Towards a New Paradigm About Hypertensive Heart Disease

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A new paradigm is emerging related to the impact of chronic hypertension on the cardiac parenchyma. In fact, although macroscopic left ventricular hypertrophy (LVH) is the hallmark of hypertensive heart disease (HHD), a number of changes in the cardiomyocyte and the noncardiomyocyte components of the myocardium also develop in hypertension that alter the composition and structure of the myocardium. The occurrence of these alterations may explain why the presence of LVH is independently associated with increased risk of cardiac complications, namely heart failure (HF), in hypertensive patients. Whereas LVH may be detected early and accurately in hypertensive patients by electrocardiography and echocardiography, newer cardiac imaging methods and the monitoring of several circulating biomarkers holds promise as a noninvasive tool for the diagnosis of myocardial remodeling. A large number of clinical studies have shown that long-term antihypertensive treatment may be associated with regression of LVH, and this is associated with the decrease of the risk of cardiovascular morbidity and mortality. However, because the remaining risk is unacceptably high, new therapeutic strategies aimed not just to decrease left

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ventricular mass, but also to repair myocardial remodeling are necessary. All these aspects are reviewed in brief in this article.

**CHANGING THE PATHOPHYSIOLOGIC VIEW OF HHD**

The essential criterion in defining HHD is the presence of LVH in the absence of a cause other than arterial hypertension. Beyond macroscopic hypertrophy, however, complex changes in myocardial composition, which are responsible for the structural remodeling of the myocardium, develop in arterial hypertension. Whereas cardiomyocyte hypertrophy leading to LVH provides the adaptive response of the heart to pressure overload in an attempt to normalize systolic wall stress, pathologic remodeling develops as the consequence of a number of pathologic processes, mediated by hormones, growth factors, and cytokines acting on the cardiomyocyte and other cells of the myocardium (Fig. 1).¹

**Cardiomyocyte Hypertrophy**

Hypertrophic growth of cardiomyocytes is the primary mechanism by which the heart reduces stress on the ventricular wall imposed by pressure overload. It entails stimulation of intracellular signaling cascades that activate gene expression and promote protein synthesis, protein stability, or both, with consequent increases in protein content and in the size and organization of force-generating units (sarcomeres) that, in turn, will lead to increased size of individual cardiomyocytes.²

The long-held views are that these morphologic and genetic changes, in response to pressure overload, serve to restore cardiac muscle economy back to normal and counteract myocardial dysfunction. However, evidence exists that a blunting of cardiomyocyte hypertrophy and an attenuation of the fetal gene re-expression did not result in dysfunction or failure, despite pressure overload. Therefore, a shift in paradigm is occurring in the sense that genetic reprogramming associated with cardiomyocyte hypertrophy is no longer considered as an adaptive process.³ In fact, a detailed analysis of the genetic changes that accompany cardiomyocyte hypertrophy allows us to conclude that they will translate into derangements in energy metabolism, contractile cycle and excitation-contraction coupling, cytoskeleton and

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**Fig. 1.** General pathways involved in the development of LVH and myocardial remodeling in HHD.

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membrane properties, and autocrine functions that, in turn, will provide the basis for the cardiomyocyte malfunctioning that is associated with LVH and that predisposes to diastolic and systolic dysfunction and HF. 

**Myocardial Remodeling**

Hypertensive myocardial remodeling involves increased rates of cardiomyocyte cell death, myocardial fibrosis, and alterations of the coronary microcirculation (Fig. 2). Two types of findings suggest that nonhemodynamic factors also contribute to these lesions in human hypertension. First, they have been identified in the left and right ventricles, the interventricular septa, and the left atria of patients with HHD. Second, it has been shown that the ability of antihypertensive treatment to reverse these lesions in hypertensive patients is independent of its antihypertensive efficacy. Thus, myocardial remodeling could be the consequence of the loss of reciprocal regulation that normally exists between proremodeling and antiremodeling molecules (Box 1).

Historically, there are three types of cell death: apoptosis, autophagy, and necrosis. Although the three types of cardiomyocyte death have been observed simultaneously in failing human hearts as a consequence of pressure overload, apoptosis is the most thoroughly characterized form of cell death in the hypertensive myocardium.

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Fig. 2. Components of myocardial remodeling: cardiomyocyte apoptosis (upper left panel, arrow, FITC stain, magnification ×20), interstitial fibrosis (upper right panel, arrow, picro-sirius red stain, magnification ×20), perivascular fibrosis (lower left panel, arrow, picro-sirius red stain, magnification ×20), and intramyocardial artery wall thickening and lumen narrowing (lower right panel, arrow, hematoxylin-eosin stain, magnification ×20).
Several observations suggest that apoptosis of cardiomyocytes may contribute to the development of left ventricular dysfunction or failure through different pathways. First, an association of increased cardiomyocyte apoptosis with diminished cardiomyocyte number has been found in the failing heart of hypertensive patients. Thus, apoptosis may be one of the mechanisms involved in the loss of contractile mass and function in HHD. Second, impaired myocardial contractile function may reflect not only a decrease in the number of viable, fully functional cardiomyocytes, but also a decrement in the function of viable cardiomyocytes, or a combination of these mechanisms. It has been recently reported that caspase-3 cleaves cardiac myofibrillar proteins, resulting in an impaired force/Ca\(^{2+}\) relationship and myofibrillar adenosine triphosphatase (ATPase) activity. Finally, cytochrome C plays a major role in ATP production through mitochondrial oxidative phosphorylation. Thus, it has been hypothesized that release of cytochrome C from mitochondria during the occurrence of the apoptotic process could interfere with cardiomyocyte energy production and lead to functional impairment.

Myocardial fibrosis secondary to an exaggerated accumulation of collagen type I and type III fibers within the interstitium and surrounding intramural coronary arteries and arterioles is one of the key features of structural remodeling of the hypertensive hypertrophied left ventricle. Excess of myocardial collagen present in LVH is suggested to be the result of both increased collagen synthesis by fibroblasts and phenotypically transformed fibroblast-like cells, or myofibroblasts, and unchanged or decreased collagen degradation by matrix metalloproteinases.

Fibrosis might contribute to the increased risk of adverse cardiac events in hypertensive patients with LVH through different pathways. First, a linkage between fibrosis and left ventricular dysfunction or failure may be established. Initially, the accumulation of collagen fibers compromises the rate of relaxation, diastolic suction, and passive stiffness, contributing to impaired diastolic function. Continued accumulation of fibrotic tissue, accompanied by changes in the spatial orientation of collagen fibers, further impairs diastolic filling and compromises transduction of cardiomyocyte contraction into myocardial force development, thus impairing systolic performance. Second, impaired coronary flow reserve associated with LVH might be related to

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**Box 1**

*Main molecules that participate in the process of myocardial remodeling in arterial hypertension*

**Excess of proremodeling molecules**
- Vasoactive substances (norepinephrine, angiotensin II)
- Hormones (thyroid hormone, aldosterone)
- Growth factors (transforming growth factor-β)
- Cytokines (cardiotrophin-1)
- Other (reactive oxygen species)

**Deficit of antiremodeling molecules**
- Vasoactive substances (nitric oxide, prostacyclin)
- Hormones (glucocorticoids)
- Growth factors (insulin-like growth factor-1)
- Cytokines (tumor necrosis factor-α)
- Other (endogenous PPAR-α ligands)
several factors, including perivascular fibrosis. In fact, it has been demonstrated that
the amount of perivascular collagen correlated inversely with coronary flow reserve in
hypertensive patients with LVH. Third, fibrosis may also contribute to ventricular
arrhythmias in hypertensive LVH. It has been reported that patients with arrhythmias
exhibited higher values of left ventricular mass and myocardial collagen than patients
without arrhythmias, the ejection fraction and the frequency of coronary vessels with
significant stenosis being similar in the two groups of patients. Fibrosis would induce
conduction abnormalities, as promoters of local re-entry, and thereby arrhythmias.

Hypertensive LVH is characterized by different structural alterations in the small in-
tramycocardial vessels.9 On the one hand, hyperplasia and hypertrophy, and altered
alignment of vascular smooth muscle cells leading to encroachment of the tunica
media into the lumen, cause both an increase in the medial thickness/lumen ratio
and a reduction in the maximal cross-sectional area of intramyocardial arteries. On
the other hand, if the density of arterioles and capillaries is estimated as the vessel
number per unit area, there is a relative decrease in arteriolar and capillary density
in LVH. This can be caused by both capillary rarefaction (ie, the vessels are actually
missing or temporarily not perfused or “recruited”) and inadequate vascular growth
(ie, impaired angiogenesis) in response to increasing muscle mass.

These structural alterations of microcirculation, together with increased arteriolar
tone, endothelial dysfunction, and extravascular systolic compression account for
the decrease in coronary vasodilator response present hypertensive patients with
LVH.10

BUILDING A NEW CLINICAL APPROACH TO HHD

The time has come to revisit the current management of HHD simply focused on de-
tecting and treating LVH. It is necessary to develop new approaches aimed at early
identification of hypertensive patients highly exposed to develop LVH, more accurate
measurement of left ventricular anatomy and function, assessment of those patho-
logic changes responsible for myocardial remodeling, and repair of the molecular
and cellular alterations of the myocardium that compromise its structure and function
(Box 2). In so doing, the adverse risk associated with HHD will be reduced in a more-
effective manner.

Early Detection

Although in most studies and meta-analyses the relationship between changes in
office blood pressure and left ventricular mass was relatively weak (correlation coeffi-
cient <0.50), emerging evidence indicates that 24-hour monitoring of blood pressure
may help to identify those hypertensive patients highly exposed to developing LVH
(ie, patients with an early morning rise in blood pressure and patients with a nondipping
profile) and more prone to benefit from the ability of some antihypertensive drugs to
prevent it.11

Left ventricular mass is a complex phenotype influenced by the interacting effects of
multiple genetic and environmental (ie, nutritional and hygienic) factors. Genetic vari-
ation probably contributes to interindividual differences in left ventricular mass by
virtue of effects on blood-pressure level, as well as via pathways that are not captured
by measurements of blood pressure. It is possible that identification of genes that
influence the mass of the left ventricle may enhance the ability to detect those patients
who deserve early treatment to prevent the development of LVH. In this regard,
a recent meta-analysis of case-controlled studies and association studies has shown
that the D allele of the insertion/deletion polymorphism of the angiotensin-converting enzyme gene behaved as a marker for LVH in untreated hypertensive patients. Plasma concentration of cardiotrophin-1, a cytokine that induces cardiomyocyte hypertrophy, has been found to be abnormally increased in hypertensive patients, in particular in those with echocardiographic LVH. It is interesting to point out that 31% of hypertensive patients without echocardiographic LVH already exhibited concentrations of cardiotrophin-1 abnormally elevated, suggesting that the circulating levels of this cytokine increase early during the evolution of arterial hypertension, and thus may be useful to identify those patients prone to developing LVH.

**Optimized Diagnosis**

New three-dimensional techniques for imaging the heart, including MRI and three-dimensional echocardiography, can measure left ventricular mass and dimensions more accurately than conventional echocardiographic techniques, and may thus offer an advantage. Being largely used for research purposes, the diffusion of these techniques for the routine assessment of hypertensive LVH is still hampered by practical and economic reasons.

On the other hand, special ultrasound methodologies (ie, analysis of backscatter) aimed to assess myocardial texture may be useful for the detection of myocardial remodeling as well, and in particular, fibrosis. MRI is another promising technique for characterizing the composition of the myocardium; in particular, the presence of late gadolinium enhancement areas in the myocardium probably represent regions characterized by fibrosis.
Nuclear imaging techniques, especially single-photon emission tomography and positron emission tomography are well suited for cardiac molecular imaging because of the large number of potentially available molecular targets, relatively high intrinsic sensitivity, and excellent depth of penetration. MRI is also rapidly evolving within the field of cardiac molecular imaging, with the introduction of an increasing number of high-affinity molecular probes imaged at exceptionally high spatial resolution. Within the field of myocardial remodeling, molecular imaging is rapidly expanding to involve imaging and monitoring of apoptotic cell loss and collagen matrix turnover.\textsuperscript{17}

The identification of biochemical markers of potential usefulness for the clinical handling of cardiac diseases evolving to HF has been a prolific field in recent years. However, for a circulating molecule to be considered a biochemical marker of hypertensive LVH and myocardial remodeling, it must fulfill several criteria.\textsuperscript{18} Up to now, two molecules have been characterized as biochemical markers of hypertensive myocardial remodeling: Annexin A5 as a marker of cardiomyocyte apoptosis, and the carboxy-terminal propeptide of procollagen type I as a biochemical marker of myocardial fibrosis.

**Global Treatment**

In the treatment of patients with HHD, beyond controlling blood pressure and reducing left ventricular mass, it is necessary to pay attention also to the correction of alterations in left ventricular function and electrical activity, and coronary microcirculation that associate with LVH. Although several trials have been performed to analyze these aspects, methodologic problems of design and the confounding influence of factors, such as the antihypertensive and antihypertrophic effects of treatment, make evaluating the available information difficult. Nevertheless, from the reported findings it appears that the use of pharmacologic agents interfering with the production and actions of angiotensin II provides a higher benefit than the use of other agents.\textsuperscript{19,20}

There is no doubt that all classes of antihypertensive drugs possess the ability to reduce the quantity of left ventricular mass in patients with LVH. However, as mentioned above, it is not so clear if they also restore the structural quality of the re-modeled myocardium. For example, it has been shown that despite similar antihypertensive and antihypertrophic efficacy, the angiotensin type 1 receptor antagonist losartan, but not the calcium channel blocker amlodipine, was able to reduce cardiomyocyte apoptosis and myocardial fibrosis in patients with HHD.\textsuperscript{21,22} Of interest, the reduction of myocardial fibrosis by losartan is associated with the decrease in left ventricular chamber stiffness and the improvement of diastolic filling.\textsuperscript{23} From these data it seems that the goal of repairing myocardial remodeling is achievable in patients with HHD using specific antihypertensive agents. Furthermore, this preliminary information sets the stage for large and long-term clinical trials aimed at determining whether the reversal of myocardial remodeling in HHD is associated with higher beneficial effects on the patient’s cardiac function and prognosis than just the regression of LVH.

On the other hand, most of the antihypertensive agents that have antihypertrophic effects target outside-in signaling cardiac cells, but their effectiveness seems limited, and so attention has recently turned to the potential of targeting intracellular events. Hypothetically, these novel therapeutic interventions could be directed to the following aspects:\textsuperscript{24–26} (i) to block the detrimental intracellular mechanisms activated in mechanical stress-based cardiomyocyte hypertrophic response (eg, inhibiting oxidative stress, kinases such as Rho-kinase, and phosphatases such as calcineurin); (ii) to prevent inhibition of negative-signaling modulators and negative-interacting proteins that are repressed in the mechanical stress-based cardiomyocyte hypertrophic
response (eg, increasing the availability and actions of cyclic guanosine monophosphate); (iii) to take advantage of beneficial mechanisms inherent in mechanical stress-based cardiomyocyte hypertrophic response (eg, via enhancement of important aspects of the IGF1/PI3K/Akt pathway, such as angiogenesis); (iv) to block the deleterious modulation that pathologic stresses impose on protein synthesis (eg, through inhibition of histone deacetylases or sets of microRNAs); (v) to preserve functioning cardiomyocytes (eg, through the inhibition of the process of apoptosis or preservation of cell-survival mechanisms); (vi) to regenerate lost cardiomyocytes (eg, using stem cell therapy); and (vii) to restore the normal turnover of collagen network (eg, restoring the balance between fibrillar collagen synthesis/deposition and collagen fiber degradation/removal).

**SUMMARY**

A new pathophysiologic paradigm on HHD is emerging. This entity is the result of the pathologic structural remodeling of the myocardium in response to a mosaic of hemodynamic and nonhemodynamic factors altered in hypertension more than just the adaptive hypertrophy of the left ventricular wall to increased pressure. The potential clinical relevance of this paradigm is given by the fact that it entails a new approach to HHD in terms of more detailed diagnosis and more demanding treatment. But this novel view of HHD may also have epidemiologic importance. In fact, the possibility that myocardial individuals prone to develop HHD may be detected before the appearance of clinical detectable LVH opens a new way to the prevention of cardiac complications associated with hypertension and its impact on the heart, namely heart failure.27

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