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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 prevalence of LVH, according to ECG criteria is quite low in a general population sample (about 3%), but increases to 7-40% in hypertensive patients [1].

Using the echocardiographic technique it has been demonstrated that the prevalence of LVH in the Framingham population increases from 5%, in subjects younger then 30 years to 50 % in those older then 70 years. The Framingham study has also shown that the prevalence of echocardiographic LVH is 15-20 % in mild hypertensive patients and further increases in patients with more severe hypertension [2].

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 clinic blood pressure is usually weak. Twenty-four hours blood pressure recordings have shown a much closer correlation between LV mass and average daily blood pressure. Non-hemodynamic factors, such as age, sex, race, body mass index, diabetes, dietary salt intake may contribute to determine who among hypertensive patients develop LVH and to what degree LVM is increased.

LVH seems to be associated with an inflammatory state (as indicated by elevated CRP levels), although the relationship might be mediated by comorbid conditions. 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 cardio-metabolic risk factors, notably hypercholesterolemia and hyperglycemia, 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 similar LV mass values more than dizygotic twins. Cardiac adaptation with age and during chronic pressure overload may differ according to gender since women develop more concentric LV geometry, retaining higher indices of systolic function [3]. Women tend to have greater impairment of diastolic function , as related to interstitial fibrosis, which may explain the evolution toward heart failure with preserved ejection fraction.

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 (2), except in obese patients [4]. Electrocardiography can be also 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 ECG [2].

Proper evaluation includes calculation of LV mass according to M-mode measurements, under two-dimensional control, of LV internal diameter and wall thicknesses, according to ASE Recommendations or the "Penn Convention" [2]. These methods have been validated with measurements obtained at necroscopic examination. Measurements of LV wall thicknesses and internal dimensions from 2D images can be also performed.

Although the relationship between LV mass and incidence of cardiovascular events is continuous, ESH/ESC guidelines indicate that the thresholds of 115 g/m2 BSA in men and 95 g/m2 in women may be used for conservative estimates of LVH [2].

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 the individual patient [5]. Geometric adaptation of the left ventricle to increased cardiac load may be different 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 [2,6]. 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. The dilated concentric hypertrophy is associated with the highest risk of CV events.

It has been proposed to evaluate LV mass increase taking into account gender and cardiac loading conditions, in order to discriminate the amount of LV mass adequate to compensate the hemodynamic 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 the single subject exceeds the amount needed to adapt to stroke work for that given gender and body size [7].

In addition echocardiography may measure other parameters (regional and global LV systolic and diastolic function, left atrium dimensions and volume), all associated with an increased incidence of major CV events [6]. Left atrial enlargement is present in a relevant fraction of the hypertensive population, mainly in those with LVH, increasing the risk of atrial fibrillation and stroke [6].

LV mass measurement may be obtained by cardiac magnetic resonance Imaging (MRI), with a higher reproducibility than echocardiography; the improvement in reproducibility has relevant practical implications, such as more precise detection of serial changes in individual patients in a shorter time interval and smaller sample size design in clinical trials targeting LVH regression during antihypertensive treatment. Late gadolinium enhancement (LGE)-cardiac MRI may allow the detection of myocardial fibrosis [8]. Unfortunately MRI has still a relatively high cost and limited availability. The use of 3D echocardiography may give further insight in to the assessment of LV structure and function and could be of increased usefulness in the future, thanks to the continuous technical improvement. Speckle tracking echocardiography may also be used to measure functional markers of myocardial fibrosis [9].

Prognostic value of LVH and of its regression by treatment

A large number of studies have reported on the relationship between LVH at baseline examination, measured either by ECG or by echocardiography, and the risk of subsequent morbid or mortal cardiovascular and renal events in clinical or epidemiological populations, even in elderly patients. [10]

Despite 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 both at baseline and during antihypertensive treatment [1]. The predictive power of voltage criteria for ECG-LVH is not evident in obese patients [4].

LV mass directly measured 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 from other risk factors such as hypercholesterolemia, age, and blood pressure measured in the clinic or by 24 hours blood pressure monitoring [6]. 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 conventional LVH [7].

The prognostic significance of changes in ECG criteria of LVH has been demonstrated in the Framingham population [11], in hypertensives with isolated systolic hypertension and in high CV risk patients [12].

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 [13-15]. 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. More recently it has been suggested that a residual risk may persist in patients with LVH regression, showing that cardiovascular risk was higher in patients with LVH regression than in those with persistently normal left ventricular mass [16]. Further information come from the LIFE echocardiographic sub study, performed according to a prospective, interventional, controlled design. In this study, including 930 patients with ECG LVH, a decrease of 25 gr/m2 (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 [17].

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 and without LVH at baseline, followed by their family doctors, in the LIFE study all patients had ECG-LVH, 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 isolated systolic hypertension, with obesity and a 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 the development of a concentric geometry during treatment have been found associated to a greater incidence of cardiovascular events, independent of changes in LV mass [18].

The better prognosis associated to 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 left atrial enlargement and cardiac arrhythmias. ESC/ESH guidelines do suggest that echocardiography should be performed in patients at low or intermediate CV risk in order to better identify the global cardiovascular risk, and to more appropriately start 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 factors evaluation and ECG), thus substantially changing the original risk stratification [19]. There is no clear evidence that an echocardiographic study may modify the therapeutic antihypertensive strategy in patients at high or very high CV risk. However, 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 anatomic and functional alterations, and eventually also to refine pharmacological treatment.

Regression of echocardiographic-determined inappropriate LVM during treatment is associated with an improvement in prognosis, and the evaluation of changes in LVM appropriateness may add prognostic information, in particular in patients with persistence or development of traditionally defined LVH [20].

Techniques based on 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 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 hours blood pressure values, may determine a significant reduction, and even a normalization of LVH [21]. The results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) [22] and SPRINT (Systolic Blood Pressure Intervention Trial) [23] trials have shown that targeting a systolic BP to a more intensive (<120 mm Hg) when compared with a less aggressive target (<140 mm Hg) produces a greater reduction in ECG criteria of LVH in hypertensive patients with and without diabetes mellitus at high cardiovascular risk.

On the other hand, 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 [24,25]. The most recent metanalysis of comparative studies evaluating the effect of treatment with different classes of antihypertensive drugs on LV mass changes has shown a superiority of Angiotensin II blockers versus betablockers [25]. The decrease in heart rate and the lesser effect on central aortic pressure may explain these findings. Some recent studies have documented by cardiac MRI the effect of treatment on LV mass changes in hypertensive patients. LVH normalization during antihypertensive treatment may be more difficult to obtain in women, or in patients with isolated systolic hypertension or with obesity [26].

Echo-reflectivity studies have suggested that tissue composition of the left ventricle may vary and that drugs favouring LVH regression may differently affect myocardial fibrosis [27].

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 therefore should undergo frequent and accurate clinical controls for blood pressure and other risk factors assessment. At present time regression of LVH represents the most clinically useful intermediate end-point, together with proteinuria, for the evaluation of the efficacy and the cardiovascular protecting effect of antihypertensive treatment.

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