REVIEW

OF

LITERATURE
The end of natural history of untreated hypertension is an increased likelihood of premature disability or death from cardiovascular diseases. The pathogenesis of hypertension involves structural changes in the resistance arterioles described under term remodeling and hypertrophy.

Diastolic and systolic dysfunction have been observed early in the course of hypertension and either or both may lead to heart failure. Such disatolic dysfunction may reflect more vigorous atrial emptying (Ahmed et al) or abnormal diastolic relaxation (de Simone et al). In established hypertension, abnormal relaxation has been observed in two trials of patients with normal LV systolic function (Rusconi et al).

Left ventricular hypertrophy (LVH) is detected in 25% to 305 of all hypertensive patients and in 1% to 9% of normotensive individuals. When present concomitant to hypertension, LVH is initially a useful compensatory process that represents an adaptation to increased ventricular wall stress. However, LVH is also the first step toward to development of overt clinical disease such as congestive heart failure, cardiac, dysrhythmias, and ischemic heart disease.

LVH represent an important risk factor for cardiovascular morbidity and mortality, independent of causal blood pressure, and more powerful than hypertension per se, cigarette smoking, or
hypercholesterolemia\textsuperscript{1}. In fact, a large number of studies have noted, in both clinical and epidemiological populations, the relationship between LVH at baseline examination and the risk of subsequent morbidity or mortality events.

A number of studies have used electrocardiographic criteria to document the relationship between LVH and an adverse prognosis\textsuperscript{2-5}. The Framingham Heart study has shown that LVH detected by electrocardiography (ECG) increases the risk for coronary heart disease, sudden death, cardiac failure, stroke and occlusive peripheral arterial disease. The study also found that ST and T-wave abnormalities enhance the risk associated with increased R-wave amplitude, suggesting that the risk attributed to LVH found by ECG is caused not only by hemodynamic overload but also by the coexistence of coronary disease.

Echocardiography is a specific and repeatable technique for the assessment of cardiac anatomy and function. It is more sensitive than ECG for the diagnosis of LVH. Direct measurement of left ventricular mass (LVM) by echocardiography has proved this parameter to be a strong predictor of subsequent morbidity and mortality. In several studies, patients with LVH, measured as high LVM consistently had at least two- to four-fold higher rates of cardiovascular complications than hypertensive individuals without LVH, although differences existed in the rate of adverse events depending on the end point considered and in the level of risk in the population being studied.

The echocardiographic technique has demonstrated that the geometric adaptation of left ventricle to increased cardiac load may
differ among patient. The three variations of adaptation are concentric remodeling concentric hypertrophy, and eccentric hypertrophy. Concentric remodeling occurs with an increase of thickness with respect to radius, without an increase in mass. Concentric hypertrophy is characterized by increased mass and increased relative wall thickness. Eccentric hypertrophy characterized by increased mass while relative wall thickness remains below 0.45. Concentric hypertrophy appears to carry the highest cardiovascular risk, followed by eccentric hypertrophy with an intermediate risk. Concentric remodeling seems only to be associated with a small though consistent risk.\textsuperscript{11} In the Framingham study, individuals with concentric hypertrophy also had the greatest LVM. Any increase in rate of unfavorable clinical out comes seen in this group of patients was largely attenuated after adjustment for baseline differences in LVM and cardiovascular risk factors.\textsuperscript{12} It has been concluded, therefore, that knowledge of the left ventricular geometry provided little prognostic information beyond that derived from evaluation of LVH and major cardiovascular risk factors.

Several mechanism have been proposed to explain the association of LVH with increased cardiovascular risk.\textsuperscript{13,14} Firstly, LVH may lead to diastolic filling abnormalities that predispose to congestive heart failure. Secondary, LVH may be associated with dysfunctional autonomic nervous system activity and reduced coronary reserve.

Thirdly, LVH may predispose to ventricular arrhythmias and a greater risk of sudden death.\textsuperscript{15} In addition, LVH may be a sensitive
indicator of changes in vascular structure in both large and small arteries.

Echocardiographic determination of midwall shortening is a sensitive method for evaluation of ventricular function, and can identify a consistent proportion of asymptomatic hypertensive patients exhibiting reduced left ventricular myocardial performance as well as hemodynamic characteristics associated with increased cardiovascular risk. It has been proposed that the presence of depressed midwall shortening is a predictor of adverse outcome in arterial hypertension and that the combination of increase LVM and reduced midwall shortening identifies patients at markedly increased risk.

Determinants of left ventricular mass in hypertension

Arterial pressure

Arterial blood pressure is usually considered the most powerful determinant of LVM in hypertension; However, LVM correlates poorly with casual systolic and diastolic blood pressure. Blood pressure fluctuates from beat to beat and it is therefore unlikely that a few blood pressure measurements can be representative of the total pressure burden of a hypertensive individual. However, the use of ambulatory blood pressure techniques have permitted the finding of a closer correlation between 24-hour average blood pressure and LVM.

Much attention has been directed recently to the importance of daytime and night-time values of blood pressure and, in particular, to the lack of nocturnal decrease of blood pressure in patients with LVH. However, it has been observed that the subdivision of
patients into ‘dippers’ is at present only arbitrary, and that the reproducibility of classification into these two categories is rather poor. It should also be considered that a blunted diurnal blood pressure rhythm could be the consequence and not necessarily the cause, of target – organ damage and LVH.\textsuperscript{18}

The prevalence of LVH increases progressively with age.\textsuperscript{19} This trend has been observed not only in hypertensive patients but also in normotensive individuals. The increase in LVM with age may be largely explained by a reduction in aortic impedance an increase in blood pressure and possibly the presence of subclinical degenerative processes (i.e., fibrosis or amyloidosis). In some studies, it has been found that for any given level of arterial blood pressure, black patients have larger LVM than white patients with comparable parameters. The Framingham study has shown that in those under 50 years of age, LVH is more common in men, while in those over 50 years of age LVH is more common in women. The increase in LVM with age seems to be more pronounced in women. Obesity is also strongly related to LVH which is more frequently of the eccentric type.

Offspring of hypertensive patients seem to have a greater LVM than that seen in the general population, although it is not clear whether this might just be a consequence of slightly higher blood pressure values in the offspring. In addition several studies have indicated that hypertension is frequent in normotensive individuals with increased LVM.\textsuperscript{20,21}

In recent years, several studies reported a relationship between polymorphism of the reninangiotensin system (RAS) gene and
cardiovascular structural changes of disease. Although there is some evidence of an associated between RAS gene polymorphism and LVH, the association is not predictable. Further studies are needed to define genetic characteristics that may be accepted as generalized susceptibility markers for LVH.\textsuperscript{22-24}

It has been shown in several studies that LVM is correlated with the degree of urinary sodium excretion over 24 hours, which is a measure of daily salt intake.\textsuperscript{25} Intravascular volume increase when sodium intake is high, with a consequent development of eccentric LVH. Conversely, low salt intake reduces or prevents the development of LVH.

Recently, it has been shown that LVH is common in chronic alcoholics with essential hypertension.\textsuperscript{26} This may be related to the stimulating effect of alcohol on the sympathetic nervous system and/or to its direct effect on vascular smooth muscle.

Experimental studies indicate that noradrenaline is able to induce LVH, even at subpressor doses. The importance of sympathetic nervous system activity in facilitating the development of LVH in essential hypertension in humans is not known.\textsuperscript{27} LVH is not frequent in patients which pheochromocytoma.\textsuperscript{28} However, patients with essential hypertension often have impaired cardiopulmonary reflexes and a reduced response to beta-adrenergic stimulation.

He results of several experimental and a few clinical studies have suggested that both the RAS and the excess of aldosterone play an important role in the pathogenesis of LVH. In experimental trials, angiotensin II was found to cause hypertrophy and/or
hyperplasia in myocardial cells. Further more, excess aldosterone has been related to extracellular matrix and collagen deposition and there fore to myocardial fibrosis. Definitive proof of the contribution in humans of the RAS and aldosterone excess to the pathogenesis of LVH and myocardial fibrosis is still lacking, although their role is suggested by findings in patients with primary aldosteronism and renovascular hypertension.

Other humoral factors related to the presence of LVH include parathyroid hormones, growth hormone, and insulin.

Long-standing LVH leads to impairment of contractile function with progressive dilation of the left chamber and finally, to the development of congestive heart failure. Left ventricular pump function may show early impairment during exercise, concentric LVH is frequently associated with a reduced midwall fractional shortening.

Left ventricular compliance is reduced by thickening of the ventricular wall. Diastolic dysfunction of LVH is related to both decreased early-diastolic relaxation and decreased late-diastolic compliance. LVH is frequently associated with ventricular ectopy. The mechanism for such arrhythmias is not clear, but appears to be related to the process of hypertrophy and accompanying fibrosis, in addition to coexisting coronary artery disease or possibly to diuretic-induced hypokalemia. Whether ventricular ectopy can explain the increased prevalence of sudden death observed in patients with LVH remains to be demonstrated.

A decrease in coronary reserve parallels the development of LVH in hypertension. This impairment in coronary reserve is related to disease of the large coronary arteries and to cardiac microvascular
disease, as well as to an increased hemodynamic load and an increased left ventricular muscle mass, both of which require more oxygen.

Several hundred human and experimental studies have established that blood pressure reduction may reverse hypertensive LVH. Recent evidence from the study on Ambulatory Monitoring of Pressure and Lisinopril evaluation (SAMPLE) has shown that this regression is more accurately predicted by measurements of average blood pressure, using ambulatory monitoring, than by clinic or home blood pressure recordings.\textsuperscript{32} Non-pharmacological intervention, such as weight reduction or reduced dietary salt intake, also leads to a successful reduction in LVH.\textsuperscript{25,33}

The various classes of antihypertensive drugs differ in their ability to reduced LVM. The reason for this disparity may be due to differing effects on certain non-hemodynamic factors, such as the RAS, the sympathetic nervous system, and other growth factors, which may contribute to either the development or the reversal of LVH.

This hypothesis was suggested for the first time in reports of the elegant studies of Sen and Tarazi of spontaneously hypertensive rats.\textsuperscript{34} The researchers observed that although methyldopa, hydralazine, and minoxidil resulted in an equivalent reduction of blood pressure, ventricular mass was reduced after treatment with methyldopa but increased after treatment with minoxidil. Sen and Tarazi suggested that the failure of direct vasodilators to regress LVH may be result of adrenergic stimulation.
In humans, few studies with sympatholytics, including methyldopa, clonidine and reserpine have reported a significant regression of LVH. One study reported that methyldopa led to a significant reduction of LVM despite only small changes in blood pressure. However, vasodilators such as minoxidil and hydralazine did not induce any significant regression of LVH despite a satisfactory control of blood pressure.

Angiotensin – converting enzyme (ACE) inhibitors, which reduce blood pressure through peripheral vasodilation but, in contrast to other vasodilators, do not induced reflex adrenergic stimulation, consistently reduce LVH. Conflicting results have been reported with the use of diuretics and beta- blockers; although most studies with these agents have reported that the antihypertensive effect of these agents is associated with a reduction in LVM. Recent studies have suggested that indapamide may be more effective than other diuretics in reducing LVH. The various pharmacological classes of calcium – channel blockers have all been found to have significant reducing effects on LVM, despite the fact that dihydropyridine compounds are sometimes associated with measurable, albeit small , adrenergic stimulation.

Dahlof et al performed a meta- analysis of all relevant published studies on echocardiographically demonstrable reversal of LVH obtained through the use of antihypertensive drugs. A total of 109 studies comprising more than 2300 patients were considered. Dahlof et al concluded that ACE inhibitors, beta- blockers, and calcium-channel blockers all reduced LVH by reversing wall hypertrophy, whereas diuretics reduced LVM mainly by decreasing left ventricular
volume. The authors calculated in these meta-analyses that the reduction of LVM was most pronounced with ACE inhibitors similar conclusion were reached by Cruickshank et al in their meta-analysis of 104 published studies.  

However, these data cannot be considered definitive because of serious limitations in the studies. In fact most of the studies considered in this meta-analysis were small (involving an average of 10-15 patients per patients per study), open nonrandomized, and non-comparative. Further problems include short study durations (less than 6 months), poor characterization of patients, and lack of blinding of echocardiographic measurements.

In a later meta-analysis, Schumieder found only 8% (39/471) of available studies that were randomized, double-blind, parallel, group comparisons, were performed in patients with World Health Organization (WHO) class I or II hypertension without concomitant cardiac disease. The analysis indicated firstly that the fall in blood pressure and the initial LVM determines the reduction of LVH, and secondary that both ACE inhibitors and calcium-Channel blockers are more effective than beta-blockers or diuretics in this respect.

In addition, it should be considered that the efficacy of different classes of drugs on specific patient's populations may modify the final effect on LVH. Dahlof et al observed a greater effect on LVM of ACE inhibitors compared with diuretics in a group of 28 Caucasian men. Schulman et al found that a calcium-channel blockers induced a greater reduction in LVM than induced by a beta-blockers in a group of 42 elderly patients, predominantly of the African-American race. These results correspond with the expected differences in efficacy of
different classes of antihypertensive drugs between black and white, and young and elderly patients.

In the large multicenter Treatment of Mild Hypertension Study (TOMHS) a total of 819 mildly hypertensive individuals underwent an echocardiographic study at baseline then at least once during the 4-year treatment period. All study participants received a highly effective nutritional lifestyle intervention, which consisted of nonpharmacological interventions such as weight reduction and reduced sodium intake. Approximately 70% (668/819) of patients were randomized to additional active therapy with low doses of a representative diuretic, betablocker, ACE inhibitor, or calcium – channel blockers. The nutritional- lifestyle approach was very effective and reduced blood pressure and LVM so successfully that only limited information about the effects of antihypertensive drugs on the heart could be obtained. In fact, only chlorthalidone achieved a further slight reduction in LVN (-7g compared with placebo) and did so mainly by decreasing left ventricular volume.

The Ramipril Cardioprotective Evaluation (RACE) study group have carried out a trial designed to compare the effect on LVH of blood pressure lowering by the ACE inhibitor ramipril with that of a similar blood pressure reduction by the beta –blocker atenolol. Study was multicentered with central-blind readings of the echocardiograms, in accordance with the Prospective Randomized Open Blinded Endpoint (PROBE) study design. Of the 193 patients enrolled in the sixteen centers, II gave echocardiograms that could be quantitatively evaluated. The study demonstrated that for the same reduction of blood pressure, LVH was significantly reduced by
ramipril only. Thus, this study agrees with the results of the meta-
analysis performed by Dahlof et al and Cruickshank et al.\textsuperscript{39,40}

In a comparative echocardiographic study involving 151
patients, the effect of 6 months of treatment with the diuretic
indapamide on regression of LVH was compared with the effect of the
calcium-channel blocker nifedipine, the ACE inhibitor enalapril, the
beta-blocker atenolol, and the classic diuretic hydrochlorothiazide in
four parallel, double-blind studies.\textsuperscript{37} For a similar reduction in blood
pressure, the drugs, with the exception of hydrochlorothiazide,
induced a similarly significant reduction in LVM. The reduction in LVM
during indapamide treatment was obtained through a decrease of left
ventricular wall thickness.

Gottdiener et al have recently published the results of the
Veterans Affairs Cooperative Study on Single-drug Therapy in Mild
– to –Moderate Hypertension.\textsuperscript{46} The study was designed to compare
the effects on echocardiographic LVM of anti-hypertensive
monotherapy with six different agents in a group of 584 males with
hypertension (85% were black). After 1 year of treatment, the
greatest reductions in LVM were obtained with captopril (reduction of
15g,p+0.05), and hydrochlorothiazide( reduction of 14g,p+0.08). No
significant changes were observed with atenolol, diltiazem, clonidine,
or prazosin. However, this study could not produce consistent results
due to the high drop-out rate left less than 40 patients in each
treatment arm and to the fact that no women were studied.

In conclusion, available data support the hypothesis that
antihypertensive drugs that inhibit the activity of the RAS or, a lesser
extent, the sympathetic nervous system reduce LVH more
consistently than drugs that stimulate these systems ACE inhibitors may have particularly beneficial effects on LVM because of their ability to inhibit or antagonize the action of growth factors. Increased production of bradykinin and, hence nitric oxide may confer further benefit to treatment by ACE inhibition. However, all or most antihypertensive drugs, if used for sufficiently long periods, may reduce LVM. Any apparent difference between the classes of antihypertensive drugs in the reversal of LVH may reflect temporal differences only. Rapid reversal of LVH, nevertheless, may be clinically important, because reducing arterial pressure in the absence of a concomitant reduction in LVM may lead to important of coronary perfusion.\textsuperscript{47}

Several studies have indicated that the reversal of LVH is associated with an improvement of the functional consequences of increased LVM.\textsuperscript{13} In fact, it has been shown that reduction of LVM does not impair and may even improve systolic function as assessed by the usual echocardiographic indices of left ventricular performance. Results of studies concerning the changes of diastolic filling after reversal of LVH have been conflicting. This is probably due to the use of different methodologies by the studies. In several studies an improvement of the diastolic filling pattern has been demonstrated with the reduction of cardiac hypertrophy. A change toward normalization of autonomic nervous system activity, particularly of cardiopulmonary reflexes, and a possible reduction in arrhythmias have also been described in association with the reversal of LVH. In addition, a possible improvement of coronary flow reserve has been found to be associated with LVH regression.
To date only four studies have examined the potential clinical benefits of regression of LVH. Levy et al analyzed the data from 524 participants in the Framingham Heart Study, in which the diagnosis of LVH was based on ECG criteria. The report observed that the decrease of LVH toward normal, assessed by biannual serial ECG examination over a mean follow-up of 5 years, was associated with a reduction in cardiovascular risk.

Two other studies measured LVM changes detected by echocardiography. A study by Koren et al has shown that 166 hypertensive patients evaluated by echocardiography and followed up for 5.5 years; cardiovascular events occurred in 16% of patients whose LVM increased from baseline and in only 6% patients whose LVM decreased.

In the second relevant study, by Yurenev et al, 304 patients with LVH or high normal LVM at baseline echographic examination were studied for 4 years and retrospectively divided into two groups according to the presence or absence of cardiovascular complications. LVH regression or progression was strongly associated with the likelihood of morbid events. In fact LVH was significantly reduced only in the group without cardiovascular complications. However, in this study there was no central-blind reading of echocardiograms. Muesan et al studied 151 patients with uncomplicated hypertension who underwent a good quality echocardiogram for left ventricular anatomy evaluation. The echocardiographic examination was repeated after a mean period of 10 years. In these patients, changes in LVM were evaluated in relation to the incidence of nonfatal cardiovascular events. After
adjustment for the traditional cardiovascular risk factors, the cumulative incidence of nonfatal cardiovascular events was significantly higher in the group of patients without regression of LVH. Cox survival analysis showed the pressure of LVH at the end of follow-up to be the most important independent predictor of cardiovascular events (Relative risk +3.53, P < 0.001 in patients with persistence of LVH and 1.38, P < 0.1 in patients with regression of LVH).

As the follow-up in this study was relatively long, this allowed the observation that normalization of cardiac mass in patients with previous LVH was associated with a reduced risk cardiovascular events. This reduced risk became similar to that in patients without cardiac hypertrophy from baseline to end of follow-up. The results also demonstrate that either increase or lack of decrease in LVM in treated hypertensive patients, as determined by echocardiography, is associated with a worse prognosis, which becomes evident after several years.

These data strongly suggest that LVH regression carries an improved prognosis for hypertensive patients. Therefore, reversal of LVH represents a major goal for the treatment of these patients, in addition to and beyond the goal of blood pressure reduction.

Controlled studies with a strict control of treatment type changes in clinic and monitored blood pressure, and other relevant covariates, will prove the worth of LVH as a valid intermediate end point for clinical trials of hypertension.

LVH is a powerful predictor of cardiovascular morbidity and mortality, independent of blood pressure and other cardiovascular
risk factors. Available data indicate that patients who fail to achieve a reduction in LVH are more likely to suffer cardiovascular events than those in whom LVM is reduced or even normalized by antihypertensive treatment.

Further studies are needed in order to learn more about the anatomo-functional assessment of LVM and the role of LVH in the evolution of cardiovascular disease. At present, however, enough is known to consider detection, prevention, and reversal of LVH a major goal in the evaluation and treatment of hypertensive patients.