

## Mechanisms of Left Ventricular Hypertrophy in Hypertension: More than Just Blood Pressure

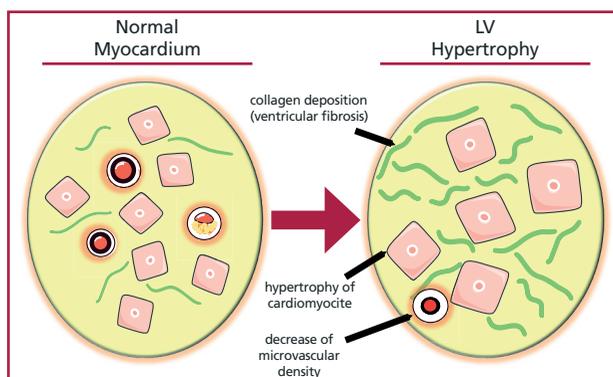
*Mecanismos de la hipertrofia ventricular izquierda en la hipertensión: más que solo la presión arterial*

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Hypertension is associated with a constellation of cardiac structural and functional changes, including increased left ventricular (LV) mass, and LV systolic and diastolic dysfunction. (1) Of the several adverse changes in cardiovascular morphology and function that occur in association with hypertension, LV hypertrophy is an established and independent prognostic factor for major cardiovascular events, including sudden cardiac death, acute myocardial infarction, stroke, and congestive heart failure. (2-6) Furthermore, there is a wealth of literature which demonstrates that decrease of LV mass in hypertensive patients results in improved survival rates. (7)

Pathological changes of the left ventricle during long-term exposure to chronic pressure overload include an increase in the size of the cardiomyocyte, alterations in the extracellular matrix with accumulation of fibrosis, and abnormalities of the intramyocardial coronary vasculature, including medial hypertrophy and perivascular fibrosis (8) (Figure). However, given the detrimental contribution of LV hypertrophy to survival and cardiovascular events, most attention has also been focused on other mechanisms which may explain the risk associated with LV hypertrophy, and on the beneficial effects of anti-hypertensive pharmacological treatment. (1, 9-11)

The mechanisms responsible for progression to hypertrophy include not only a mere response to the mechanical stress from elevated blood pressure (BP), but also the influence of neurohormones, growth factors, and cytokines. (1,12) Specifically, among factors promoting the progression of LV pathological remodeling, secretion and production of vasoactive peptides (such as angiotensin II, endothelin-1 and norepinephrine) are increased during the process and play critical roles in the hypertrophic response to systemic hypertension. (1) Oxidative stress, heat shock proteins, calcineurin, and some kinases are also involved in the hypertrophic process. (13)



**Fig. 1.** Pathological changes of the left ventricle during long-term exposure to chronic pressure overload.

Thus, LV hypertrophy may be considered a biomarker integrating the long-term exposure to both pressure overload and several non-hemodynamic factors, which may promote progression and destabilization of atherosclerotic lesions ultimately leading to adverse clinical events. (5)

In this context, the analysis by Llambi and co-workers (14) published in the current issue of the Journal adds further data which need to be combined with the extensive previous literature on the mechanisms and treatment of LV hypertrophy in essential hypertension. Through a rigorous experimental approach, they evaluated the ability of several different anti-hypertensive treatments (losartan, hydralazine, and carvedilol) in the prevention and inhibition of LV hypertrophy in spontaneously hypertensive rats (SHR). Furthermore, they analyzed changes in myocardial oxidative metabolism and the antioxidant activity of BP-lowering drugs. (14) Briefly, they documented that all antihypertensive treatment strategies prevented the development of LV hypertrophy by reducing BP. However, only losartan normalized the response to beta-adrenergic stimulation by isoproterenol.

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Also interestingly, in their attempt to recognize factors other than BP reduction participating on the development of LV hypertrophy, Llambi and coworkers specifically evaluated the effect of the thioredoxin system. (14) The thioredoxin system is a thiol-reducing mechanism expressed in almost all living cells that functions through the reversible oxidation of vicinal cysteines of thioredoxin and through reduction by thioredoxin reductase. (15)

Results of the analysis by Llambi and coworkers support the notion that decreased antioxidant activity participates in the development of LV hypertrophy. (14, 15) Specifically, they confirmed that increased expression of redox-regulating proteins (thioredoxins) during antihypertensive treatment increases the antioxidant response against oxidative stress in hypertension, and that cytosolic thioredoxin can protect the heart against oxidative stress and inhibit cardiac hypertrophy via its antioxidant activity. These results highlight the concept that prolonged periods of hypertension produce LV remodeling, hypertrophy and oxidative stress. (15)

Previous experimental studies indicated that plasma concentrations of thioredoxins are associated with the severity of oxidative stress overload in hemodynamically compromised status, (16) and the dynamic change of thioredoxin levels seems closely related with progression of hypertensive LV hypertrophy in a rat transaortic constriction model. (15)

Although cellular redox balance may play an important role in cardiac hypertrophy and its regression and reactive oxygen species seem to actively participate in signal transduction during cellular growth and differentiation under hypertensive stress, the ultimate net effects of changes in redox status under pathophysiological conditions are complex and incompletely defined. (13, 17, 18) In this respect, the mechanism whereby the thioredoxin system affects the classic paradigm of hypertensive heart disease (increased LV mass in response to elevated BP as a compensatory mechanism to minimize wall stress and subsequently LV dilatation and LV ejection fraction decline) remains to be elucidated. (12) Moreover, it is worth mentioning that the mechanisms through which changes in LV mass parallel the risk of major cardiovascular events in hypertensive subjects remain to be extensively assessed.

Health professionals need to consider that although antihypertensive treatments are able to reduce elevated BP levels, they are not always effective in slowing down or preventing LV hypertrophy. (11) In this context, experimental studies performed in animal models demonstrate that some humoral factors, by suppressing the biochemical hypertrophic responses, could prevent their cardiac complications independently of their possible anti-hypertensive effects. (13) For example, cyclosporine-A, scutellarin, and spironolactone are included among these antihypertrophic substances. (2) New drugs derived from these mol-

ecules or humoral factors affecting BP-independent mechanisms promoting LV mass change might be the next tools to antagonize LV hypertrophy in the near future.

#### Conflicts of interest

None declared

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