Evaluation of Subclinical Target Organ Damage for Risk Assessment and Treatment in the Hypertensive Patients: Left Ventricular Hypertrophy

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At some point in the natural history of hypertension, the compensatory increase in left ventricular mass (LVM) is not beneficial anymore. In fact, it becomes a preclinical disease and an independent risk factor for congestive heart failure, ischemic heart disease, arrhythmia, sudden death, and stroke. In addition to elevated BP, several mechanisms are involved, including body size, age, gender, race, fibrogenic cytokines, and neurohumoral factors, notably angiotensin II, which favor interstitial collagen deposition and perivascular fibrosis. These tissue changes are responsible for the insidious contractile dysfunction that is associated with LVH, consequent to decreased coronary reserve and altered diastolic ventricular filling and relaxation. The cardinal investigations are echocardiography and electrocardiography. All antihypertensive drugs regress LVH, notably those that act on the renin-angiotensin-aldosterone system, which also could 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.

Assessment and Treatment in the Hypertensive Patients: Left Ventricular Hypertrophy

The high prevalence of LV hypertrophy (LVH) in hypertension reflects the increased afterload imposed on the left ventricle, although other important determinants are demographic characteristics (e.g., age, gender, race), neurohumoral and growth factors, and underlying genetic factors. Hypertension is the fundamental trigger to the sequence of biologic events that lead to the development of LVH. LVM is more closely related to average 24-h BP (2–4). Volume load, inotropy, and arterial compliance also are important determinants of the development and the degree of LVH. Other contributing factors include stage of hypertensive disease, genetics, demographic factors, comorbid diseases (e.g., diabetes, obesity, coronary artery disease), possibly mediated via cardiac load. Obesity, which compounds hemodynamic load independent of a clear-cut increase in BP, is a major determinant of LVM, because it is associated with increased plasma volume and cardiac output (5). It has been suggested that considering these measurable factors and hemodynamic load, echocardiographic LVM could be assessed in the individual patient as deviation from the value that is appropriate for a given cardiac workload, corrected for gender and body size. LVH that overcompensates for hemodynamic load tends to cluster with metabolic risk factors and is associated with high cardiovascular risk (6,7). The definition and the clinical evaluation of “inappropriate” LVM require further study.

Among the main nonhemodynamic factors that may contribute to the development of LVH, a variety of neurohumoral and growth factors (e.g., catecholamines, angiotensin II [AngII], aldosterone, endothelins) are included. The effect of sympathetic nervous system activity is evident in experimental models but less clear-cut in humans: in pheochromocytoma LVH prevalence is relatively low and LVM seems to increase proportionately to BP, then in essential hypertension, LVH is associated with altered autonomic activity and a blunted response to β-adrenocceptor stimulation (8–10). Experimental studies also highlighted the role of the renin-angiotensin-aldosterone system (RAAS) in mediating LVH (11,12). AngII induces hypertrophy and hyperplasia in myocytes and vascular smooth muscle cells and may regulate collagen synthesis. Excess AngII production may regulate the expression of fibrogenic cytokine TGF-β1 and favor perivascular and interstitial fibrosis. In addition, AngII may interfere with the process of collagen degradation, modulating the activity of metalloproteinases (a family of zinc-containing proteins that include stromelysins, collagenses, and gelatinases) and their inhibitors (12). Aldosterone also may stimulate extracellular collagen deposition and myocardial fibrosis.

The pathogenic role of the RAAS in the development of
hypertensive LVH requires confirmation, although LVM is significantly increased in renovascular hypertension and primary aldosteronism compared with essential hypertension (13,14). Increased activity of the RAAS and sympathetic nervous system, hyperinsulinaemia, and anemia all may influence the increase of LVM in patients with renal disease.

Hypertensive LVH often is associated with insulin resistance and high insulin levels (15). The involvement of IGFBP-I could clarify the link among obesity, BP 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, therefore indicating the involvement of myocardial leptin receptors in cardiac remodeling (16). Other major metabolic cardiovascular risk factors, notably hypercholesterolemia and hyperglycemia, also may have an influence on LVM and the prevalence of LVH (17).

Several studies have suggested that approximately 30% of LVM variance is genetically determined (18). Studies of genetic influence on LVM have focused mainly and are ongoing on the role of candidate genes, including those that are related to the RAAS, α- and β-adrenoceptors, and components of the signal transduction mechanisms involved in cardiac hypertrophy.

**Methods of Assessing LVH**

As recommended by the European Society of Hypertension and European Society of Cardiology (19), LVH is diagnosed most commonly using electrocardiography (ECG) and M-mode and two-dimensional echocardiography. New ECG criteria in addition to repolarization abnormalities and increased voltage have been proposed, the Cornell method probably being the most sensitive (20). The ECG also can be used to detect patterns of ventricular overload (“strain”) or ischemia, which indicate higher cardiovascular risk. ECG and echocardiographic LVH both predict mortality independent of each other and other cardiovascular risk factors, thus conveying, at least in part, different prognostic information (21,22). Echocardiography has some advantages because it provides comprehensive wall, chamber, and LVM measures, together with systolic and diastolic performance indices, while remaining reasonably cheap, widely available, and wholly noninvasive. The relation between LVM and cardiovascular risk is continuous, although the threshold of 125 g/m²² for men and 110 g/m²² for women currently is used most widely for conservative estimates of LVH, according to the recent European Society of Hypertension–European Society of Cardiology guidelines (19). Despite its advantages, echocardiography may entail a possible technical error as a result of the method itself, the quality of the examination, or observer inexperience. It has been established that a biologic significance can be attributed to changes in LVM that exceed 10 to 15% (23).

Echocardiography also is useful in assessing the different types of LV geometric adaptation to increased cardiac load (24), evaluating the increase in mass and/or in relative wall thickness. More accurate and sophisticated techniques, such as magnetic resonance imaging or cine computerized tomography, are more expensive or time-consuming and are still of limited availability.

Methods have been developed to quantify tissue composition. Studies in animals and humans have shown that LV acoustic properties under physiologic and pathologic conditions are influenced by several tissue components (myocardium, contractile and elastic tissue, collagen and inelastic tissue, arteries, veins, myocytes, and sarcomeres). Results with videodensitometry and integrated backscatter to characterize tissue in several diseases that are associated with abnormal myocardial tissue, including hypertensive LVH and diabetes, indicate that these techniques can complement clinical evaluation by revealing preclinical end-organ damage (25,26). Further reproducibility and feasibility studies are required to assess the clinical applications of these techniques.

**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 for 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 (27). Concentric hypertrophy seems to carry the highest risk and eccentric hypertrophy an intermediate risk, whereas concentric remodeling is probably associated with a smaller, albeit noteworthy, risk.

The structural remodeling of cardiomyocytes, nonmyocytes, and fibroblasts that occurs in cardiac hypertrophy contributes to perivasculair fibrosis, initially around intramural coronary arteries and thereafter in the interstitial space, leading to progressive abnormalities of diastolic ventricular filling and relaxation, systolic dysfunction, arrhythmias, and conduction disturbances, thereby greatly compounding the risk that is associated with LVH (1).

The resulting pathophysiologic and clinical changes that account for increased risk in hypertensive LVH include both diastolic and systolic dysfunction. 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 that comprises ST-segment and T-wave abnormalities was strongly associated with an increased incidence of acute myocardial infarction and sudden death (3–6), suggesting that altered repolarization reflects reduced coronary perfusion.

LVH is associated with structural and functional changes in both large (28,29) and small (14,30,31) arteries. These structural changes are particularly evident in concentric LVH. The association between LVH and extracranial carotid atherosclerosis also might explain the increased risk for cerebrovascular events. The vascular changes that consistently are observed in LVH are also responsible for the reduced coronary reserve. Concomitant atherosclerosis in epicardial coronary vessels and structural alterations and rarefaction of small coronary vessels (32) limit blood supply when oxygen demand is increased. Compensatory angiogenesis is inadequate during the development of adult LVH. Decreased subendocardial coronary perfusion leads to myocyte necrosis and reparative fibrosis, favoring...
the progression to heart failure. Other extravascular mechanisms that compound the impairment of coronary reserve include changes of oxygen demand related to wall tension, heart rate, and contractility. Functional changes further weaken the vasodilator response of the coronary microcirculation. In fact, endothelial dysfunction precedes morphologic 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 arrhythmia in hypertensive LVH, explaining the risk for sudden death. Impaired ventricular filling, left atrial enlargement, and slowing of atrial conduction velocity all encourage atrial fibrillation, increasing the risk for thromboembolism. In addition, in patients with LVH (and abnormal LV geometry), higher urinary albumin excretion has been observed, suggesting that cardiac and glomerular vascular damage may parallel, independent of the hemodynamic load. Because hypertensive LVH is an independent risk factor for cardiovascular morbidity and mortality, the possibility of reversal or even prevention by lowering BP and modifying other pathogenetic factors is a major goal of antihypertensive therapy.

LVH Regression by Antihypertensive Treatment

LVM can be decreased by nonpharmacologic intervention, notably weight loss, which is effective in obese hypertensive patients independent of BP changes. As shown by the multicenter Treatment of Mild Hypertension Study (TOMHS), lifestyle intervention may reduce BP significantly and decrease LVM substantially in 30% of patients. However, there is still no hard evidence of an independent effect by dynamic exercise, dietary sodium, or alcohol restriction.

Multiple studies have shown that BP reduction reverses LVH. The main determinants are treatment duration and degree of BP reduction, in particular of average 24-h BP; subsequent evidence also has shown the importance of homogeneity, or minimal daily fluctuation, in BP control, as expressed in the “smoothness index” (33,34).

Because BP is not the sole determinant of LVH and fibrosis, the differing response of LVM to various classes of antihypertensive drugs can be ascribed to interference with nonhemodynamic factors such as the RAAS and sympathetic nervous system. Several meta-analyses have been conducted, including the main studies demonstrating reversal of echocardiographic LVH using various antihypertensive drugs, and they have shown that baseline LVM and the degree of BP reduction are the main determinants of LVH regression; in addition angiotensin-converting enzyme inhibitors, AngII receptor blockers, and calcium channel blockers have been more effective than β blockers and diuretics given the same decrease in BP (35). Large, randomized, blinded studies that have compared two or more different antihypertensive drugs have provided further data, confirming, at least in large part, the results of meta-analyses.

However, it should be kept in mind that interdrug differences tend to fade with time, because treatment duration is associated with progressive BP control and decrease in LVM. In addition, most major intervention trials that have compared the effects of single antihypertensive drugs on LVM in fact largely have been comparisons of combination therapies, because most patients were taking more than one drug.

There is increasing interest in the effect of antihypertensive treatment on myocardial tissue composition, particularly on perivascular and interstitial fibrous tissue. Recent experimental and human evidence suggests that angiotensin-converting enzyme inhibitors and AngII antagonists are particularly effective in inducing regression of myocardial fibrosis.

Clinical and Prognostic Significance of LVH Regression

Because LVH is such an important independent risk factor in hypertension, there is consensus as to the desirability of its regression and prevention. Regression is associated with numerous benefits, such as improved systolic midwall performance, normalized autonomic function, enhanced coronary reserve, and, possibly, improved diastolic filling and decreased ventricular arrhythmia. It remains to be assessed extensively whether LVM changes may improve parallel vascular and/or renal damage modifications.

The improved prognosis associated with LVH regression has been demonstrated in several studies using ECG measures. The large long-term Losartan Intervention for Endpoint (LIFE) study showed that the greater regression of LVH with losartan was associated with fewer cardiovascular events (36).

Further observations using the more sensitive echocardiographic technique have shown that patients who achieve LVH regression during follow-up are much less likely to experience morbid events as compared with those with persistence of LVH (odds ratio 0.41) (37). In the echocardiographic substudy of the LIFE trial that included 960 patients who were followed for >4 yr, the better prognosis that was associated with the significant decrease in LVM from baseline to end of study was due mainly to a decrease in the incidence of stroke (38).

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

Whereas complete regression significantly reduces cardiovascular risk, an increase in echocardiographic LVM during antihypertensive therapy or a failure to decrease confers a worse prognosis. In addition, the response of LV geometry to treatment may have prognostic significance, independent of changes of LVM (39).

Future Goals

Focuses of future interest 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 BP changes, neurohumoral activation, and the development of structural alterations in other organs. Techniques such as tissue characterization and noninvasive quantitative analysis of coronary coronary
flow will describe the respective contributions of perivascular and intraventricular fibrosis and myocardial ischemia to the mechanisms of LVH risk and, hopefully, indicate ways in which these advances can be translated into the 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.

References


