

# Pathophysiology and treatment of hypertensive left ventricular hypertrophy

Enrico Agabiti-Rosei,\* MD, FESC; Maria Lorenza Muiesan,† MD

\*Full Professor of Internal Medicine - University of Brescia - Brescia - ITALY

†Associate Professor of Internal Medicine - University of Brescia - Brescia - ITALY

*At some point in the natural history of hypertension, the compensatory increase in left ventricular (LV) mass ceases to be beneficial. LV hypertrophy (LVH) becomes a preclinical disease and an independent risk factor for congestive heart failure, ischemic heart disease, arrhythmia, sudden death, and stroke. The multiple mechanisms involved, in addition to elevated blood pressure, include body size (obesity), demographics (age, gender, and race), and contributions by fibrogenic cytokines and neurohumoral factors, notably angiotensin II, which favor interstitial collagen deposition and perivascular fibrosis. These tissue changes, in conjunction with geometric abnormalities, primarily concentric hypertrophy, are responsible for the insidious dysfunction associated with LVH, beginning with decreased coronary reserve and altered diastolic ventricular filling and relaxation. The cardinal investigation is echocardiography: [Doppler transmitral flow velocities expressed as the early (E) to atrial (A) wave ratio reveal LVH as a state of potential or actual myocardial ischemia]. All antihypertensive drugs regress LVH, notably the angiotensin-converting enzyme inhibitors, which may also target the detrimental tissue changes. Regression enhances systolic midwall performance, normalizes autonomic function, and restores coronary reserve. The resulting improvement in prognosis has enshrined the detection, prevention, and reversal of LVH in the current guidelines of hypertension management*

**Keywords:** left ventricular hypertrophy; regression; antihypertensive treatment; cardiovascular risk; clinical trial

**Address for correspondence:** Prof Enrico Agabiti-Rosei, Internal Medicine, Medical and Surgical Sciences, University of Brescia, c/o 2a Medicina Spedali Civili di Brescia, Piazza Spedali Civili 1, 25100 Brescia, Italy (e-mail: agabiti@med.unibs.it)

*Dialogues Cardiovasc Med.* 2005;10:3-18

At some point in the natural history of hypertension, the compensatory increase in left ventricular (LV) mass ceases to be beneficial. It becomes a preclinical disease and an independent risk factor for congestive heart failure, ischemic heart disease, arrhythmia, sudden death, and stroke.<sup>1</sup>

LV hypertrophy (LVH) is adequately and most commonly diagnosed using electrocardiography (ECG) and, more particularly, M-mode and two-dimensional (2D) echocardiography, which provide comprehensive wall, chamber, and LV mass measures, together with systolic and diastolic performance indices, while remaining cheap, widely available, and wholly noninvasive (Table I). Sophisticated and more accurate techniques, such as magnetic resonance imaging (MRI) or cine computerized tomography, are inevitably more expensive and time-consuming, and of limited availability.

- Left ventricular geometry, left atrium, aortic root
- Left ventricular systolic dysfunction
- Diastolic filling abnormalities
- Stroke work
- Total artery compliance
- Myocardial ischemia (stress echocardiography)

**Table I.** Left ventricular hypertrophy (LVH) parameters measured by echocardiography.

## DETERMINANTS OF HYPERTENSIVE LVH

The high prevalence of LVH in hypertension reflects the increased afterload imposed on the LV. However, other important determinants include demographic characteristics, the nature of the hemodynamic load, neurohumoral and growth factors, and underlying genetic factors.

## Blood pressure

Hypertension is the fundamental trigger to the sequence of biological events leading to the development of LVH. However, the relationship between LV mass and clinic blood pressure is rather weak. LV mass is more closely related to mean 24-hour blood pressure.<sup>2</sup>

### SELECTED ABBREVIATIONS AND ACRONYMS

<b>CATCH</b>	Candesartan Assessment in the Treatment of Cardiac Hypertrophy
<b>ELSA</b>	European Lacidipine Study on Atherosclerosis
<b>ELVERA</b>	Effects of amlodipine and lisinopril on Left VEntricular mAss and diastolic function
<b>HOPE</b>	Heart Outcomes Prevention Evaluation
<b>IGF-I</b>	insulin-like growth factor-I
<b>LIFE</b>	Losartan Intervention For Endpoint reduction in hypertension
<b>LIVE</b>	LVH regression: Indapamide Versus Enalapril
<b>LVH</b>	left ventricular hypertrophy
<b>MAPK</b>	mitogen-activated protein kinase
<b>PIUMA</b>	Progetto Iperensione Umbria Monitoraggio Ambulatoriale
<b>PRESERVE</b>	Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement
<b>QTL</b>	quantitative trait loci
<b>RAAS</b>	renin-angiotensin-aldosterone system
<b>RACE</b>	RAMipril Cardioprotective Evaluation
<b>REASON</b>	PREterax in regression of Arterial Stiffness in a contrOLled double-bliNd study
<b>REGAAL</b>	LVH REGression with the Angiotensin Antagonist Losartan
<b>SAMPLE</b>	Study on Ambulatory Monitoring of blood Pressure and Lisinopril Evaluation
<b>SILVHIA</b>	Swedish Irbesartan Left Ventricular hypertrophy Investigation Versus Atenolol
<b>SNP</b>	single nucleotide polymorphism
<b>TGF-<math>\beta</math>1</b>	transforming growth factor $\beta$ 1
<b>TIMP-1</b>	tissue inhibitor of metalloproteinase-1
<b>TOMHS</b>	Treatment Of Mild Hypertension Study
<b>VA</b>	Veterans Administration (cooperative study)

Several studies investigating the relative importance of day and night blood pressure have focused on the absence of a nocturnal dip in blood pressure.<sup>3,4</sup> However, the dipper/nondipper classification is arbitrary and poorly reproducible. There is also the possibility that increased blood pressure is the consequence, rather than the cause, of LVH and associated vascular structural changes. Volume load, inotropy, and arterial compliance are also important determinants of the development and degree of LVH.

## Demographics

Age, gender, race, and body size can all influence LV mass, possibly mediated via cardiac load. Thus, LVH prevalence increases with age, in both hypertensives and normotensives, perhaps due to the combination of age-related blood pressure elevation and declining aortic compliance. Aging also accounts for specific tissue changes, notably interstitial fibrosis and myocyte loss. Similarly, there is a gender difference in LV mass, which becomes evident in adolescence and remains constant during adult life; although the age-related increase in LV mass is greater in postmenopausal women than in men, gender is not a significant determinant of cardiovascular complications or of the prognostic impact of LVH. Hypertensive LVH is more evident in blacks than in whites at similar increases in blood pressure; certain cardiovascular complications, such as heart failure and sudden death, are also more common in blacks.

Body size, notably obesity, which compounds hemodynamic load independently of a clear-cut increase in blood pressure, is a major determinant of LV mass. With dietary sodium, it is associated with increased plasma volume and cardiac output, and may be responsible for hypertensive LVH.<sup>5</sup>

It has been suggested that by considering these measurable factors and hemodynamic load, echocardiographic LV mass could be assessed in the individual patient by deviation from the value appropriate for a given cardiac workload, corrected for gender and body size. Patients with an LV mass inappropriate to the stroke work for their gender and body size tend to cluster with metabolic risk factors. LV mass that overcompensates for hemodynamic load is associated with high cardiovascular risk. However, it is not yet known whether the morphological alteration conferring the higher risk is the presence of inappropriate LV mass or the development of LVH per se.<sup>6,7</sup> The definition and clinical evaluation of "inappropriate" LV mass require further study.



### Neurohumoral factors

Early experiments showed that the sympathetic nervous system induced LVH in a number of situations: even subhypotensive doses of norepinephrine increased LV mass. In humans, the effect is less clear-cut: if in pheochromocytoma LVH prevalence is relatively low and LV mass appears to increase proportionately to blood pressure, in essential hypertension LVH is associated with altered autonomic activity and a blunted response to  $\beta$ -adrenoceptor stimulation.<sup>8-10</sup>

Experimental studies also revealed the role of the renin-angiotensin-aldosterone system (RAAS) in mediating LVH. By stimulating the angiotensin receptor, angiotensin II induces hypertrophy and hyperplasia in myocytes and smooth muscle cells, and may regulate myofibroblast collagen synthesis. Excess angiotensin II production may regulate the expression of fibrogenic cytokine transforming growth factor- $\beta$ 1 (TGF- $\beta$ 1). Autocrine induction by TGF- $\beta$ 1 of the genes coding for extracellular matrix proteins determines perivascular and interstitial fibrosis. Angiotensin II may also depress collagenase activity, hence favoring interstitial collagen deposition.

Aldosterone may also stimulate extracellular collagen deposition and myocardial fibrosis.<sup>11,12</sup> A key determinant of collagen degradation is the activation of metalloproteinases (a family of zinc-containing proteins that also includes stromalysins, collagenases, and gelatinases) and a multifunctional protein, tissue inhibitor of metalloproteinase-1 (TIMP-1), produced by connective tissue cells and macrophages, and probably regulated by angiotensin II.<sup>13</sup>

The pathogenic role of the RAAS in the development of hypertensive LVH requires confirmation, although LV mass is significantly increased in renovascular hypertension and primary aldosteronism compared with essential hypertension.<sup>14,15</sup> There is also a correlation between LV mass and plasma aldosterone, which is independent of blood pressure.<sup>12</sup>

### Insulin

Hypertensive LVH is often associated with insulin resistance and high insulin levels. Significant correlation between LV mass and insulin and insulin-like growth factor-I (IGF-I) was observed in a cohort of 101 essential hypertensives with normal glucose tolerance from the Progetto Ipertensione Umbria Monitoraggio Ambulatoriale (PIUMA); in addition, IGF-I was a main de-

terminant of LV mass and geometry, independent of blood pressure.<sup>16</sup> Very high LVH prevalence (>70%) has been repeatedly observed in diabetics, associated with changes in systolic and diastolic function disproportionate to the increase in blood pressure. The involvement of IGF-I may clarify the link between obesity, blood pressure elevation, LVH, and the metabolic syndrome.

Leptin is another possible neuroendocrine determinant. LVH in an animal model of leptin deficiency (the *ob/ob* mouse) reversed rapidly in response to exogenous leptin, suggesting that myocardial leptin receptors could be involved in cardiac remodeling.<sup>17</sup> Other major metabolic cardiovascular risk factors, notably hypercholesterolemia and diabetes, also determine LV mass and the prevalence of LVH. Thus, low plasma high-density lipoprotein (HDL) cholesterol levels have been associated with increased LV mass, independently of blood pressure.

### Genetics

Analysis of LV mass heritability in 2624 subjects in the Framingham Heart Study showed a closer correlation between LV mass in first-degree relatives than in second-degree relatives or couples, suggesting that about 30% of LV mass variance is genetic.<sup>18</sup> Studies of genetic influence on LV mass have focused on candidate genes, ie, gene polymorphisms that may be involved in the hypertrophic cell process, using the genomewide scan technique to screen for a large number of genetic polymorphisms associated with the phenotype.

Polymorphisms associated with the RAAS were the initial target. In 1994, Schunkert et al described an association between insertion/deletion polymorphism of the angiotensin-converting enzyme (*ACE I/D*) and ECG LVH.<sup>19</sup> Attempts at confirmation brought mixed results: a 1997 meta-analysis of five case-control studies in 3285 subjects found no association between the *D* allele and an increased risk of echocardiographic LVH.<sup>20</sup> The *ACE I/D* genotype may only have a significant effect on LV mass in particular circumstances, eg, vigorous exercise, hypertension, renal failure, or cardiac ischemia.

There is unconfirmed evidence of an association between LVH and aldosterone synthase genetic polymorphism.<sup>21</sup> Studies are ongoing on the role of other candidate genes, including those related to  $\alpha$ - and  $\beta$ -adrenoceptors and components of the signal transduction mechanisms involved in cardiac hypertrophy, ie, G proteins, and mitogen-activated protein kinase

(MAPK) regulated by calcium-dependent phosphatase. Genomewide scans are becoming easier to perform thanks to DNA microarray technology and the increasing number of single nucleotide polymorphisms (SNP) that have been identified. Putative chromosomal quantitative trait loci (QTL) influencing the variability of cardiac mass have been described in animals, but not as yet any specific genes related to increased LV mass—nor have any similar results been obtained in humans.

### METHODS OF ASSESSING LVH

LVH has become integral to the diagnostic workup and treatment strategy in hypertension, as recommended by the European Society of Hypertension (ESH) and European Society of Cardiology (ESC).<sup>22</sup>

The most common diagnostic tools are the ECG and echocardiogram. ECG remains the conventional method, despite low sensitivity compounded by increasing age and body weight. New ECG criteria in addition to repolarization abnormalities and increased voltage have been proposed in recent years, the Cornell method being the most sensitive.<sup>23</sup> The ECG can also be used to detect patterns of ventricular overload (“strain”) or ischemia, indicating higher risk.

Since ECG and echocardiographic LVH predict mortality independently of one another and other cardiovascular risk factors, they convey, at least in part, different prognostic information,<sup>24</sup> in particular when the ECG shows a strain pattern.<sup>25</sup>

Echocardiography is now widely available in the industrialized world for determining LV mass. It is time- and cost-effective, specific, ideal for serial mass and function follow-up, and more sensitive than ECG.

LV mass is calculated from the LV interventricular septum and posterior wall thicknesses and internal diameter using the Penn or American Society of Echocardiography (ASE) formulas, each of which has been validated by autopsy.<sup>26,27</sup> All studies evaluating the prognostic significance of changes in LV mass have applied one or both formulas to M-mode measures made under 2D control. Values obtained using different formulas have given superimposable results.<sup>28</sup> However, despite its advantages, echocardiography is not infallible, and technical error is always possible, due to the method itself, the quality of the examination, or interpreter inexperience. An Italian Society of Hypertension study of the reliability of repeat echocardiography recordings and interpretations in 260 normotensive

and hypertensive subjects in 16 centers attributed biological significance to changes in LV mass exceeding 10% to 15%.<sup>29</sup> Similarly, the Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement (PRESERVE) found an intraclass correlation coefficient of 0.93 between two measures (screening and randomization) of echocardiographic LV mass in 183 hypertensive patients with LVH.<sup>30</sup> Changes  $\pm 35$  g and  $\pm 17$  g represented probabilities of biological significance of 95% and 80%, respectively.

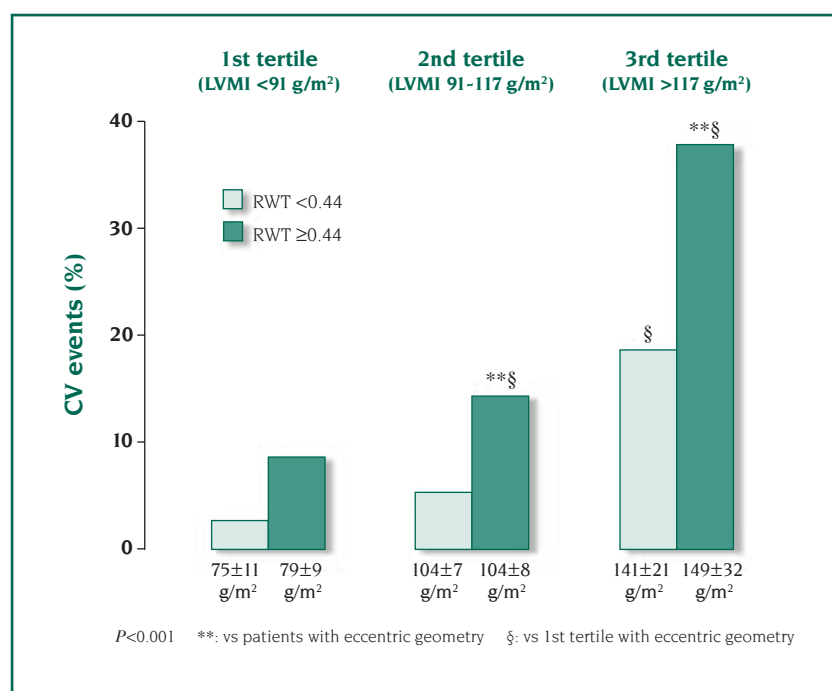
Under normal cardiac loading conditions, body size, and in particular lean body mass, is the most important determinant of heart size. For this reason, LV mass is usually normalized to body size. Normalization to body weight or other size measures (eg, body surface area) are inaccurate when body composition is altered, as in obesity. A surrogate of lean mass, body height, with LV mass indexed to height to the allometric power of 2.7, is particularly useful when evaluating the impact of abnormal body composition on LV anatomy, as in obesity or anorexia nervosa, but it is no better than other indices for prognostic purposes. Two main definitions of echocardiographic LVH based on prognostic data are in current use: (i) LV mass indexed to height ( $m^{2.7}$ )  $\geq 51$  g in both genders<sup>31</sup>; and (ii) LV mass indexed to body surface area ( $m^2$ )  $>125$  in both genders (*Table II*).

LV mass/h ( $g/m^{2.7}$ )	$>51$ (M & F)
LV mass/BSA ( $g/m^2$ )	$>125$ (M & F)
LV mass/BSA ( $g/m^2$ )	$\geq 117$ (M); $\geq 104$ (F)
LV mass/BSA ( $g/m^2$ )	$\geq 125$ (M); $\geq 110$ (F)
LV mass/BSA ( $g/m^2$ )	$\geq 131$ (M); $\geq 100$ (F)
LV mass/h ( $g/m$ )	$\geq 143$ (M); $\geq 102$ (F)
LV mass/h ( $g/m$ )	$\geq 149$ (M); $\geq 114$ (F)
LV mass/h ( $g/m^{2.7}$ )	$>50$ (M); $>47$ (F)

**Table II.** Left ventricular hypertrophy (LVH) diagnostic values.

**Abbreviations:** BSA: body surface area; F: females; h, height; M: males.

Echocardiography is also useful in assessing the different types of LV geometric adaptation to increased cardiac load (*Figure 1*).<sup>32</sup> The characteristics of concentric hypertrophy are increases in both mass and relative wall thickness, whereas those of eccentric hypertrophy are increased mass and a relative wall thickness  $< 0.45$ . Remodeling is said to be concentric when thickness increases with respect to radius, but without an increase in LV mass. Concentric hypertrophy ap-



**Figure 1.** Cardiovascular events associated with concentric versus eccentric geometry.

Abbreviations: LVMI: left ventricular mass index; RWT: relative wall thickness.

Reproduced from reference 32: Muesan ML, Solvetti M, Monteduro C, et al. Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients. *Hypertension*. 2004;43:1-8. Copyright © 2004, American Heart Association, Inc.

and improved the display of changes in the segmental contractility of the LV wall. However, given the difficulty of obtaining accurate orientation of the 2D planar images, their time-consuming planimetric reconstruction in 3D and identification of the external border of LV walls, technological advance is required before there can be a dramatic increase in use. Methods have been developed to quantify tissue composition. Studies in animals and humans have shown

pears to carry the highest risk and eccentric hypertrophy an intermediate risk, while concentric remodeling is probably associated with a smaller, albeit noteworthy risk. Geometries also differ in their hemodynamics, with elevated total peripheral resistance and low cardiac output in concentric hypertrophy, and normal total peripheral resistance and high cardiac output in eccentric hypertrophy. Whether the geometries represent structural alterations of myocardial tissue is unknown.

Geometric patterns of LV adaptation have mechanical consequences. LV systolic performance can be measured both at the endocardium by fractional shortening, reflecting chamber function, and at the midwall, where circumferential fiber contraction makes a greater contribution to stroke volume.<sup>33</sup> Midwall fractional shortening has important prognostic significance.<sup>34,35</sup> In addition, Doppler transmitral flow and LV outflow tract studies can be used to measure several indices of diastolic function, reflecting both passive filling and active relaxation.

Newer imaging methods such as MRI offer more accurate measures of LV mass, even in ventricles with asymmetrically increased thickness or abnormal contractility. MRI has provided important pathophysiologic information (midwall mechanics), but the duration, complexity, and cost of the examination hinder wider use. 3D reconstruction of 2D echocardiographic images has increased the reproducibility of LV mass measurements

that LV acoustic properties under physiological and pathological conditions are influenced by several tissue components, in particular myocardium, contractile and elastic tissue, collagen and inelastic tissue, as well as by structures such as arteries, veins, myocytes, and sarcomeres. Results with videodensitometry and integrated backscatter to characterize tissue in several diseases associated with abnormal myocardial tissue, hypertensive LVH, and diabetes indicate that this technique can complement clinical evaluation by revealing preclinical end-organ damage.<sup>36,37</sup> Further reproducibility and feasibility studies are required to assess the clinical applications of these techniques in patients with hypertension and other risk factors.

### PROGNOSTIC SIGNIFICANCE OF LVH

Whether assessed by ECG or echocardiography, LVH is a well-documented harbinger of morbidity and mortality. In several studies the adjusted risk of cardiovascular morbidity associated with baseline LVH ranges from 1.5 to 3.5 with a weighted risk ratio of 2.3 for all studies combined (*Table III, page 8*)<sup>38-40</sup>; the adjusted risk of all-cause mortality associated with baseline LVH ranges from 1.5 to 8, with a weighted mean risk ratio of 2.5 for all studies combined.<sup>41</sup>

The structural remodeling of cardiomyocytes, non-myocytes, and fibroblasts that occurs in cardiac hypertrophy contributes to perivascular fibrosis, initially around

Study	Patients	n	Age (y)	Left ventricular mass index	LVH prevalence (%)	Follow-up (years)	RR
Levy et al, 1990 <sup>38</sup>	Framingham	3220	56	≥143 g/m (M)	16	4	1.53
				≥102 g/m (F)	21		1.55
Koren et al, 1991 <sup>39</sup>	HTN/CVD/DM	280	47	≥125 g/m <sup>2</sup>	27	10	2.2
Muiesan et al, 1995 <sup>40</sup>	Hypertension	151	45	≥134 g/m <sup>2</sup> (M)	44	10	3.6
				≥110 g/m <sup>2</sup> (F)			

**Table III.** Studies of the association between baseline left ventricular hypertrophy (LVH) and cardiovascular events.

**Abbreviations:** CVD: cardiovascular disease; DM: diabetes mellitus; HTN: hypertension; LVH: left ventricular hypertrophy; LVMI: left ventricular mass index; RR: relative risk.

intramural coronary arteries and thereafter in the interstitial space.<sup>42</sup> Increases in fibrillar collagen types I and III lead to progressive abnormalities of diastolic ventricular filling and relaxation, systolic dysfunction, arrhythmias, and conduction disturbances, thus greatly compounding the risk associated with LVH.<sup>1</sup> Excess ventricular collagen may be due to increased collagen synthesis, but also to insufficient collagen degradation by interstitial collagenase.

The resulting pathophysiological and clinical changes accounting for increased risk in hypertensive LVH include both diastolic and systolic dysfunction, the latter being initially detected only during exercise. LV systolic function depends closely on myocardial afterload, as shown by the linear relationship between LV endocardial fractional shortening and end-systolic stress. In most cases of mild-to-moderate hypertension, LV systolic function is well preserved. Indeed, "supranormal" LV ejection fraction and fractional shortening have been found in hypertensive subgroups with mild LVH, possibly reflecting enhanced myocardial contractility. However, this contrasts not only with experimental data showing progressive impairment of contractility during gradual hypertension onset, but also with the Framingham evidence that hypertension remains, directly or indirectly, the most important predictor of congestive heart failure in the general population.

The paradox has been resolved by showing that LV fractional shortening or ejection fraction, measured at the endocardium, reflects chamber dynamics, but does not necessarily provide a direct measure of myocardial fiber shortening<sup>43</sup>: the circumferential fibers responsible for LV short-axis shortening are located in the midportion of the LV walls, between two longitudinal shells responsible for long-axis shortening and twisting. Switching to a more physiologic midwall mechanics index related to circumferential end-systolic stress

reveals that myocardial chamber function is often overestimated in hypertension, particularly if LV wall thickness is increased.<sup>35</sup> Several studies have shown that LV midwall function is commonly reduced by 15% to 20% in hypertensive patients. The subgroup with depressed LV midwall function displays other features associated with an elevated cardiovascular risk profile, eg, concentric geometry, elevated peripheral resistance and heart rate, overweight, or obesity. Higher midwall fractional shortening is associated with female gender, in both hypertensive patients and the general population. Low midwall fractional shortening has proved an independent predictor of cardiovascular morbidity and mortality in hypertensive patients, as well as in healthy elderly subjects and American Indians in two general population-based surveys.<sup>35,36,44,45</sup>

Diastolic dysfunction may be observed early in the natural history of hypertension and also in the normotensive children of hypertensive parents.<sup>46</sup> It becomes more frequent in the presence of hypertensive LVH, and is influenced by advancing age, high heart rate and obesity. There is also a gender difference: in hypertensive LVH, impaired diastolic relaxation affects exercise capacity more severely in women, particularly if elderly, than in men.

LV diastolic dysfunction has been increasingly diagnosed in asymptomatic hypertension thanks to echocardiography, initially from measurements made on M-mode tracings and subsequently from Doppler transmitral flow velocities,<sup>50</sup> corrected for a number of well-characterized determinants such as age, gender, heart rate, and blood pressure. The velocities—A wave (atrial contraction and emptying) and E wave (early LV filling)—occur in three patterns representing worsening diastolic LV filling: (i) slowed relaxation, with an inverted E/A ratio, slowed deceleration time, and increased isovolumic relaxation time; (ii) pseudonormalization,



with a preserved E/A ratio, but shortened deceleration time due to abnormalities of both relaxation and compliance; and (iii) restrictive pattern, with an increased E/A ratio ( $>1.5$ – $2$ ) associated with a very abrupt deceleration time, suggestive of elevated atrial pressure, and an abnormal pressure rise in a stiff LV. Pseudonormalization is best diagnosed by analyzing pulmonary venous filling patterns and/or the Valsalva maneuver.

The PIUMA study showed an association between E/A ratio changes and significant increases in cardiovascular events in a cohort of 1839 middle-aged hypertensives.<sup>48</sup> Even more recent data come from a community survey in 2042 subjects aged 45 years or older that found diastolic dysfunction, evaluated by comprehensive transmitral, outflow tract and pulmonary flow Doppler examination, in 47% of hypertensives and 25.5% of subjects with a normal ejection fraction ( $>50\%$ ). The frequency of congestive heart failure increased dramatically with the severity of diastolic dysfunction.<sup>49</sup> Diastolic dysfunction is thought to precede systolic dysfunction, although evidence to this effect from longitudinal studies is lacking. Several studies using various techniques have shown that diastolic LV performance significantly influences exercise capacity in hypertensive LVH. Diastolic dysfunction (combined with incipient systolic dysfunction) is more prevalent in LVH, suggesting that it represents an accelerated transition phase from compensatory LVH to heart failure. Indeed, heart failure is diastolic in one third of cases or more. Although it may be associated with a lower mortality rate than other forms of heart failure, morbidity is high. Early recognition and appropriate therapy could help to prevent progression to diastolic heart failure and death. Although several studies have evaluated the effect of antihypertensive treatment on diastolic function, the clinical implications remain to be established.<sup>46</sup>

LVH and failure are frequently associated with coronary artery disease, and hypertension is a major risk factor for coronary atherosclerosis. In ECG LVH, use of a “definite LVH” pattern comprising ST-segment and T-wave abnormalities was strongly associated with an increased incidence of acute infarction and sudden death.<sup>3-6</sup> The association was weaker when LVH was defined by voltage criteria, suggesting that altered repolarization reflects reduced coronary perfusion.

LVH is associated with structural and functional changes in arteries, both large<sup>50,51</sup> and small.<sup>15,52,53</sup> Structural changes are particularly evident in concentric LVH. The association between LVH and extracranial carotid atherosclerosis might also explain the increased risk of

cerebrovascular events (stroke and transient ischemic attacks) in ECG or echocardiographic LVH. LVH is thus a risk factor for vascular events.

The vascular changes consistently observed in LVH are largely responsible for the reduced coronary reserve. Concomitant atherosclerosis in epicardial coronary vessels<sup>53</sup> and structural alterations and rarefaction of small coronary vessels<sup>54</sup> limit blood supply when oxygen demand is increased by the greater tissue mass. Compensatory angiogenesis is inadequate during the development of adult LVH. Decreased subendocardial coronary perfusion leads to myocyte necrosis and reparative fibrosis, encouraging the progression to heart failure. Other extravascular mechanisms compounding the impairment of coronary reserve include changes in wall tension, heart rate, and contractility, at a time when the oxygen requirement, measured by the triple product (heart rate  $\times$  LV mass  $\times$  end-systolic stress), is progressively increased compared with patients with normal LV mass and geometry.

The ability to regulate coronary flow is weakest during exercise when oxygen demand increases. Under resting conditions, the reduction in coronary flow reserve may not have important consequences, but during the exercise-induced increase in oxygen requirement it becomes symptomatic and a factor in progressive LV dysfunction. Functional changes further weaken the vasodilator response of the coronary microcirculation. Endothelial dysfunction precedes morphological changes in the vascular wall and triggers remodeling. In summary, LVH is a state of potential or actual myocardial ischemia.

There is a predisposition to ventricular arrhythmias in hypertensive LVH, explaining the risk of sudden death. Proposed causes include repolarization abnormalities (QT dispersion) due to the concomitant increase in fibrous tissue, changes in coronary structure and function, diuretic-induced hypokalemia, and autonomic dysfunction (adrenergic hyperactivity and reduced cardiac responsiveness to  $\beta$ -adrenergic stimulation). Impaired ventricular filling, left atrial enlargement, and slowing of atrial conduction velocity all encourage atrial fibrillation, increasing the risk of cerebrovascular thromboembolism.

Since hypertensive LVH is an independent risk factor for cardiovascular morbidity and mortality, the possibility of reversal or even prevention by lowering blood pressure and modifying other pathogenetic factors is a major goal in antihypertensive therapy.

Study	Patients (n)	Treatment duration (y)	Drug comparison
CATCH	182	1	Candesartan = enalapril
ELSA	174	4	Lacidipine = atenolol
ELVERA	166	2	Amlodipine = lisinopril
LIFE	960	4.5	Losartan > atenolol
LIVE	269	1	Indapamide > enalapril
PRESERVE	235	1	Nifedipine = enalapril
RACE	111	0.5	Ramipril > atenolol
REASON	124	1	Perindopril/indapamide > atenolol
REGAAL	183	1	Losartan > atenolol
SILVHIA	112	1	Irbesartan > atenolol
VA Cooperative Study	230	1	HCTZ, captopril > clonidine, diltiazem, prazosin, atenolol

**Table IV.** Studies comparing left ventricular hypertrophy (LVH) regression on different antihypertensive drugs.

**Study acronyms:** see box on page 4.

### LVH REGRESSION ON ANTIHYPERTENSIVE TREATMENT

LV mass can be decreased by nonpharmacological intervention, notably weight loss, which is effective in obese hypertensives independently of blood pressure. The multicenter Treatment Of Mild Hypertension Study (TOMHS) monitored echocardiographic LV mass in 819 mild hypertensives annually for 4 years and found that lifestyle intervention reduced blood pressure significantly and decreased LV mass substantially in 30% of patients.<sup>55</sup> However, there is still no hard evidence of an independent effect by dynamic exercise, dietary sodium, or alcohol restriction.

Multiple studies have shown that blood pressure reduction reverses LVH. The important determinants are treatment duration and the degree of blood pressure reduction. The Study on Ambulatory Monitoring of blood Pressure and Lisinopril Evaluation (SAMPLE) showed that changes in LV mass on ACE inhibitor therapy were significantly related not to changes in office blood pressure, but to the degree of mean 24-hour blood pressure control.<sup>56</sup> Subsequent evidence has also shown the importance of homogeneity, or minimal daily fluctuation, in blood pressure control, as expressed in the "smoothness index."<sup>57</sup>

However, since blood pressure is not the sole determinant of LVH and fibrosis, the differing response of LV mass to different classes of antihypertensive drugs was ascribed to interference in nonhemodynamic factors such as the RAAS and sympathetic nervous system. Several meta-analyses were therefore conducted of stud-

ies demonstrating reversal of echocardiographic LVH using different antihypertensive drugs. Dahlöf et al<sup>58</sup> calculated that for the same decrease in blood pressure the decrease in LV mass was greatest with ACE inhibitors, a conclusion confirmed by Cruickshank et al.<sup>59</sup> Three years later, however, in a comparative review of diuretics,  $\beta$ -blockers, calcium channel blockers, and ACE inhibitors, Fagard showed that each reduced LV mass to a degree similar to that of the other three classes combined, and that direct comparison could not separate ACE inhibitors from calcium channel blockers.<sup>60</sup> Two more recent meta-analyses, by Jennings and Wong<sup>61</sup> and Klingbeil et al,<sup>62</sup> confined to randomized, double-blind parallel group comparisons, have confirmed that the main determinants of LVH regression are the degree of blood pressure reduction and baseline LV mass. However, both studies also observed that ACE inhibitors, angiotensin II receptor blockers, and calcium channel blockers were more effective than  $\beta$ -blockers and diuretics given the same decrease in blood pressure.

Large randomized blinded studies (*Table IV*) comparing two or more different antihypertensive drugs have provided other data. The TOMHS results were the least instructive, due to the low prevalence of LVH and the efficacy of lifestyle intervention.<sup>58</sup> The RAMipril Cardio-protective Evaluation (RACE) study showed significant LVH regression on the ACE inhibitor versus none on atenolol, at comparable levels of blood pressure reduction.<sup>63</sup> Unfortunately, high dropout rendered largely inconclusive the comparison by the Department of Veterans Affairs Cooperative Study Group of 1 year's monotherapy with six different antihypertensive agents



in 587 male hypertensives.<sup>64</sup> Two other randomized double-blind parallel studies employing centralized echocardiographic LVH criteria compared the effect on LV mass of an ACE inhibitor and a calcium antagonist (PRESERVE [Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement]: enalapril vs nifedipine<sup>65</sup>; ELVERA [Effects of amlodipine and lisinopril on Left VENTRICULAR mAss and diastolic function (E/A ratio)]: lisinopril versus amlodipine).<sup>66</sup> Both found similar benefits with both drugs, as did the European Lacidipine Study on Atherosclerosis (ELSA) study with the calcium antagonist lacidipine and the  $\beta$ -blocker atenolol after treatment for 1 and 4 years.<sup>67</sup>

The results of the comparative LVH regression: Indapamide Versus Enalapril (LIVE) study showed a reduction in LV mass on indapamide, suggesting that diuretics can also regress LVH.<sup>68</sup> As for angiotensin II antagonists, they have been found more effective than the  $\beta$ -blocker atenolol,<sup>69-71</sup> and similar to enalapril.<sup>72</sup> The Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial versus atenolol in hypertensive ECG LVH confirmed the superiority of angiotensin II antagonists over  $\beta$ -blockers.<sup>73</sup> Finally, a very recently published study (REASON, PREterax in regression of Arterial Stiffness in a contrOLled double-bliNd study) found that the low-dose combination strategy, now proposed in several cases by the ESH/ESC guidelines, demonstrated superior LVH regression using perindopril/indapamide versus atenolol.<sup>74</sup>

However, it should be kept in mind that interdrug differences tend to fade with time, since treatment duration is associated with progressive blood pressure control and decrease in LV mass, although  $\beta$ -blockers seem to be less effective in reversing LVH than other classes of drugs. In addition, blood pressure may be resistant if there is target-organ damage requiring the use of combination antihypertensive therapy. Several major intervention trials comparing the effects of single antihypertensive drugs on LV mass have in fact largely been comparisons of combination therapies in that most patients were taking more than one drug. Thus, over 50% of SAMPLE patients received lisinopril plus a diuretic,<sup>56</sup> while about 90% of LIFE patients received a diuretic in addition to their  $\beta$ -blocker or angiotensin II blocker.<sup>73</sup>

The RACE patients were also stratified by the addition or nonaddition of a diuretic to their basal therapy: LV mass was similarly reduced in each subgroup, with ramipril proving superior to atenolol both alone and in combination.<sup>63</sup>

There is increasing interest in the effect of antihypertensive treatment on myocardial tissue composition, with particular respect to perivascular and interstitial fibrous tissue. Thus, for similar decreases in blood pressure after treatment for 6 months, Brilla et al showed that lisinopril decreased myocardial collagen and hydroxyproline content, and improved some diastolic function parameters, whereas hydrochlorothiazide had none of these effects, and only reduced myocyte diameter.<sup>75</sup> Recent experimental and human evidence suggests that angiotensin II antagonists may also regress myocardial fibrosis.<sup>76</sup>

Long-term studies thus indicate that all classes of antihypertensive drugs can lower blood pressure and regress LVH, with any initial interclass differences tending to fade with time. Differences in the reduction of LV mass for similar decreases in blood pressure are generally marginal, although there remains the possibility that drug classes differ markedly in their effect on cardiac structure and composition.

### CLINICAL AND PROGNOSTIC SIGNIFICANCE OF LVH REGRESSION

Since LVH is such an important independent risk factor in hypertension, there is no lack of consensus as to the desirability of regression and prevention. Regression is associated with numerous benefits such as enhanced systolic midwall performance, normalized autonomic function, enhanced coronary reserve, and, possibly, enhanced diastolic filling and decreased ventricular arrhythmia. All contribute to the improved prognosis (*Table V*) demonstrated in several studies over

Presence of LVH	Reversal of LVH
Systolic dysfunction (midwall depression)	→ Unchanged (or improved at midwall)
Diastolic filling abnormalities	→ Unchanged or improved
Autonomic dysfunction	→ Autonomic near-normalization
Predisposition to ventricular arrhythmias	→ Fewer arrhythmias
Reduced coronary reserve	→ Improved coronary reserve
Associated vascular structural changes	→ Improved

**Table V.** Pathophysiological and clinical consequences of left ventricular hypertrophy (LVH) regression.

**Levy et al,<sup>77</sup> 1994**

- 524 patients; 52% males; mean follow-up: 5.1 years; ECG voltage and repolarization criteria for LVH; 269 cardiovascular (CV) events
- Greater 2-year age-adjusted incidence of CV events in patients with increased voltage and/or repolarization criteria

**Mathew et al,<sup>78</sup> 2001**

- 8281 patients at high risk (HOPE, Heart Outcomes Prevention Evaluation) mean follow-up 5 years Sokolow criteria for LVH
- 925 events (12.3%) in 7539 patients with LVH regression or prevention vs 117 (15.8%) in 742 patients with LVH development/persistence

**Devereux et al,<sup>81</sup> 2002**

- 9193 hypertensives (LIFE, Losartan Intervention For Endpoint reduction in hypertension), mean follow up 4.5 years, Sokolow and Cornell criteria for LVH
- 13% CV events risk reduction in patients treated with losartan (15.3 % mean decrease of ECG LVH) in respect to patients treated with atenolol (9 % decrease in ECG LVH)

**Table VI.** Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy (LVH).

the years using ECG measures. Normalization of ECG LVH in 524 Framingham subjects over a mean 5-year follow-up was associated with reduction in cardiovascular risk. Regression of Sokolow LVH criteria in the Heart Outcomes Prevention Evaluation (HOPE) study was similarly associated with a reduction in cardiovascular events; no change—or worsening—of this simple ECG index implied a less favorable outcome. The large long-term LIFE study showed that the greater regression of LVH with losartan was associated with fewer cardiovascular events (*Table VI*).<sup>73,77,78</sup>

In addition, further observations in a smaller number of patients using the more sensitive echocardiographic technique have shown that patients who fail to achieve LVH regression or who develop LVH during follow-up are much more likely to suffer morbid events (*Table VII*).

We ourselves demonstrated this for the first time in 151 uncomplicated hypertensives followed for 10 years: Cox survival analysis adjusted for conventional cardiovascular risk factors showed the persistence of LVH at the end of follow-up as the most important independent predictor of cardiovascular events.<sup>40</sup>

Moreover, regression of LVH was associated with a significantly lower cardiovascular risk not statistically different from that observed in patients who never developed LVH during follow-up. Verdecchia et al obtained similar results in a larger group of 430 patients over a shorter period (3.2 years).<sup>79</sup> In 172 hypertensive patients followed for 11.3 years, Koren et al observed cardiovascular events in 29% with LVH at follow-up versus in 9% of those without.<sup>80</sup>

In the echocardiographic substudy of the LIFE trial that included 941 patients followed for over 4 years, the better prognosis associated with the significant decrease in LV mass from baseline to end of study was due mainly to a decrease in the incidence of stroke.<sup>81</sup>

These cumulative findings highlight the prognostic value of the LV mass response to treatment. Blood pressure was not significantly associated with cardiovascular events in these studies, although it cannot be excluded that the changes observed in the LV mass index at least partially reflected blood pressure control.

Baseline LV geometry confers differing cardiovascular risk in hypertension, concentric hypertrophy being the least favorable. We recently evaluated the relationship between prognosis and the response of LV geometry to antihypertensive treatment in 436 uncomplicated

**Table VII.** Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy (LVH).

Reference	Patients (n)	Events (n)	Events (%) by LVH status		
			Persistence	Regression	None
Muiesan et al, <sup>40</sup> 1995	151	23	38	12.5	5
Verdecchia et al, <sup>79</sup> 1998	430	31	21	6.2	5.4
Koren et al, <sup>80</sup> 2002	172	34	19.8	8.8	9.6
<b>Total</b>	<b>753</b>	<b>88</b>	<b>26.3</b>	<b>9.2</b>	<b>6.7</b>



hypertensives (M: n=249; F: n=187; age 18-71 years) over 6.4 years.<sup>82</sup> Persistence of LVH from baseline to follow-up was confirmed as an independent predictor of cardiovascular events. Cardiovascular morbidity and mortality were significantly greater with concentric than eccentric geometry, whether in the presence ( $P=0.04$ ) or absence of LVH ( $P=0.02$ ) at follow-up. Cardiovascular events were significantly more frequent with persistent concentric geometry ( $P<0.0001$ ) for similar LV mass at follow-up (Figure 1).<sup>82</sup>

Thus, an increase in echocardiographic LV mass in response to antihypertensive therapy, or a failure to decrease, confers a worse prognosis, while complete regression significantly reduces—indeed virtually normalizes—cardiovascular risk. In addition, the response of LV geometry to treatment may also have prognostic significance with and without LVH.

### FUTURE GOALS

Focuses of future concern will include the biochemistry of the adaptive changes in energy metabolism and contractile proteins, notably the role of transmitters and transductional factors, as well as the timing of these responses to blood pressure changes, neurohumoral activation, and the development of structural alterations in other organs.

Techniques such as tissue characterization and non-invasive quantitative analysis of coronary flow will describe the respective contributions of perivascular and intraventricular fibrosis and myocardial ischemia to the mechanisms of LVH risk, and hopefully reveal ways in which these advances can be translated into individual patient benefit. However, we already know more than enough to realize that a major goal in the management of hypertension is the detection, prevention, and reversal of LVH.

### THREE KEY QUESTIONS

The story of left ventricular hypertrophy (LVH) in hypertension is that of a good thing gone bad: hypertension initially triggers a potentially beneficial compensatory increase in left ventricular mass, but this ultimately evolves to a problem, becoming a disease in its own right, as well as a risk factor, endangering the heart and the patient's life. The turning point in the pathophysiology of LVH is fibrosis, which, added to concentric hypertrophy, heralds left ventricular dysfunction. Antonello Ganau and Giuseppe Talanas take a close look at the pathogenesis of LVH, and ask: **“Do coronary circulation abnormalities play an important role in the pathogenesis of hypertensive LVH?”** and establish a firm link, even though the chicken-and-egg conundrum remains entire: is LVH the cause or the consequence of a defect in myocardial perfusion in hypertension? In view of the pivotal role of tissue alterations in the disease process, Javier Díez addresses the question: **“How important is it to assess and attempt to control cardiac fibrosis in hypertension?”** In doing so he opens up exciting preventive and therapeutic prospects. Bernhard M. W. Schmidt and Roland E. Schmieder examine another important question: **“Hypertension and left ventricular hypertrophy: how much attention should we pay to the renin-angiotensin-aldosterone system?”** This question is of particular relevance in view of evidence that drugs modulating the RAAS have beneficial effects that are additive to, and independent of, their blood-pressure-lowering effect. To conclude, by whichever means, LVH regression has benefits and as such detection, prevention, and reversal of LVH are now major targets in the management of hypertension.

## REFERENCES

### 1. Frohlich ED.

Risk mechanisms in hypertensive heart disease.

*Hypertension*. 1999;34:782-789.

### 2. Parati G, Pomidossi G, Albini E, Malaspina D, Mancia G.

Relationship of 24-hour blood pressure mean and variability to severity of target-organ damage in hypertension.

*J Hypertens*. 1987;5:93-98.

### 3. Verdecchia P, Schillaci G, Guerrieri M, et al.

Circadian blood pressure change and left ventricular hypertrophy in essential hypertension.

*Circulation*. 1990;81:528-536.

### 4. Rizzoni D, Muiesan ML, Montani G, Zulli R, Calebich S, Agabiti-Rosei E.

Relationship between initial cardiovascular structural changes and daytime and nighttime blood pressure monitoring.

*Am J Hypertens*. 1992;5:180-186.

### 5. de Simone G, Devereux RB, Roman MJ, Alderman MH, Laragh JH.

Relation of obesity and gender to left ventricular hypertrophy in normotensive and hypertensive adults.

*Hypertension*. 1994;23:600-606.

### 6. de Simone G, Palmieri V, Koren M, Mensah G, Roman MJ, Devereux RB.

Prognostic implications of the compensatory nature of left ventricular mass in arterial hypertension.

*J Hypertens*. 2001;19:119-125.

### 7. Palmieri V, Watchell K, Gerdtts E, et al.

Left ventricular function and hemodynamic features of inappropriate left ventricular hypertrophy in patients with systemic hypertension: the LIFE study.

*Am Heart J*. 2001;141:784-791.

### 8. Grassi G, Gianattasio C, Cleroux J, Cuspidi C, Sampieri L, Mancia G.

Cardiopulmonary reflex before and after regression of left ventricular hypertrophy in essential hypertension.

*Hypertension*. 1988;12:227-237.

### 9. Rizzoni D, Agabiti-Rosei E, Castellano M, et al.

The effect of loading and unloading cardiopulmonary receptors on atrial natriuretic peptide in hypertensive patients with and without left ventricular hypertrophy.

*Clin Exp Hypertens*. 1992;14:717-732.

### 10. Trimarco B, De Luca N, Ricciardelli B, et al.

Cardiac function in systemic hypertension before and after reversal of left ventricular hypertrophy.

*Am J Cardiol*. 1988;62:745-750.

### 11. Duprez D, Bauwens F, De Buyzere M, et al.

Influence of arterial blood pressure and aldosterone on left ventricular hypertrophy in moderate essential hypertension.

*Am J Cardiol*. 1993;71:17A-20A.

### 12. Schlaich MP, Schobel HP, Hilgers K, Schmieder RE.

Impact of aldosterone on left ventricular structure and function in young normotensive and mildly hypertensive subjects.

*Am J Cardiol*. 2000; 85:1199-1206.

### 13. Woessner JF.

Matrix metalloproteinases and their inhibitors in connective tissue remodeling.

*FASEB J*. 1991;5:2145-2154.

### 14. Rizzoni D, Muiesan ML, Porteri E, et al.

Relations between cardiac and vascular structure in patients with primary and secondary hypertension.

*J Am Coll Cardiol*. 1998;32:985-992.

### 15. Rossi GP, Sacchetto A, Pavan E, et al.

Remodeling of the left ventricle in primary aldosteronism due to Conn's adenoma.

*Circulation*. 1997;95:1471-1478.

### 16. Verdecchia P, Reboldi G, Schillaci G, et al.

Circulating insulin and insulin growth factor-1 are independent determinants of left ventricular mass and geometry in essential hypertension.

*Circulation*. 1999;100:1802-1807.

### 17. Barouch LA, Berkowitz DE, Harrison RW, et al.

Disruption of leptin signaling contributes to cardiac hypertrophy independently of body weight in mice.

*Circulation*. 2003;108:754-759.

### 18. Post W, Larson M, Myers RH, Galderisi M, Levy D.

Heritability of left ventricular mass.

*Hypertension*. 1997;30:1025-1028.

### 19. Schunkert H, Hense HW, Holmer SR, et al.

Association between a deletion polymorphism of the angiotensin converting enzyme gene and left ventricular hypertrophy.

*N Engl J Med*. 1994;330:1634-1638.

### 20. Staessen J, Wang JG, Ginocchio G, et al.

The deletion/insertion polymorphism of the angiotensin-converting enzyme and cardiovascular-renal risk.

*J Hypertens*. 1997;15:1579-1592.

### 21. Castellano M, Rossi F, Rivadossi F, et al.

Aldosterone synthase gene polymorphism and cardiovascular phenotypes in a general population.

*J Hypertens*. 2000;18(suppl 4):174. Abstract.

**22. Guidelines Committee.**

2003 European Society of Hypertension–European Society of Cardiology guidelines for the management of arterial hypertension. *J Hypertens.* 2003;21:1011-1053.

**23. Devereux RB, Roman MJ.**

Evaluation of cardiac and vascular structure and function by echocardiography and other non-invasive techniques. In: Laragh JH, Brenner BM, eds.

*Hypertension: Pathophysiology, Diagnosis and Management.* 2nd ed. New York, NY: Raven Press; 1995:1969-1985.

**24. Sundstrom J, Lind L, Arnlow J, et al.**

Echocardiographic and electrocardiographic diagnoses of left ventricular hypertrophy predict mortality independently of each other in a population of elderly men.

*Circulation.* 2001;103:2346-2351.

**25. Okin P, Roman MJ, Lee ET, Galloway JM, Howard B, Devereux RB.**

Combined echocardiographic left ventricular hypertrophy and electrocardiographic ST depression improve prediction of mortality in American Indians. *The Strong Heart Study.*

*Hypertension.* 2004;43:769-774.

**26. Sahn DJ, DeMaria A, Kisslo J, Weyman A.**

The Committee on M-mode Standardization of the American Society of Echocardiography: recommendations regarding quantitation in M-mode echocardiography. Results of a survey of echocardiographic measurements.

*Circulation.* 1978;58:1072-1083.

**27. Devereux RB, Alonso DR, Lutas EM, et al.**

Echocardiographic assessment on left ventricular hypertrophy: Comparison to necropsy findings.

*Am J Cardiol.* 1986;57:450-458.

**28. Muiesan ML, Salvetti M, Monteduro C, Donato F, Rizzoni D, Agabiti-Rosei A.**

Various ways of calculating echocardiographic left ventricular mass and their relative prognostic values.

*J Hypertens.* 1998;16:1201-1206.

**29. de Simone G, Muiesan ML, Ganau A, et al.**

Reliability and limitations of measurement of echocardiographic measurement of left ventricular mass for risk stratification and follow-up in single patients: the RES trial. Working Group on Heart and Hypertension of the Italian Society of Hypertension. Reliability of M-mode Echocardiographic Studies.

*J Hypertens.* 1999;17:1960-1964.

**30. Palmieri V, Dahlof B, DeQuattro V,**

Reliability of echocardiographic assessment of left ventricular structure and function. *The PRESERVE study.*

*J Am Coll Cardiol.* 1999;34:1625-1632.

**31. de Simone G, Devereux RB, Daniels SR, Koren MJ, Alderman MH, Laragh JH.**

Effect of growth on variability of left ventricular mass: assessment of allometric signals in adults and children and of their capacity to predict cardiovascular risk.

*J Am Coll Cardiol.* 1995;25:1056-1062.

**32. Ganau A, Devereux RB, Roman MJ, et al.**

Patterns of left ventricular hypertrophy and geometric remodeling in arterial hypertension.

*J Am Coll Cardiol.* 1992;19:1550-1558.

**33. Shimuzu G, Zile MR, Blaustein AS, Gaasch WH.**

Left ventricular chamber filling and midwall fiber lengthening in patients with left ventricular hypertrophy: overestimation of fiber velocities by conventional midwall measurements.

*Circulation.* 1985;71:266-272.

**34. de Simone G, Devereux RB, Koren MJ, Mensah GA, Casale PN, Laragh JH.**

Midwall left ventricular mechanics. An independent predictor of cardiovascular risk in arterial hypertension.

*Circulation.* 1996;93:259-265.

**35. Muiesan ML, Salvetti M, Rizzoni D, Castellano M, Monteduro C, Agabiti-Rosei E.**

Persistence of left ventricular hypertrophy is a stronger indicator of cardiovascular events than baseline LV mass or systolic performance. A ten years follow-up.

*J Hypertens.* 1996;14(suppl 5):S43-S51.

**36. Di Bello V, Pedrinelli R, Giorgi D, et al.**

Ultrasonic videodensitometric analysis of two different models of left ventricular hypertrophy: athlete's heart and hypertension.

*Hypertension.* 1997;29:937-944.

**37. Ciulla M, Paliotti R, Hess B, et al.**

Echocardiographic patterns of myocardial fibrosis in hypertensive patients: endomyocardial biopsy versus ultrasonic tissue characterization.

*J Am Soc Echocardiogr.* 1997;10:657-664.

**38. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP.**

Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study.

*N Engl J Med.* 1990;322:1561-1566.

**39. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH.**

Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension.

*Ann Intern Med.* 1991;114:345-352.

**40. Muiesan ML, Salvetti M, Rizzoni D, Castellano M, Donato F, Agabiti-Rosei E.**

Association of change in left ventricular mass with prognosis during long-term antihypertensive treatment.

*J Hypertens.* 1995;13:1091-1097.

**41. Vakili B, Okin P, Devereux RB.**

*Prognostic implications of left ventricular hypertrophy.*

*Am Heart J.* 2001;141:334-341.

**42. Weber KT.**

*Collagen matrix synthesis and degradation in the development and regression of left ventricular hypertrophy.*

*Cardiovasc Rev Rep.* 1991;12:61-69.

**43. Aurigemma GP, Silver KH, Priest MA, Gaasch WH.**

*Geometric changes allow normal ejection fraction despite depressed myocardial shortening in hypertensive left ventricular hypertrophy.*

*J Am Coll Cardiol.* 1995;26:195-202.

**44. Verdecchia P, Schillaci G, Reboldi G, Ambrosio G, Pede S, Porcellati C.**

*Prognostic value of midwall shortening fraction and its relation with left ventricular mass in systemic hypertension.*

*Am J Cardiol.* 2001;87:479-482.

**45. Aurigemma GP, Gottdiener JS, Shemanski L, Gardin J, Kitzman D.**

*Predictive value of systolic and diastolic function for incident congestive heart failure.*

*J Am Coll Cardiol.* 2001;37:1042-1048.

**46. Agabiti-Rosei E, Muiesan ML.**

*Hypertension and diastolic function.*

*Drugs.* 1993;46(suppl 2):61-67.

**47. Quinones MA, Otto C, Stoddard M, Waggoner A, Zoghbi W.**

*Recommendations for quantifications of Doppler echocardiography: a report from the Doppler quantification Task Force of the Nomenclature and Standards Committee of the American Society of Echocardiography.*

*J Am Soc Echocardiogr.* 2002;15:167-184.

**48. Schillaci G, Pasqualini L, Verdecchia P, et al.**

*Prognostic significance of left ventricular diastolic dysfunction in essential hypertension.*

*J Am Coll Cardiol.* 2002;39:2005-2011.

**49. Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ.**

*Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic.*

*JAMA.* 2003;289:194-202.

**50. Roman MJ, Pickering TG, Schwartz JE, Pini R, Devereux RB.**

*Association of carotid atherosclerotic and left ventricular hypertrophy.*

*J Am Coll Cardiol.* 1995;25:83-90.

**51. Muiesan ML, Pasini GF, Salvetti M, et al.**

*Cardiac and vascular structural changes. Prevalence and relation to ambulatory blood pressure in a middle-aged general population in Northern Italy. The Vobarno Study.*

*Hypertension.* 1996;27:1046-1052.

**52. Lucarini A, Spessot M, Picano E, et al.**

*Lack of correlation between cardiac mass and arteriolar structural changes in mild-to-moderate hypertension.*

*J Hypertens.* 1991;9:1187-1191.

**53. Niteberg A, Anthony I.**

*Epicardial coronary arteries are not adequately sized in hypertensive patients.*

*J Am Coll Cardiol.* 1996;27:115-123.

**54. Rizzoni D, Palombo C, Porteri E, et al.**

*Relationship between coronary vasodilator capacity and small artery remodeling in hypertensive patients.*

*J Hypertens.* 2003;21:615-621.

**55. Neaton JD, Grimm RH, Prineas RJ, et al, on behalf of Treatment of Mild Hypertension Study Research Group.**

*Treatment of Mild Hypertension Study. Final results.*

*JAMA.* 1993;270:713-724.

**56. Mancia G, Zanchetti A, Agabiti-Rosei E, Benemio G, et al, for the Sample Study Group.**

*Ambulatory blood pressure is superior to clinic blood pressure in predicting treatment-induced regression of left ventricular hypertrophy.*

*Circulation.* 1997;95:1464-1470.

**57. Parati G, Omboni S, Rizzoni D, Agabiti-Rosei E, Mancia G.**

*The smoothness index: a new reproducible and clinically relevant measure of the homogeneity of the blood pressure reduction with treatment for hypertension.*

*J Hypertens.* 1998;16:1685-1693.

**58. Dahlöf B, Pennert K, Hansson L.**

*Reversal of left ventricular hypertrophy in hypertensive patients. A meta-analysis of 109 treatment studies.*

*Am J Hypertens.* 1992;5:95-110.

**59. Cruickshank JM, Lewis J, Moore V, Dodd A.**

*Reversibility of left ventricular hypertrophy by differing types of antihypertensive therapy.*

*J Human Hypertens.* 1992;6:85-90.

**60. Fagard RH.**

*Reversibility of left ventricular hypertrophy by antihypertensive drugs.*

*Neth J Med.* 1995;47:173-179.

**61. Jennings G, Wong J.**

*Reversibility of left ventricular hypertrophy and malfunction by antihypertensive treatment. In: Hansonn L, Birkenhager WH, eds.*

*Handbook of Hypertension (vol 18): Assessment of Hypertensive Organ Damage.* Elsevier Science BV; 1997:185-223.

**62. Klingbeil A, Schneider M, Martus P, Messerli F, Schmieder R.**

*A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension.*

*Am J Med.* 2003;115:41-46.



**63. Agabiti-Rosei E, Ambrosioni E, Dal Palu C, Muiesan ML, Zanchetti A, on behalf of the RACE Study Group.**

*ACE-inhibitor ramipril is more effective than the beta-blocker atenolol in reducing left ventricular hypertrophy in hypertension. Results of the RACE (Ramipril Cardioprotective Evaluation) study.*  
*J Hypertens.* 1995;13:1325-1334.

**64. Gottdiener J, Reda D, Massie BM, Materson BJ, Williams DW, Anderson RJ.**

*Effect of single-drug therapy on reduction of left ventricular mass in mild to moderate hypertension comparison of six antihypertensive agents: the Department of Veterans Affairs Cooperative Study Group on Antihypertensive agents.*  
*Circulation.* 1997;95:2007-2014.

**65. Devereux RB, Palmieri V, Sharpe N, et al.**

*Effects of once daily angiotensin-converting enzyme inhibition and calcium channel blockade-based antihypertensive treatment regimens on left ventricular hypertrophy and diastolic filling in hypertension. The Prospective Randomised Enalapril Study Evaluating Regression of Ventricular Enlargement (PRESERVE) trial.*  
*Circulation.* 2001;104:1248-1254.

**66. Terpstra WF, May JF, Smit AJ, et al.**

*Long-term effects of amlodipine and lisinopril on left ventricular mass and diastolic function in elderly, previously untreated hypertensive patients: the ELVERA trial.*  
*J Hypertens.* 2001;19:303-309.

**67. Agabiti-Rosei E, Muiesan ML, Trimarco B, Reid J, Hennig M, Zanchetti A.**

*Changes of LV mass and ABPM during long-term antihypertensive treatment in ELSA.*  
*J Hypertens.* 2002;20(suppl 4):S4. Abstract.

**68. Gosse P, Sheridan DJ, Dubourg O, et al.**

*Regression of left ventricular hypertrophy in hypertensive patients treated with indapamide SR 1.5 mg versus enalapril 20 mg: The L.I.V.E. Study.*  
*J Hypertens.* 2000;18:1465-1475.

**69. Thurmann P, Kenedi P, Schmidt A, Harder S, Rietbrock N.**

*Influence of the angiotensin II antagonist valsartan on left ventricular hypertrophy in patients with essential hypertension.*  
*Circulation.* 1998;98:2037-2042.

**70. Malmqvist K, Kahan T, Edner M, et al.**

*Regression of left ventricular hypertrophy in human hypertension with irbesartan.*  
*J Hypertens.* 2001;19:1167-1176.

**71. Dahlof B, Zanchetti A, Diez J, et al, for the REGAAL Study Investigators.**

*Effects of losartan and atenolol on left ventricular mass and neurohormonal profile in patients with essential hypertension and left ventricular hypertrophy.*  
*J Hypertens.* 2002;20:1855-1864.

**72. Cuspidi C, Muiesan ML, Valagussa L, Salvetti M, Di Biagio C, Zanchetti, on behalf of the CATCH investigators.**

*Comparative effects of candesartan and enalapril on left ventricular hypertrophy in patients with essential hypertension: the Candesartan Assessment in the Treatment of Cardiac Hypertrophy (CATCH) study.*  
*J Hypertens.* 2002;20:2293-2300.

**73. Okin PM, Devereux RB, Jern S, et al, for the Losartan Intervention For Endpoint reduction in hypertension (LIFE) Study Investigators.**

*Regression of electrocardiographic left ventricular hypertrophy by losartan versus atenolol. The Losartan Intervention For Endpoint reduction in hypertension. (LIFE) Study.*  
*Circulation.* 2003;108:684-690.

**74. de Luca N, Mallion JM, O'Rourke MF, et al.**

*Regression of left ventricular mass in hypertensive patients treated with perindopril/indapamide as a first-line combination: the REASON echocardiographic study.*  
*Am J Hypertens.* 2004;17:660-667.

**75. Brilla CG, Funck RC, Rupp H.**

*Lisinopril-mediated regression of myocardial fibrosis in patients with hypertensive heart disease.*  
*Circulation.* 2000;102:1388-1393.

**76. Lopez B, Querejeta R, Varo N, et al.**

*Usefulness of serum carboxy-terminal propeptide of procollagen type I in assessment of the cardioreparative ability of antihypertensive treatment in hypertensive patients.*  
*Circulation.* 2001;104:286-291.

**77. Levy D, Salomon M, D'Agostino RB, Belanger AJ, Kannel WB.**

*Prognostic implications of baseline electrocardiographic features and their serial changes in subjects with left ventricular hypertrophy.*  
*Circulation.* 1994;90:1786-1793.

**78. Mathew J, Sleight P, Lonn E, et al, for the Heart Outcomes Prevention Evaluation (HOPE) Investigators.**

*Reduction of cardiovascular risk by regression of electrocardiographic markers of left ventricular hypertrophy by the angiotensin-converting enzyme inhibitor ramipril.*  
*Circulation.* 2001;104:1615-1621.

**79. Verdecchia P, Schillaci G, Borgioni I, et al.**

*Prognostic significance of serial changes in left ventricular mass in essential hypertension.*  
*Circulation.* 1998;97:48-54.

**80. Koren MJ, Ulin RJ, Koren AT, Laragh JH, Devereux RB.**

*Left ventricular mass changes during treatment and outcome in patients with essential hypertension.*  
*Am J Hypertens.* 2002;15:1021-1028.

**81. Devereux RB, Watchell K, Gerdts E, et al.**

*Prognostic significance of left ventricular mass change during treatment of hypertension.*

**JAMA.** 2004;292:2350-2356.

---

**82. Muiesan ML, Solvetti M, Monteduro C, et al.**

*Left ventricular concentric geometry during treatment adversely affects cardiovascular prognosis in hypertensive patients.*

**Hypertension.** 2004;43:1-8.

---