Left Ventricular Hypertrophy study; BP, blood pressure; CAD, coronary artery disease; HOPE, Heart Outcome Prevention study; HR, hazard ratio; LIFE, Losartan Intervention for Endpoint Reduction in a Hypertension study; LVH, left ventricular hypertrophy; MRI, magnetic resonance imaging; MRFIT, Multiple Risk Factor Intervention Trial; NH, nutritional-hygienic; PIUMA, Progetto Ipertensione Umbria Monitoraggio Ambulatoriale; PRESERVE, Prospective Randomised Enalapril Study Evaluating Reversal of Ventricular Enlargement study; RAAS, renin-angiotensin-aldosterone system; RR, relative risk; TOMHS, Treatment of Mild Hypertension Study.

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