

Left Ventricular Hypertrophy and Systemic Arterial Hypertension

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ABSTRACT

Left ventricular hypertrophy (LVH) is an important and independent cardiovascular risk factor. In this Editorial are the main causes of LVH, in addition to hypertension, such as neurohumoral and genetic factors. Are also addressed some of its major complications, as there is much to know: stroke, heart failure, coronary artery disease and sudden death. There is strong evidence that reversal of LVH may reduce the incidence of these adverse events, a goal that can be obtained with several antihypertensive drugs. It seems essential, however, blockade of the renin-angiotensin-aldosterone system (RAAS).

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Key words: Left ventricular hypertrophy; Hypertension; Cardiovascular risk

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EDITORIAL

Left ventricular hypertrophy (LVH) is a strong and independent cardiovascular risk factor when diagnosed both by electrocardiogram and echocardiogram^[1].

LVH may be diagnosed by electrocardiogram, transthoracic

echocardiogram, chest radiography, and magnetic resonance imaging. In the clinical practice, however, the first two tests are more frequently used, not only because they are more widely available, but mainly because of the prognostic relationship that predicts increased cardiovascular risk when LVH is detected by these tests^[2].

Several factors, whether genetic or acquired, may lead to changes in the left ventricular mass. Some of these factors are pathophysiologically associated with LVH. Additionally, they may interact with each other, thus limiting the interpretation of the role of each of them individually. The major causes of LVH include: systemic arterial hypertension (SAH), genetic factors, age, gender, ethnicity, diabetes mellitus, obesity, excessive salt and alcohol intake, humoral factors, blood viscosity, and presence of some heart diseases such as stenoses or valvular regurgitations.

A clear association between blood pressure (BP) and LVH exists, and the latter is interpreted as an evidence of target-organ damage. However, not always is there a linear relationship between the process of LVH and blood pressure levels, thus suggesting the participation of other mechanisms in this process, particularly of neurohumoral and genetic factors^[3]. The relationship is stronger with measurements assessed by ambulatory and home blood pressure monitoring, especially with systolic blood pressure and with absence of nocturnal dip^[4].

Since the middle of the past century, LVH has been related to adverse cardiovascular effects, and it was from the pioneering investigations of the Framingham Heart Study that its clinical relevance was quantified^[1,5]. The Framingham studies identified LVH as the most important known risk factor for stroke, heart failure, coronary artery disease, peripheral obstructive arterial disease, and sudden death; it is also a strong predictor of all causes of cardiac death in adults above 40 years of age^[6].

The complexity of the origin of LVH, involving several mechanisms, is also related to the endothelial function. In an analysis of 4121 patients, Sciarretta *et al* found a relationship between LVH, as assessed by electrocardiogram, and the presence of albuminuria and renal damage^[7].

As previously pointed out, in addition to SAH, some other mechanisms are implicated in the processes of LVH and left ventricular (LV) remodeling, such as mechanical, humoral and genetic stimuli. Among the humoral factors, we should point out

some substances such as norepinephrine, angiotensin II, endothelin, alpha tumor necrosis factor alpha (TNF-alpha), interleukin 1-beta, cardiotrophin, and insulin-like growth factor 1 (IGF-1-like) which exert paracrine, autocrine and endocrine actions, in addition to calcium, which works as an intracellular signal transducer of growth^[8-9]. The sequence of events resulting from these mechanical, humoral and genetic stimuli leads to pathological tissue growth, i.e., LVH accompanied by contractile dysfunction, with an inevitable progression to heart failure.

The phenomenon by which a mechanical stimulus activates intracellular growth pathways is known as mechanotransduction^[10]. In addition to this mechanism, cytokines have also been implicated in the process of LVH, both in *in vivo* and in *in vitro* studies. Cytokines from the interleukin-6 and cardiotrophin family activate gp 130 membrane receptors and rapidly stimulate cytoplasmic kinases called JAK (cytoplasmic Janus kinases). These kinases phosphorylate other cytoplasmic proteins – the STAT (signal transducers and activators of transcription). Several components of the gp 130-JAK-STAT pathway were able to induce both *in vivo* and *in vitro* myocardial hypertrophy in transgenic mice. Plasma levels of these cytokines are increased in patients with congestive heart failure, and the objective of the most advanced treatments proposed for this syndrome is to inhibit the effects of these agents^[11].

On the other hand, myocytes are surrounded by a collagen fibrillar network and arranged in muscle bundles, which are also surrounded by this network whose structure is quite complex and has a well-defined hierarchy. This structure plays a key role in the maintenance of the ventricular shape during the process of cardiac growth. Collagen is mainly synthesized by fibroblasts, but may also be produced by smooth muscle cells of the vessel wall, depending on some pathological stimuli such as the mechanical stress generated by SAH. Most of the signaling pathways of myocyte hypertrophy promote fibroblast hyperplasia, therefore having an effect on collagen production. Hypertrophic and failing hearts frequently show a significant increase in interstitial fibrosis, which stiffens the ventricle and causes abnormalities in the diastolic function and, later, in the systolic function^[12-13].

The process of LVH encompasses not only the myocytes, but also the fibroblasts, vessel smooth muscle, and, moreover, the cardiac collagen fibers. Cardiomyocytes are known to occupy approximately 70% of the cardiac volume, but they account for only one third of the structural components. We should recall that the increase in myocyte thickness is an adaptive response to LV overload. However, it is important to explain that there is a simultaneous proliferation of the other components of the cardiac structure, especially of collagen fibers, thus promoting remodeling of the extravascular space. This can contribute to the pathological degeneration of the myocardial hypertrophy, thus reducing the ventricular compliance and the coronary flow reserve. All these changes comprise the ideal substrate for the occurrence of arrhythmias, heart failure, and sudden death^[14]. It is important to point out that for every 1.0 mm-increase in the interventricular septal or LV posterior wall thickness there is a two-to three-fold elevation in the incidence of complex ventricular arrhythmias^[15].

The classical geometric pattern of LVH that occurs in long-term SAH is concentric, as a consequence of pressure overload and increased systolic LV wall stress, leading to increased myocyte thickness because of the addition of sarcomeres in parallel. Interventricular septal and LV posterior wall thickening then occurs, which is the usual adaptation to increased afterload. This geometric pattern is known to be related to a worse prognosis^[16]. However, this

concept of severity of the geometric pattern is still controversial. Tovillas-Moran *et al*^[17] analyzed the progression of LVH according to its geometrical pattern and did not find associations between the geometrical pattern and cardiovascular events, in a 12-year follow-up.

In relation to treatment, reversal of LVH is known to improve the changes observed in systole and diastole, in interstitial fibrosis, in coronary reserve and in ventricular arrhythmias. However, whether improving these events with reversal of LVH will translate into further decrease in morbidity and mortality in addition to that triggered by a reduction in blood pressure levels is yet to be known.

In a very-well conducted study by Verdecchia *et al*^[18], the authors showed that patients with reversed LVH on transthoracic echocardiogram had an event rate of 1.58%, whereas in those without reversal, the rate was 6.27%. It is important to point out that these differences remained significant after multivariate analysis, when the influence of BP changes was excluded by ambulatory blood pressure monitoring.

A meta-analysis of four studies involving 1064 hypertensive patients undergoing echocardiogram at the beginning and at the end of the study showed that the cardiovascular risk was 59% lower among those who had reversal of LVH in comparison to those whose hearts remained hypertrophic. However, the cardiovascular risk of hypertensive patients without LVH was 36% lower than that of patients with reversal of LVH. Thus, a question remained: did the reduction in LVH really decrease the risks to values similar to those of individuals who never had LVH^[19]?

Some studies have shown reversal of LVH with the use of different classes of drugs: angiotensin II converting enzyme inhibitors (ACEI), central adrenergic inhibitors, some calcium channel antagonists (CCA), and certain betablockers (BB). Noteworthy, although the use of direct vasodilators such as minoxidil and hydralazine reduced BP levels significantly, they also caused an additional increase in the cardiac mass. Conversely, in experimental studies, alpha-methyldopa was able to reduce the myocardial mass, even without reducing BP levels, thus showing the complexity of the mechanisms and variables involving the relationship between SAH and LVH^[20].

In a meta-analysis of 109 studies, Dahlöf *et al*^[21] investigated the four antihypertensive drugs most commonly used in the clinical practice (diuretics, BB, CCA, and ACEI) and observed different degrees of regression of LVH, and that enalapril – an ACEI, proved to be more efficient in the reversal of LVH.

Another meta-analysis of 80 studies published in 2003 showed that angiotensin II receptor blockers (ARB II) were the most effective drugs in the reduction of LV mass, with diuretics and betablockers being less effective than ACEIs and calcium channel antagonists^[22].

More recently, in 2009, Fagard *et al*^[23] carried out a systematic review and updated the findings of a previous publication of their own authorship, taking into consideration better comparative criteria. They analyzed the efficacy of LVH regression among the five major classes of antihypertensive drugs – ARB II, ACEI, CCA, diuretics and BB, using pairwise comparison of drug classes and multivariate regression analysis. The results showed a reduction by 10.3%±0.88% ($p<0.001$) in the left ventricular mass and by 11.0%±0.60% ($p<0.001$) in the left ventricular mass index in relation to baseline values. In the comparison among the five classes, the differences found were less LVH regression by BB and more pronounced regression by ARB II. No difference was observed when diuretics, ACEI and CCA were compared. However, when BB were excluded from the analysis, the superiority of ARB II over the other three groups was not as expressive. More robust clinical studies are further necessary

to confirm a significant superiority of one drug class over the others. We should keep in mind that LVH regression was assessed by means of the reduction in LV posterior wall thickness, comparing all five classes of antihypertensive drugs, and diuretics showed a relevant additional reduction in the LV internal diameter. In the multivariate analysis, only BB showed an independent negative effect on LVH regression in all treatment arms.

Overall, antihypertensive drugs that act on the renin-angiotensin-aldosterone system (RAAS) seem to have a greater effect on LVH regression. Further information is also required regarding aliskiren – a direct renin inhibitor - in this context. In a clinical study, the combination of aliskiren and losartan did not show significant reduction in LVH when compared to the use of ARB II alone^[24].

In conclusion, the choice of the antihypertensive drug, when LVH is present, should prioritize the effective control of hypertension and, whenever possible, RAAS blockade. This is the goal to be attained, because there is enough evidence pointing that reversal of LVH provides patients with a lower cardiovascular risk, with a lower incidence of severe complications such as stroke, heart failure and ischemic heart disease. For this reason, when treating SAH, special attention should be given to this serious and independent risk factor for the occurrence of significant cardiovascular complications^[25-26].

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

- Kannel WB, Gordon T, Offutt D. Left ventricular hypertrophy by electrocardiogram: prevalence, incidence, and mortality in the Framingham Study. *Ann Intern Med* 1969; **71**: 89-105
- Levy D, Anderson KM, Savage DD, Kannel WB, Christiansen JC, Castelli WP. Echocardiographically detected left ventricular hypertrophy: prevalence and risk factors: the Framingham Heart Study. *Ann Intern Med* 1988; **108**: 7-13
- MacMahon S, Collins G, Rautaharju P, Cutler J, Neaton J, Prineas R, et al. Electrocardiographic left ventricular hypertrophy and effects of antihypertensive drug therapy in hypertensive participants in Multiple Risk Factor Intervention Trial. *Am J Cardiol* 1989; **63**: 202-210
- Stergiou GS, Argyraki KK, Moysakis I, Mastorantonakis SE, Achimatos AD, Karamanos VG, et al. Home blood pressure is a reliable as ambulatory blood pressure in predicting forget-organ damage in hypertension. *Am J Hypertens* 2007; **20(6)**: 616-21
- Kreger BE, Cupples LA, Kannel WB. The electrocardiogram in prediction of sudden death: Framingham Study experience. *Am Heart J* 1987; **113**: 377-382
- Kannel WB. Prevalence and natural history of electrocardiographic left ventricular hypertrophy. *Am J Med* 1983; **Suppl 3A**: 4-11
- Sciarretta S, Pontremoli R, Rosei EA, Ambrosioni E, Costa V, Leonetti G, et al. Independent association of ECG abnormalities with microalbuminuria and renal damage in hypertensive patients without overt cardiovascular disease: data from Italy-Developing Education and awareness on microalbuminuria in patients with hypertensive disease study. *J Hypertens* 2009; **27(2)**: 410-417
- Laycock SK, McMurray J, Kane KA, Parratt JR. Effects of chronic norepinephrine administration on cardiac-function in rats. *J Cardiovasc Pharmacol* 1995; **26**: 584-589
- Ishikawa M, Saito Y, Miyamoto Y, Harada M, Kuwahara K, Ogawa E, Nakagawa O, Hamanaka I, Kajiyama N, Taka-
- hashi N, Masuda I, Hashimoto T, Sakai O, Hosoya T, Nakao K. A heart-specific increase in cardiostrophin-1 gene expression precedes the establishment of ventricular hypertrophy in genetically hypertensive rats. *J Hypertens* 1999; **17**: 807-816
- Sadoshima J, Izumo S. Mechanotransduction in stretch-induced hypertrophy of cardiac myocytes. *J Recept Res* 1993; **13**: 777-794
- Braunwald E, Bristow MR. Congestive heart failure: fifty years of progress. *Circulation* 2000; **102**: 4-14
- Bing OHL, Matsubara S, Farburg BL, Levine HJ. Mechanical properties of rat cardiac muscle during experimental hypertrophy. *Circ Res* 1971; **28**: 234-245
- Matsubara LS, Matsubara BB, Okoshi MP, Cicogna AC, Janicki JS. Alterations in myocardial collagen content affect rat papillary muscle function. *Am J Physiol-Heart Circ Physiol* 2000; **279(4)**: H1534-1539
- Weber KT, Brilla CG. Pathological hypertrophy and cardiac interstitium: fibrosis and renin-angiotensin-aldosterone system. *Circulation* 1991; **83**: 1849-1865
- Ghali JK, Kadakia S, Cooper RS, Liao YL. Impact of left ventricular hypertrophy on ventricular arrhythmias in the absence of coronary artery disease. *J Am Coll Cardiol* 1991; **17(6)**: 1277-1282
- Ganau AI, Devereux RB, Roman MJ, de Simone G, Pickering TG, Saba PS, Vargiu P, Simongini I, Laragh JH. Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol* 1992; **19**: 1550-1558
- Tovillas-Moran FJ, Zabaleta-del-Olmo E, Dalfó-Baqué A, Vilaplana-Cosculluela M, Galcerán JM, Coca A. Cardiovascular morbidity and mortality and left ventricular geometric patterns in hypertensive patients treated in primary care. *Rev Esp Cardiol* 2009; **62(3)**: 246-254
- Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Gattobigio R, Zampi I, et al. Prognostic significance of serial changes in left ventricular mass in essential hypertension. *Circulation* 1998; **97**: 48-54
- Verdecchia P, Angeli F, Borgioni C, Gattobigio R, De Simone G, Devereux RB, et al. Changes in cardiovascular risk by reduction of left ventricular mass in hypertension: a meta-analysis. *Am J Hypertens* 2003; **16**: 895-899
- Chien Y, Frohlich ED. Reserval of left ventricular hypertrophy and cardiac performance. *Curr Opin Cardiol* 1991; **6**: 716-723
- Dahlöf B, Penner K, Hansson L. Reversal of left ventricular hypertrophy in hypertensive patients: a meta-analysis of 109 treatment studies. *Am J Hypertens* 1992; **5**: 95-110
- Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieider RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. *Am J Med* 2003; **115(1)**: 41-46
- Fagard RH, Celis H, Thijs L, Wouters S. Regression of left ventricular mass by antihypertensive treatment: a meta-analysis of randomized comparative studies. *Hypertension* 2009; **54(5)**: 1084-1091
- Solomon SD, Appelbaum E, Manning WJ, Verma A, Berglund T, Lukashevich V, Cherif Papst C, Smith BA, Dahlöf B. Effect of the direct renin inhibitor aliskiren, the angiotensin receptor blocker losartan, or both on left ventricular mass in patients with hypertension and left ventricular hypertrophy. *Circulation* 2009; **119(4)**: 530-537
- Ruwalid AC, Westergaard B, Sehested T, Kjeldsen SE, Lindholm LH, Wachtell K, et al. Losartan versus atenolol-based antihypertensive treatment reduces cardiovascular events especially well in elderly patients: the Losartan Intervention For Endpoint reduction hypertension (LIFE) study. *J Hypertens* 2012; **30(6)**: 1252-1259

- 26 Misra KH, Das MC, Ramani YR. Effect of telmisartan on the regression of the left ventricular hypertrophy in the patients of essential hypertension. *J Clin Diagn Res* 2013; 7(7): 1352-1355

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