Cardiac remodeling in systemic hypertension

Satish Kenchaiah, MD, MPH\textsuperscript{a,b,*},
Marc A. Pfeffer, MD, PhD\textsuperscript{a,c}

\textsuperscript{a}Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA
\textsuperscript{b}Boston University School of Medicine, Boston, MA, USA
\textsuperscript{c}Partners Healthcare System, Boston, MA, USA

The cardiac chambers adapt in configuration and mass to the external work requirements. In utero right and left ventricular size and configuration are relatively similar. With an infant’s first breath dramatic changes in pulmonary and systemic vascular resistances occur so that the workload of the right ventricle becomes proportionally lower than that of the left ventricle. After birth, the proportional growth of the left ventricle exceeds the right in concert with their respective evolving hemodynamic patterns. The differential growth pattern of these chambers reflects the adaptive biologic hypertrophic response that continues to match structure to workload. So too across various species of adult animals a close relationship exists between cardiac chamber weight and stroke work [1]. These relationships between organ size and function underscore one of the basic biologic compensatory properties: inherent ability to increase or decrease mass (hypertrophy or atrophy) and to alter tissue configuration in direct relationship to functional requirements.

Historical perspective

Pathologic associations, such as shrunken kidneys with heavy hearts, in subjects with “hardened arteries” are generally attributed to Bright [2].

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* Corresponding author.
E-mail address: skenchaiah@rics.bwh.harvard.edu (S. Kenchaiah).

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It was Johnson [3], however, who apparently first associated elevated blood pressure (BP) with left ventricular hypertrophy (LVH). The ability of the heart to respond to elevated BP by augmenting ventricular mass was reported over 70 years ago in an animal model of hypertension produced by renal ischemia [4]. Chanutin and Barksdale [5] demonstrated a clear relationship between the height of the BP elevation and the increase in the heart weight to body surface area with the production of experimental hypertension. Moreover, they demonstrated that the weight of the heart was increased as a consequence of increased myocyte fiber diameter, a clear indication of hypertrophy rather than hyperplasia.

**Hypertension and left atrial remodeling**

Although the effect of hypertension on the left ventricle is well studied, that on the left atrium (LA) is less well defined. Electrocardiographic (ECG) or echocardiographic LA enlargement occurs commonly in hypertensive patients [6–10]. In one study 21% of hypertensive patients without ECG evidence of LVH had LA enlargement of greater than 4 cm [11]. In subjects with ECG LVH, the prevalence of LA enlargement is higher (56% in women and 38% in men) [10].

In older patients with isolated systolic hypertension, echocardiographic LA size is associated with systolic BP [9]. In the general population, LA enlargement is associated both with the duration of elevated BP and with the level of systolic BP [12]. LA size is significantly related to left ventricular (LV) mass and eccentric LVH [10], and the extent of atrial enlargement correlates with the degree of hypertension [10–15]. Also, LA enlargement may be an early adaptation to elevated BP that may occur before any evidence of LVH or atrial arrhythmia [8,16]. In several studies, LA enlargement has been found to be associated with an increased risk of atrial fibrillation and stroke [15,17–21]. Among 4731 participants of the Framingham study who underwent baseline echocardiography, after adjustment for established risk factors for atrial fibrillation, every 5-mm increment in LA size was associated with a 39% increase in the risk of atrial fibrillation [15]. Tsang et al [21] have reported that 30% increase in LA volume, measured echocardiographically using a biplane area-length method, was associated with a 43% increased risk of atrial fibrillation, and that LA volume was a more sensitive marker for this risk than conventional LA diameter [21].

The mechanisms by which hypertension might cause changes in LA size and function are speculative. LA enlargement in hypertensive patients may be secondary to LVH [12] or caused by changes in LV function. It may be the result of elevated LV filling pressures [22] and impairment of LV diastolic function [10,23–26]. In a small study of hypertensive patients, quinapril therapy was associated with a decrease in LA dimension with normalization of BP [27].
Hypertension and left ventricular remodeling

Systemic hypertension imparts a chronic augmentation of workload on the left ventricle and is the most common reason for LVH [28]. This structural change can be diagnosed in vivo either by ECG or by echocardiography [29,30]. Major ECG changes suggestive of LVH include increased amplitude; widening and notching of the QRS complex; left axis deviation; repolarization (ST-T wave) changes; and LA abnormality [31]. Although the specificities of various ECG criteria for the diagnosis of LVH, such as Sokolow-Lyon, Romhilt-Estes, and Cornell voltage criteria, are generally high (over 90%), their sensitivities are moderate or low, ranging from 7% to 60% [32,33]. The sensitivity of the ECG criteria is influenced by biologic factors (decreased by obesity and cigarette smoking, and increased by age and severity of LVH) and methodologic factors (increased when LV mass was indexed to body surface area instead of height) [32,33]. In the past 20 years quantitative echocardiography has been proven to be a more reliable and precise measure of chamber mass, wall thickness, and configuration providing a reproducible tool for noninvasive assessments of ventricular architecture. In a recent study from Framingham, whereas 19% of men and 24% of women satisfied the echocardiographic criteria for LVH, only 1.3% of the subjects had definite LVH by ECG criteria [34].

Mechanisms of left ventricular hypertrophy in hypertension

The causal association between hypertension and the development of LVH is well established in laboratory and epidemiologic studies. Based on a 30-year follow-up data from the Framingham Heart Study, as compared with normotensive subjects, those with definite hypertension (BP ≥ 160/95 mm Hg) had a 10-fold increase in the incidence of ECG LVH [35]. Echocardiographic LVH has been reported in children and adolescents with borderline elevations in BP [36], and in subjects who have exaggerated transient elevations in BP during mental stress, job strain, or exercise [37–39]. Further, higher average ambulatory daytime BP, and absence of nocturnal fall in BP, may contribute to the increased risk of LVH [40,41].

The development of LVH is influenced by hemodynamic factors, such as increased wall stress, and nonhemodynamic factors, such as altered genotypes [42–45], myocytes [46], matrix [47], apoptosis [48], vasculature, neurohormones [49–52], and cytokines (Fig. 1). The development of myocardial hypertrophy in relation to external work load and duration of hypertension and its transition from compensated hypertrophy to functional decompensation is schematically represented in Fig. 2.

There is evidence that elevated LV mass may precede the development of overt hypertension [53–56]. In the large Framingham cohort, after accounting for factors such as age, sex, body mass index, alcohol consumption, and systolic and diastolic BP, the risk of hypertension during
follow-up increased by 20% per increment of 26.5 g/m in LV mass index, and by 16% for every 2.5-mm increase in LV wall thickness [56]. Plausible explanations for these findings include the following: (1) increased LV mass in preclinical stages of hypertension may elevate BP because of increased contractile force; (2) LV mass is a better integrator of elevated BP than the dichotomous categorization (above and below a threshold value) of BP measurements recorded at one point in time; (3) there may be common nonhemodynamic factors, such as neurohormonal stimulation (angiotensin II, norepinephrine, epinephrine) [50–52], increased peripheral sympathetic drive [57], and endothelin [49], which may promote both hypertension and
LVH; and (4) genetic factors may predispose to the development of both hypertension [58] and cardiac hypertrophy [59–64].

Prognostic significance of left ventricular hypertrophy

Regardless of the methods (electrocardiographic or echocardiographic) used to detect LVH, its presence portends a poor prognosis. Although insensitive as a measure of mass, ECG LVH is associated with an increased risk of coronary heart disease [65], heart failure [66,67], ventricular arrhythmias [68–72], sudden death [73,74], peripheral arterial disease [75], and cerebrovascular disease [76]. The increase in cardiac risk seems to be highest in those patients in whom the ECG reveals ST segment and T wave changes indicative of a strain or ischemic pattern [77]. Echocardiographic LVH has been shown to be a risk factor for cardiovascular disease (composite of coronary heart disease, heart failure, stroke, transient ischemic attack, and intermittent claudication) [78], coronary heart disease [79], cardiovascular morbidity [80,81], ventricular arrhythmias [82–85], stroke [76,86], sudden cardiac death [87], cardiovascular death [78,81], and all-cause mortality [78,81,88]. Echocardiographic LVH is more prevalent and more sensitive for ventricular arrhythmias than ECG LVH [89]. Hypertensive patients with echocardiographically proven LVH who also meet ECG criteria have a greater LV mass than those without the expected ECG changes [90].

Mechanisms for increased risk

The exact mechanism by which enlarged LV muscle mass increases the risk of adverse cardiovascular events is not known. LVH may increase myocardial oxygen consumption but with concomitant decrease in coronary flow reserve because of such factors as coexistence of subclinical coronary artery disease, reduced density of capillaries, direct compression of the endocardial capillaries, and limitation of the ability of the coronary arteries to dilate in response to decreased perfusion or during vasodilatory stress [77,91–94]. Electrophysiologic abnormalities, action potential prolongation, easily provable early afterpotentials, altered repolarization, and excessive stretching of myocardial fibers because of increased systolic wall stress or diastolic distention may potentiate development of ventricular arrhythmias and sudden death [95–100]. Increased apoptosis or cardiac cell death has been demonstrated in hypertrophied myocardium [101]. Progressive systolic or diastolic dysfunction manifests as overt heart failure (see Figs. 1 and 2).

Regression of left ventricular hypertrophy

Animal studies

In animal models of hypertension, the regression of LVH depends on the methods used to induce hypertension and the means employed to reduce the
elevated BP [102]. When hypertension and cardiac hypertrophy is induced by mechanical means, such as aortic banding or clipping of renal artery, removal of the inciting stimulus causes a return of BP to baseline values and regression of LVH to near normal levels. In genetic hypertension models where antihypertensive agents are used to lower BP, despite equal efficacy in lowering BP, LVH may decrease (methyldopa [103], guanethidine, and angiotensin-converting enzyme [ACE] inhibitors); increase (minoxidil [104]); or remain unaffected (hydralazine) [102].

**Human studies**

Several studies in humans have shown that adequate and aggressive BP control in hypertensive patients can prevent the development of LVH and reverse it when already present. In controlled trials, such strategies as weight loss, or dietary sodium restriction, and antihypertensive therapy aimed at lowering BP have been found to decrease cardiac mass in patients with LVH [29,105–108]. In Therapy in the Treatment of Mild Hypertension Study (TOMHS), where all 844 participants received nutrition-hygienic intervention (aimed at weight loss, lowering of sodium and alcohol intake, and increasing physical activity), the mean reduction in LV mass was 24 g in the active therapy group (receiving various class of antihypertensives as monotherapy) and 18 g in the placebo group [109].

The decline in LV mass with antihypertensive therapy varies with the type of therapy used. In the TOMHS study, nutritional-hygienic therapy alone was found to be equally effective as nutritional-hygienic therapy combined with various classes of pharmacologic agents (diuretic, β-blocker, α-antagonist, calcium channel blocker, and ACE inhibitor) in reducing LV mass. In the Department of Veterans Affairs Cooperative Study evaluating the effects of monotherapy on LV mass at 1 year, however, reduction of LV mass occurred in patients on captopril, hydrochlorothiazide, and atenolol but not in those on diltiazem, clonidine, or prazosin [110]. In several small studies, after 8 to 12 months of antihypertensive therapy, LV mass has been found to decline by 8 to 19 g with β-blockers, 26 to 45 g with ACE inhibitors, and 40 to 52 g with angiotensin I receptor blockers [111]. In the Losartan Intervention for Endpoint reduction (LIFE) trial, which compared losartan with atenolol in hypertensive patients with ECG evidence of LVH, regression of LVH occurred in 77% of patients [112], and the degree of regression, using ECG criteria, was approximately twice as great at 1 year with losartan than with atenolol [113]. In an updated meta-analysis of 80 double-blind, randomized, controlled clinical trials (up to September 2002) involving over 4000 patients evaluating the efficacy of various classes of antihypertensive agents on change in LV mass, the reduction in LV mass index was 10% to 13% with the use of angiotensin II receptor blockers, calcium channel blockers, or ACE inhibitors, and 6% to 8% with the use of diuretics, and β-blockers. Further, angiotensin II receptor blockers, calcium channel blockers, and ACE inhibitors were more effective at reducing LV
mass than β-blockers. In comparison, regression is largely absent with direct vasodilators (eg, hydralazine or minoxidil) and with some calcium channel blockers despite adequate BP control [107,114,115]. The ineffectiveness of these drugs is probably explained by the reflex stimulation of hormones, such as norepinephrine and angiotensin II, which may directly promote the development of LVH [50,115]. In the recent PRESERVE (prospective randomized enalapril study evaluating regression of ventricular enlargement) trial, however, the largest prospective randomized trial, conducted on 303 ethnically diverse, hypertensive patients with LVH at baseline, enalapril therapy and long-acting nifedipine was associated with a similar reduction in BP and LV mass [116].

The time course in the regression of LVH seems to vary with the nature of the population studied. Whereas in the 844 mildly hypertensive patients of the TOMHS study the LVH regression occurred within 3 months and was maintained thereafter up to 4 years of follow-up [109], in the 754 moderately severe hypertensive participants of the LIFE study, all of whom had ECG evidence of LVH indicative of increased severity of LVH, a progressive decline in LV mass was noted over 2 years of follow-up: 27 g at 1 year with an additional decline of 11 g in the second year of therapy [111].

Regression of left ventricular hypertrophy and improvement in outcomes

Regression of LVH induced by antihypertensive therapy is associated with improved LV systolic performance [117] and diastolic filling [112], enhanced stroke volume [117], reduced risk of premature ventricular beats, and decreased vulnerability to inducible ventricular fibrillation [118], without concomitant adverse effect on myocardial perfusion [119]. In over 500 subjects of the Framingham Heart Study who had ECG evidence of LVH, those with a serial decline in voltage had a 46% to 56% lower risk, whereas those with serial increase in voltage had a 61% to 86% greater risk for cardiovascular disease [120]. In the 430 hypertensive subjects from the Progetto Ipertensione Umbria Monitoraggio Ambulatorie (PIUMA) registry in Italy, a 54% decline in the risk of adverse cardiovascular events occurred in those who had a decrease in LV mass as compared with those who had an increase in LV mass [121]. In the Heart Outcomes Prevention Evaluation (HOPE) study, as compared with subjects with development and persistence of LVH, those with regression and prevention of LVH had a decreased incidence of cardiovascular death (3.4% versus 5.7%); myocardial infarction (8.7% versus 10.9%); heart failure (9.3% versus 15.4%); all-cause death (5.4% versus 8.9%); sudden death or cardiac arrest (1.9% versus 3.8%); and possibly stroke (3.5% versus 4.7%) [122].

Hypertension and myocardial fibrosis

Although LVH is primarily caused by an increase in myocytes [123], in animal models of hypertension [124–127] and in humans [128–131]
perivascular and interstitial myocardial fibrosis occurs and is a major determinant of myocardial stiffness and diastolic dysfunction [125–127,132]. Increased collagen synthesis and decreased collagen degradation have been proposed as the possible mechanisms for myocardial fibrosis [125,127,133,134]. Disproportionate accumulation of nonmyocyte cells unrelated to myocyte growth or necrosis represents reactive fibrosis, and plays a major role in pathologic remodeling [135].

In experimental models, antihypertensive agents, such as ACE inhibitors [136–140], angiotensin receptor blockers [141,142], calcium antagonists [140,143–145], and aldosterone antagonists [146], have been found to prevent or regress myocardial fibrosis, whereas other antihypertensives, such as minoxidil [147], alpha methylldopa [148], hydrochlorothiazide [149], and hydralazine [141,150], have not been associated with regression of myocardial fibrosis. In small studies conducted on human subjects with hypertensive heart disease, ACE inhibition [151] and angiotensin receptor blockade [152] have been reported to regress myocardial fibrosis and improve LV diastolic function.

Summary

Experimental and clinical studies provide evidence that hypertension is causally related to adverse cardiac structural changes, such as LA enlargement, LV hypertrophy and myocardial fibrosis, and functional changes inclusive of LV systolic and diastolic dysfunction. These changes are induced by both hemodynamic and nonhemodynamic factors. There is accumulating evidence from several small and large clinical trials that various classes of antihypertensive therapy prevent and regress LVH and myocardial fibrosis. Prevention and reversal of LVH are associated with an improvement in cardiac function and with a decline in risk of adverse cardiovascular outcomes. Prevention of LVH should be a priority in subjects with hypertension. In patients with hypertensive heart disease, the components of therapy must comprise optimization of BP and regression of LVH. Future targets of therapy in hypertensive heart disease may include regression of myocardial fibrosis, normalization of LA size, and improvement in LV diastolic function.

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