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HYPERTENSION AND LEFT VENTRICULAR HYPERTROPHY

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In hypertension, left ventricular hypertrophy (LVH) is initially a useful compensatory process that represents an adaptation to increased ventricular wall stress; however, it is also the first step toward the development of overt clinical disease. The Framingham study has shown that the prevalence of LVH, according to EKG criteria, is quite low in a general population sample (about 3%). Using the echocardiographic technique, it has been demonstrated that the prevalence of LVH in the Framingham population increases from 5% in subjects younger than 30 years to 50% in those older than 70 years. The Framingham study has also shown that the prevalence of echocardiographic LVH is 15–20% in mild hypertensive patients and increases further in patients with more severe hypertension [1].

The increase of LV mass with age might reflect the influence that other risk factors exert with time on the development of LVH. The relationship of echocardiographic LV mass with clinical blood pressure is usually weak. Twenty-four hour blood pressure recordings have shown a much closer correlation between LV mass and average daily blood pressure [2]. Non-haemodynamic factors, such as age, sex, race, body mass index, diabetes, or dietary salt intake may contribute to determining whom, among hypertensive patients, develop LVH and to what degree LVM is increased.

In fact, the coexistence of hypertension with diabetes increases the prevalence of LVH. Moreover, insulin resistance and high insulin levels are associated with the development of LVH in hypertensive patients. Other major cardiometabolic risk factors, notably hypercholesterolemia and hyperglycaemia, may also modify the extent of LVM and the prevalence of LVH in the hypertensive population. Genetic factors might also exert a powerful modulation of LV mass; in fact, monozygotic twins have more similar LV mass values then dizygotic twins [3].

Diagnosis of LVH

Several diagnostic criteria for LVH diagnosis can be used. Electrocardiography has a low sensitivity for LVH detection, but nonetheless LVH diagnosed by the Sokolow-Lyon index or the Cornell voltage-duration product has been shown to be an independent predictor of cardiovascular events [4]. Electrocardiography can also be used to detect patterns of repolarization abnormalities and arrhythmias, including atrial fibrillation.

Echocardiography is a specific, repeatable and far more sensitive measure of LVH in comparison with EKG. Proper evaluation includes calculation of LV mass according to M-mode measurements, under two-dimensional control, of LV internal diameter and wall thickness, according to ASE recommendations or the „Penn Convention". These methods have been validated with measurements obtained by necroscopic examination. Measurements of LV wall thickness and internal dimensions from 2D images can be also performed.

Although the relationship between LV mass and incidence of cardiovascular events is continuous [5], ESH/ESC guidelines indicate that the thresholds of 125 g/m^2 BSA in men and 110 g/m^2 in women may be used for conservative estimates of LVH [6]. An assessment of LV mass reproducibility, one of the major technical limitations of echocardiography, has shown that LV mass changes of 10 to 15% may have true biological significance in individual patients [7]. Geometric adaptation of the left ventricle to increased cardiac load may differ among patients. Concentric hypertrophy is characterized by increased mass and increased relative wall thickness, whereas eccentric hypertrophy is characterized by increased mass and relative wall thickness < 0.42; concentric remodelling occurs when there is increased thickness with respect to radius, in the presence of normal LV mass [8]. These LV geometric patterns are associated with different haemodynamic characteristics, and peripheral resistances are greater in patients with concentric geometry, while cardiac index is increased in those with eccentric hypertrophy.

Evaluating LV mass increase by taking into account gender and cardiac loading conditions has been proposed in order to discriminate the amount of LV mass adequate to compensate the haemodynamic load (adequate or appropriate) from the amount in excess to loading conditions (and therefore inappropriate or not-compensatory). LV mass is inappropriate when the value of LV mass measured in a single subject exceeds the amount needed to adapt to the stroke work for that given gender and body size [9].

Prognostic value of LVH and its regression by treatment

A large number of studies have reported on the relationship between LVH at baseline examination, measured either by EKG or by echocardiography, and the risk of subsequent morbid or mortal events in clinical or epidemiological populations [4]. Despite the fact that electrocardiography has a low sensitivity for LVH detection, LVH diagnosed by the Sokolow-Lyon index or the Cornell voltage-duration product is an independent predictor of cardiovascular events [4]. Direct measurement of LV mass by echocardiography (M-mode, under two-dimensional control) has proved to be a strong predictor of the risk of cardiovascular morbidity and mortality; subjects with LVH consistently have 2 to 4 or more -fold higher rates of cardiovascular complications, independent of other risk factors such as hypercholesterolaemia, age, and blood pressure measured in the clinic or by 24-hour blood pressure monitoring [4]. Concentric hypertrophy appears to carry the highest risk and eccentric hypertrophy an intermediate risk. The presence of inappropriate LV mass is also associated with an increased number of cardiovascular events, even in hypertensive patients without LVH [10].

The prognostic significance of changes in EKG criteria of LVH has been demonstrated in the Framingham population [11], in high CV risk patients [12], in hypertensives with isolated systolic hypertension [13] or with EKG-LVH [14] (Table 1).

Other observational, prospective studies have examined the potential clinical benefits of regression of echocardiographic detectable LVH, and have demonstrated that changes in LV mass, during treatment, may imply an important prognostic significance in hypertensive patients (Table 2). The results of these studies [15–18] have also been analysed in a metanalysis [19]. They have clearly shown that subjects who failed to achieve LVH regression, or in whom LVH developed during follow-up, were much more likely to suffer morbid events than those in whom LVH regressed or never developed. In these studies, LV mass changes during antihypertensive treatment and age were the most important factors related to the occurrence of cardiovascular fatal and non-fatal events in hypertensive patients. Further information was obtained in the LIFE echocardiographic sub-study, performed according to a prospective, interventional, controlled design. In this study, including 930 patients with EKG LVH, a decrease of 25 g/m^2 (i.e. one standard deviation) of LV mass index was associated with a 20% reduction of the primary end-point, adjusting for type of treatment, basal and treatment BP, and basal LV mass index [20].

Table 1. LVH and risk of cardiovascular (CV) events

Reference	N° patients	Average follow-up yrs	CV events
Levy et al. 1994	524 Framingham population	36 EKG bi-annual examination	Decrease in voltage vs no change OR 0.46 (95% CI 0.26–0.84) ♂ OR 0.56 (95% CI 0.30–1.04) ♀
			Increase in voltage vs no change OR 1.86 (95% CI 1.14–3.03) ♂ OR 1.61 (95% CI 0.91–2.84) ♀
Matthew et al. 2001	8281 High CV risk patients	2.8	12.3% in patients with LVH regression/absence 15.8% in patients with LVH persistence/development
Fagard et al. 2004	4159 Older patients with systolic hypertension	6.1	14% decrease in cardiac events for 1 mV change in EKG voltage
Okin et al. 2004	9193 Patients with EKG LVH	4.8	20.4% decrease in composite endpoint for 10.5 mm (1 SD) Sokolow Lyon Index
			15.4% decrease in composite endpoint for 1050 mm × × msec (1 SD) Cornell product

Table 2. Regression of LVH during antihypertensive treatment (yes/no) and occurence of non-fatal cardiovascular events

Reference	N° patients	Average follow-up yrs	CV events		
Prospective studies in hypertensive patients with and without LVH, no randomized treatment			LVH regression	No LVH regression	Never LVH
Muiesan et al. 1995	151	10.1	12.5%	37%	5.1%
Verdecchia et al. 1998	430	2.8	6%	13%	5.4%
Cipriano et al. 1992	311	7.9	9.6%	13%	4.8%
Koren et al. 2001	172	11.6	6.2%	28.6%	9.6%
Muiesan et al. 2004	436	10	7.4%	28.6%	12.3%
Prospective study in patients with EKG LVH, randomized treatment					
Devereux et al. 2004	930	4.8	HR 0.80 (95% CI 0.70–0.95) of CV events for a change in LVMI of 25 g/m^2, $p = 0.009$		

The information obtained in the metanalysis and in the LIFE study should be considered complementary. In fact, while the observational prospective studies have analysed younger patients, with or without LVH at baseline, with follow-up examinations by their family doctors, in the LIFE study all patients had EKG-LVH and were older, at higher cardiovascular risk, were randomized to receive antihypertensive treatment and were followed according to a clinical prospective protocol.

The prognostic significance of LVM changes in subgroups of patients at higher CV risk (diabetics, patients with previous stroke or MI) deserves further investigation. Changes in geometric adaptation seem to imply a prognostic value, independent of changes in LV mass. The persistence, or development of, a concentric geometry during treatment has been found to be associated with a greater incidence of cardiovascular events, independent of changes in LV mass [21]. The LIFE study has provided results that confirm the prognostic influence of LV geometry, in addition to changes in LV mass [22].

A better prognosis associated with regression of LVH may be related to the improvement of systolic and diastolic function, to the increase of coronary flow reserve and to the decrease of cardiac arrhythmias. ESC/ESH guidelines suggest that echocardiography should be performed in patients at low or intermediate CV risk in order to better identify global cardiovascular risk, and to start more appropriately pharmacological treatment [6]. In fact, it has been shown that an increase of echocardiographic LV mass can be identified in 25–30% of hypertensive patients with a low or moderate CV risk (based on risk factor evaluation and EKG), thus substantially changing the original risk stratification [23, 24]. There is no evidence that an echocardiographic study may modify the therapeutic strategy in patients at high or very high CV risk.

In patients at high CV risk, and in particular in patients with aortic valve disease, or in patients with asymptomatic LV dysfunction, echocardiography may be useful to better define and follow cardiac anatomical and functional alterations.

At this time, the echocardiographic instrumentation for LV mass measurements is widely available in most western countries; hopefully, with reduction of price, its use will be expanded worldwide. Among other diagnostic procedures, usually reserved for specific indications, nuclear magnetic resonance provides the most precise measurements of LV mass and cardiac tissue constitution; however, the cost of NMR prevents large-scale use in hypertension. Techniques based on the reflectivity of cardiac ultrasound imaging have been used in order to assess the degree of cardiac fibrosis and to improve the ability of increased LV mass to predict the outcome, together with the use of new biomarkers such as circulating markers of collagen tissue composition.

It has been demonstrated that an effective, long-term antihypertensive treatment, inducing a gradual, constant and homogeneous control of 24-hour blood pressure values, may determine a significant reduction and even a normalization of LVH [25]. However, available studies have also suggested that regression of LVH may be more rapidly or more completely obtained by the use of some classes of antihypertensive drugs such as Angiotensin receptor blockers, ACE-inhibitors and calcium antagonists [26, 27]. Echo-reflectivity studies have suggested that tissue composition of the left ventricle may vary, and that drugs favouring LVH regression may affect myocardial fibrosis differently.

Conclusions

Patients with LVH at baseline and in whom LV mass reduction has not been reached during antihypertensive treatment should be considered at high risk for cardiovascular events and should therefore undergo frequent and accurate clinical controls for blood pressure and other risk factor assessment. At present, regression of LVH represents the most clinically useful intermediate end-point, together with proteinuria, for the evaluation of the efficacy of antihypertensive treatment.

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