Left Ventricular Hypertrophy in Systemic Hypertension. Benefits of its Reversal

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The complex problem of left ventricular hypertrophy (LVH) related to systemic arterial hypertension (H) has motivated several experimental, clinical and epidemiological studies. Because LVH is an important predisposing factor for heart failure [1] and because it is physiopathologically related to ischemic heart disease and ventricular arrhythmias, hypertensive left ventricular hypertrophy is an important common point for the study of several heart diseases.

LVH and Cardiovascular Risk

LVH is usually considered a response to pressure overload and to increase in ventricular wall stress and, therefore, is a compensatory mechanism that allows maintenance of normal cardiac function. However, several studies have demonstrated an increase in cardiovascular morbidity and mortality when H is followed by LVH, diagnosed by the electrocardiogram (EKG) or by echocardiography. It has been demonstrated that LVH is a more important risk factor than blood pressure (BP) level, age, high levels of cholesterol or coronary artery disease [2,3]. The incidence of arrhythmias, especially ventricular arrhythmias, is also increased in the presence of LVH [4].

Recently, it has been demonstrated that an increased index of concentric hypertrophy (detected by echocardiography), even in the presence of a normal mass index (concentric remodeling of the LV), indicated a higher risk than that observed in the presence of H without this abnormality in ventricular geometry [5]. It has also been demonstrated that LVH is a risk factor independent of coexistent coronary artery disease or ventricular dysfunction [6].

This well documented worse prognosis in hypertensive patients with LVH has lead to reduction in cardiac hypertrophy, not just BP levels, being considered one of the most important objectives of hypotensive therapy. Therefore, several studies investigating the capacity of some drugs to promote hypertrophy reversal have been developed. The positive influence of this reversal on systolic and diastolic function has also been analyzed.

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Reversal of the LVH and its influential factors

The work by Sen et al [7,8] in laboratory animals demonstrated the possibility of preventing and even reversing hypertrophy with medical therapy. Later, it was shown that there were drugs that could control the BP but did not reverse the hypertrophy, such as vasodilators like hydralazine and minoxidil. According to these authors, the inability of these drugs to reverse hypertrophy might be related to a reflex sympathetic stimulation [9].

It was also shown that, in spontaneously hypertensive rats (SHR), existing structural abnormalities in the hypertrophic heart might be influenced by age, duration of hypertension and its severity and duration and extension of hypertrophy. Hypertrophy was more sustained and its reversion more difficult when therapy was used to treat older animals [10,11].

The development of LVH in rats with renovascular hypertension is closely related to the degree of elevation in BP, while reversal of hypertrophy, either after therapy with drugs or surgery, is linearly related to the reduction in blood pressure levels [12,13].

In contrast with these findings, in the SHR these relationships are not present. These facts highlight the heterogeneity of the cardiac response in different types of hypertension and the difficulty that may occur in the correct interpretation of more or less precocious and more or less complete reversal of the cardiac hypertrophy, if these facts are not taken into consideration [14].

Structural reversal takes place gradually. The milder the decrease in BP levels, the longer the duration of the elevated BP and/or the more genetically reinforced the structural factor is, the slower and less complete is the reversal [15].

Another important factor is that mass reduction to normal levels does not mean that the ventricle is absolutely normal in its structure and composition [16].

The advent of echocardiography has made it possible to diagnose with certainty the reversal of hypertrophy with antihypertensive therapy and to adequately quantitate this reversal in humans. The first echocardiographic study to demonstrate reversal of LVH with therapy was conducted by Schlant et al [17], who also demonstrated an improvement on ventricular function with adequate control of BP (12 to 24 months).

A fundamental work was done by Fouad et al [18], who demonstrated that the capacity of methyldopa to reduce LVH during a 24-36 week period was independent of the BP level control, as had already been shown in laboratory animals.

Several studies have also failed to find any relationship between the degree of BP lowering obtained with therapy and mass variation [19-21].

While some authors have found it more difficult to obtain reversal of hypertrophy in older hypertensive patients and/or when the disease has been more prolonged, which confirms findings in laboratory animals[22], Tarazi and Fouad mention that, neither age nor duration of hypertension, could justify the differences in response to therapy and that the level of mass reversal related more closely to the mean value of daily BP than to a value casually measured [23].

In general, we can say that reversal has definitely been shown to occur with neuroadrenergic inhibitors, with most beta-blockers, with the majority of calcium antagonists and with angiotensin-converting enzyme inhibitors. As for diuretics and direct arterial vasodilators, most studies do not show significant reversal of hypertrophy when these drugs are used in isolation, which probably relates to the stimulation of the sympathetic and/or renin-angiotensin system caused by these agents.

Three recent meta-analyses [24-26] about reversal of LVH support these facts, suggesting that angiotensin-converting enzyme inhibitors are the drugs that most consistently lead to reversal of the LVH. Several studies have also shown the influence of the antihypertensive therapy on reversal of LVH, which confirms the efficacy of the drugs that interfere with the neuro-adrenergic and the renin-angiotensin systems [26,28,29] (fig. 1).

Recent works have demonstrated the efficacy of the angiotensin II receptor antagonists that, like angiotensin-converting enzyme inhibitors, can normalize the pattern of isomyosin (in experimental animals), leading to regression of interstitial fibrosis and decreasing the enhanced expression of the proto-oncogene c-fos, which seems to have a major role in induction and progression of LVH[29].

Ventricular function after regression of the LVH

When one studies LVH regression with hypotensive drugs, it is important to also analyze its impact on left ventricular function, as already mentioned.

Systolic function

Several studies about the echocardiographic evaluation of LVH reversal have shown that systolic function does not deteriorate with reversal and its index is kept normal.

The fact that a significant negative correlation remains between end-systolic stress and fractional shortening, before and after reversal of hypertrophy, and that several points remain within the limits of a 95% confidence interval of the normal correlation, supports the finding that there is no deterioration in contractility with reversal of hypertrophy. Trimarco et al [30], in a recently published work, showed that, after LVH regression with nifedipine or enalapril, the regression line for the correlation between end-systolic stress and fractional shortening showed an increase in its slope, simulating what is seen in normotensive patients or in hypertensive patients without hypertrophy. According to these authors, these results suggest that reversal of hypertrophy sensitizes the pump function to the changes in afterload thus normalizing the relationship between afterload and left ventricular systolic function.

In patients with severe hypertension [26,27] we have shown that there is no deterioration in systolic function with LVH reversal, and indexes used to evaluate inotropism remain normal or even show mild increase. An end-systolic stress kept in the normal range may have contributed to these findings.

The relationship between fractional shortening and end-systolic stress, a good contractility index, was identical to that obtained in a control group of normotensive patients [26, 27] (fig. 2), which confirmed normal systolic function.

We also observed [27,28] that hypertensive patients who had normal values of mass index, concentric hypertrophy and left ventricular wall thickness at the end of the follow-up period, reacted to the sudden increase in stress secondary to isometric exercise like normotensive patients do: significant increase in cardiac output and in the contractility index and no variation in peripheral resistance. In hypertensive patients who showed no echocardiographic reversal of hypertrophy, isometric exercise caused a significant increase in peripheral resistance, without changes in cardiac output or in inotropism [27,28] (fig. 3). Hypertensive patients, therefore, have a higher vascular reactivity to isometric exercise and a lower inotropic cardiac reserve. These findings are similar to that which has been previously found by others either during dynamic or isometric exercise or after cessation of antihypertensive therapy and consequent increase in blood pressure.

Diastolic function

Studies are contradictory when it comes to determi-

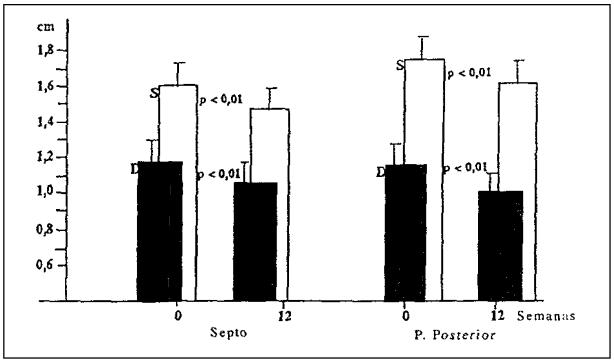

Fig. 1 - Regression of systolic and diastolic thickness of the left ventricular wall induced by the use of enalapril [27,28].

ning whether diastolic function, which is abnormal in hypertension even before development of hypertrophy, can return to normal levels after reversal of hypertrophy.

Inouye et al [31], after prescribing diuretics, beta-blockers and calcium antagonists for four months, could not demonstrate an improvement in diastolic function in study patients. Smith et al [32], on the other hand, showed a significant increase in filling velocity in hypertensive patients treated with nifedipine, but only in those who had shown ventricular mass regression.

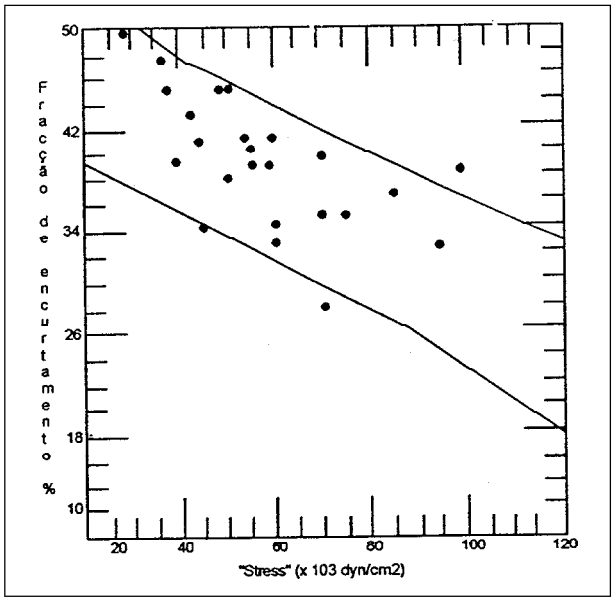

Fig. 2 - Superposition of several points in the correlation fractional shortening-end-systolic stress line of regression, at a 95% confidence interval, between hypertensive and normotensive patients [27,28].

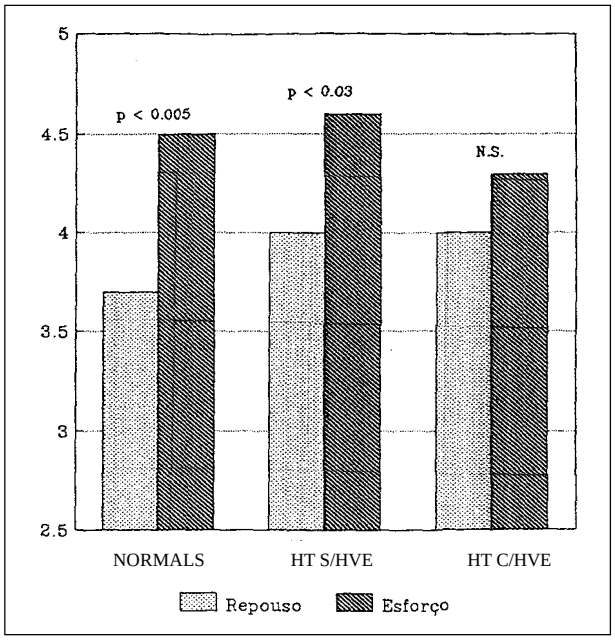

Fig. 3 – Variation on the contractile index (stress/I. systolic volume) according to isometric exercise.

Curiously, White et al [33] have recently observed that, after LV mass regression (by decrease of the wall thickness), in the sequence of therapy with metoprolol in hypertensive patients who had not previously undergone treatment, there was significant improvement in the early diastolic filling of the ventricle. These authors emphasize the fact that the absence of previous treatment was important in explaining the observed improvement in these patients.

Trimarco et al [34] and Habib et al [35] confirmed these findings and emphasize the importance of reversal of LVH and blood pressure control in improving diastolic function.

In our studies [27,28], we observed no significant changes in diastolic function parameters (fig. 4), which remained clearly abnormal. This might be explained by previous therapy (most patients had been hypertensive for several years), that might have already lead to some regression and structural remodeling and thus failed to show improvement with previous therapy, or by the coexistence of coronary artery disease or of no regression of interstitial fibrosis.

Some studies have suggested that regression of hypertrophy might even increase the percentage of fibrosis and thus make the ventricle less compliant [36]. Philips et al [37] showed that, in well controlled hypertensive patients, diastolic function remains abnormal and does not correlate with blood pressure level, duration of hypertension, age or LVH indexes. Drugs that interfere with the renin-angiotensin-aldosterone system seem to be the most effective in promoting regression of the interstitial and perivascular fibrosis [29,38].

Therefore, there can be no regression at all of the connective tissue, or it can regress in larger or smaller degrees, or even occur later on, which may or may not lead to improvement in diastolic function. The influence of different drugs on the regression of hypertrophy of myocardial cells and on contractile proteins, as well as their influence on abnormal function and/or structure of the coronary vessels and consequent changes in coronary artery reserve, can also explain the variability in functional response of the ventricles in patients who experience regression of hypertrophy.

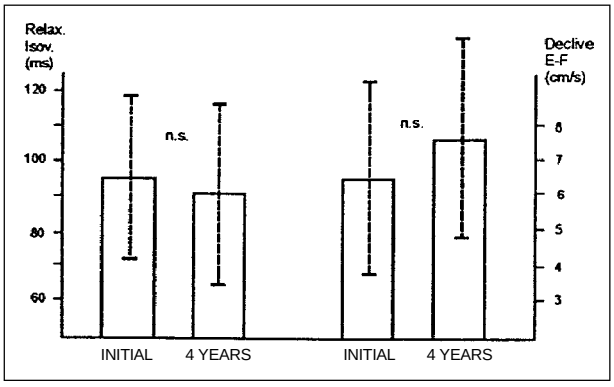

Fig. 4 – Variation on the isovolumic relaxation time and on the EF slope of the anterior mitral valve leaflet with adequate control of the blood pressure and regression of the hypertrophy obtained at the end of the follow-up period (accelerated hypertension) [27,28].

Benefits of regression of hypertrophy

Benefits of hypertrophy reversal can be evaluated by observing the degree of improvement in cardiac function (systolic and diastolic), improvement in coronary artery circulation, improvement in arrhythmias and, most of all, decrease in cardiovascular morbidity and mortality.

Although there is no definite answer to the question "Is regression of hypertrophy beneficial?", we can conclude, after everything that has been described, that with the use of some drugs, hypertrophy reversal can show a real benefit. It has been shown that it can normalize diastolic function and keep it normal and, at the same time, improve systolic function [30, 33-35]. Improvement or even normalization of the coronary artery reserve[39] and a decrease in the incidence of arrhythmias [40,41] can also occur with reversal of hypertrophy.

It was demonstrated in animal studies that reversal of hypertrophy can occur with renin-angiotensin enzyme inhibitors or with angiotensin AT1 receptor antagonists and this was followed by a decrease in mortality [42]. A recently published work by Kannel's group (Framingham Study) supports this opinion by the detection of a decrease in cardiovascular risk in men, observed only in hypertensive patients who showed a decrease of LVH on EKG (voltage criteria), but not in those where this decrease had not been observed or in whom voltage had even increased [43].

Muiesen et al [44] also observed, in a recent echocardiographic study, those hypertensive patients with regression of hypertrophy had lower cardiovascular morbidity and mortality. However, echocardiographic studies, involving a larger number of patients, are still necessary.

In conclusion, it is not only possible to induce regression of hypertrophy by the use of antihypertensive drugs but also very desirable. This is especially true when drugs are used that act not only in the muscular content promoting regression of the myocyte hypertrophy and thus normalizing the isomyosin pattern and regulating existing metabolic changes, but also promote regression of the perivascular and interstitial fibrosis and coronary artery reserve normalization. This action on the three levels of the myocardium can definitely contribute to prevention or improvement of myocardial ischemia and prevent evolution of hypertensive heart disease to an end-stage heart failure.

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