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Brief Review

A Translational Approach to Hypertensive Heart Disease

Javier Díez, Edward D. Frohlich

The spectrum of the cardiac complications of arterial hypertension includes heart failure (HF), sudden death, and cardiac dysrhythmias, as well as the exacerbation of coincidental diseases (ie, atherosclerosis and chronic renal disease).[1] However, knowledge of the cardiac impact of chronic elevation of arterial pressure has so evolved that hypertensive heart disease (HHD) may be thought as those consequences derived from left ventricular (LV) responses to fundamental disease mechanisms triggered by mechanical overload and neurohumoral stimuli.[2] For instance, the long-held views are that LV hypertrophy (LVH), as the result of cardiomyocyte growth in response to pressure overload, serves to restore heart muscle economy back to normal and to preserve LV function.[3] However, a number of alterations of the cardiomyocyte and the noncardiomyocyte components of the myocardium (including apoptosis, fibrosis, and changes in the microcirculation) also develop in HHD that lead to pathological myocardial remodeling not only in the left ventricle but also the left atrium and right ventricle.[2] These alterations may explain the overall risk of LVH and its associated cardiac and noncardiac complications in hypertensive patients.[4] Although 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 hold promise as noninvasive tools for the diagnosis of myocardial remodeling. Numerous clinical studies have shown that effective long-term antihypertensive treatment may be associated with a decreased LV mass (LVM), which has been attributed to diminished risk. However, no large study (or meta-analysis) has demonstrated that diminished risk from the contemporary reduction of arterial pressure by virtue of its a priori design. Therefore, because overall risk remains unacceptably high, especially from HF, new therapeutic strategies aimed not only to decrease arterial pressure and LVM but also to repair and even prevent myocardial remodeling are necessary. Each of these aspects are reviewed in this article.

Current Views on the Pathophysiology of HHD

Although hypertrophy provides the response of the cardiomyocyte to pressure-dependent hemodynamic overload, myocardial remodeling develops as the consequence of a number of pathological processes, mediated by hormones, growth factors, cytokines, and other proinflammatory molecules, acting on the cardiomyocyte and other cellular and noncellular myocardial components in hypertension (Figure 1).[2]

Hypertrophic Growth of Cardiomyocytes

Cardiomyocyte hypertrophy leading to LV wall thickening and LVM increase is the primary mechanism by which the heart reduces stress on the LV wall imposed by the unrelenting pressure overload (Figure 2).[3] However, only a small proportion of LVM variation is determined by hemodynamic factors, and other biological influences may also be important. Data of integrated genetic and genomic analyses implicate the gene osteoglycin as a key regulator of LVM in rodents and humans, suggesting that this gene modifies the hypertrophic response to hemodynamic factors.[5] More recently, genetic variation in NPY1R, NPY2R, NPY5R, CPE, IL15, and SFRP2 (all located in chromosome 4), detected using linkage analysis in hypertensive siblings, was found to be associated with LVM in black and white subjects.[6]

Cardiomyocytic hypertrophy entails stimulation of intracellular signaling cascades that activates gene expression and promotes protein synthesis, protein stability, or both, with consequent increases in protein content and the size and organization of force-generating units (sarcomeres) that, in turn, results in increased individual cardiomyocyte size.[7] Various molecular factors have been identified as being responsible for the coordinated control of the hypertrophic genetic program, including the following: natriuretic peptides, adrenergic system, adhesion and cytoskeletal proteins, interleukin-6 cytokine family, low-molecular weight GTPases (Ras, RhoA, and Rac), mitogen-activated protein kinases, protein kinase C, calcineurin, enzymes involved in histone deacetylases, and micro-RNAs.[8] The long-held views held that these morphological and genetic changes, in response to pressure overload, serve to restore cardiac muscle economy back to normal and thereby counteract myocardial dysfunction. However, evidence exists that blunting of cardiomyocyte hypertrophy and attenuation of the fetal gene re-expression did not result in dysfunction/failure despite pressure overload.[9] Therefore, one shift in the paradigm is occurring in the sense that genetic reprogramming associated with cardiomyocyte hypertrophy is no longer considered an entirely adaptive process. In fact, detailed analysis of the genetic changes that accompany cardiomyocyte hypertrophy
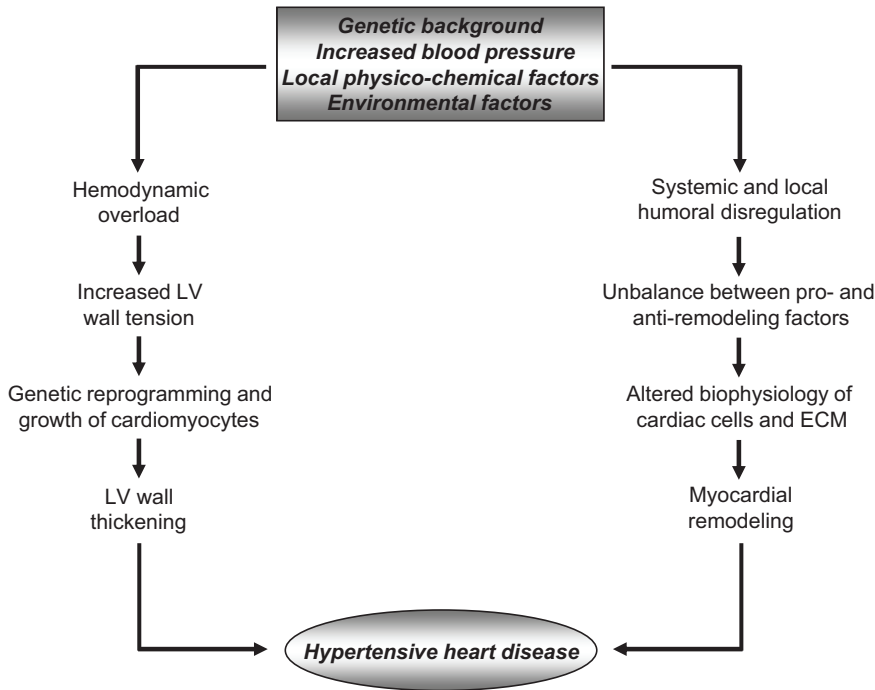
Figure 1. Mechanisms involved in the development of the lesions responsible for hypertensive heart disease. ECM indicates extracellular matrix.

permits the conclusion that they translate into derangements in energy metabolism, contractile cycle and excitation-contraction coupling, cytoskeleton and membrane properties, and autocrine functions, which, in turn, provide the basis for the cardiomyocyte malfunctioning associated with LVH and predispose the ventricular chamber to diastolic and/or systolic dysfunction and HF, as well as to arrhythmias.[10]
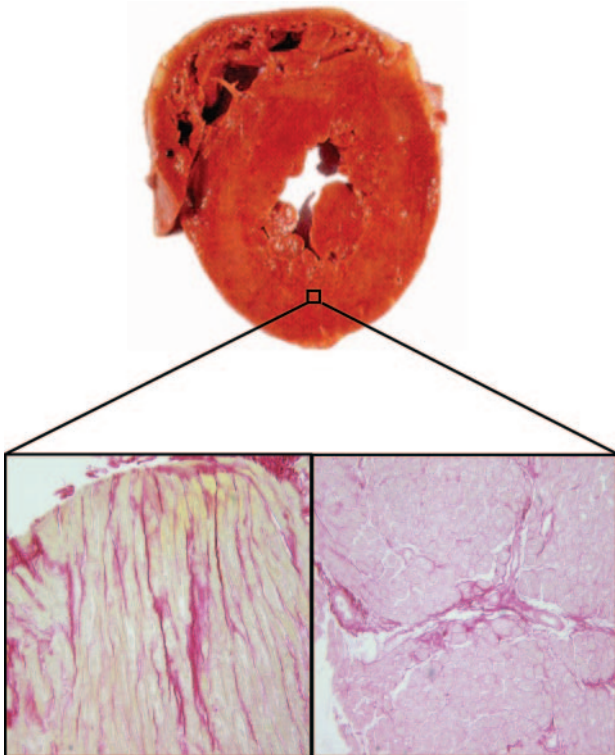

Figure 2. Interstitial (bottom left) and perivascular (bottom right) deposition of collagen fibers (picrosirius red stain, ×20) in the hypertrophied left ventricle (top) of a hypertensive patient.

Structural Remodeling of the Myocardium

The conception of remodeling was initially created to describe the anatomic changes in the left ventricle that occur after myocardial infarction.[11] Today, myocardial remodeling is used to qualify a variety of changes in the cardiomyocyte and the volume and composition of the noncardiomyocyte compartment that alter myocardial structure and function and occurring in response to myocardial infarction, pressure or volume overload, cardiomyopathic states, as well as exposure to infectious or cardiotoxic agents. In particular, hypertensive myocardial remodeling involves development of increased rates of cardiomyocyte apoptosis, interstitial and perivascular fibrosis (Figure 2), and microcirculatory changes.[2] Two types of findings suggest that nonhemodynamic factors critically determine these lesions in human hypertension.[2] First, they have been identified in both the left and right ventricles, interventricular septum, and atria of patients with HHD. Second, 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 predominant expression and/or activity of local and/or circulating molecules that simulate remodeling mechanisms over molecules that inhibit remodeling mechanisms (Table 1).[2] Of interest, recent clinical and experimental data suggest that specific genetic factors (ie, variants of the angiotensin type 1 [AT$_1$] receptor gene),[12] local inflammatory (ie, perivascular macrophage accumulation)[13] and physicochemical (ie, overabundance of reactive oxygen species) factors,[14] and environmental factors (ie, dietary sodium excess)[15] may facilitate the aforementioned imbalance between premodeling and antiremodeling molecules.

Recent observations suggest that apoptosis of cardiomyocytes may contribute to the development of LV dysfunction/failure of the hypertensive myocardium through 2 different

Table 1.   Molecules Involved in Myocardial Remodeling in HHD

Proremodeling molecules

Vasoactive substances (norepinephrine, angiotensin II)

Hormones (thyroid hormone, aldosterone)

Growth factors (transforming growth factor-β)

Cytokines (cardiotrophin 1)

Other (reactive oxygen species, endogenous peroxisome proliferator-activated receptor-γ ligands)

Antiremodeling molecules

Vasoactive substances (NO, prostacyclin, angiotensin-[1-7])

Hormones (glucocorticoids)

Growth factors (insulin-like growth factor 1)

Cytokines (tumor necrosis factor-α)

Other (endogenous peroxisome proliferator-activated receptor$-\alpha$ ligands)

pathways (Figure 3). On one hand, an association of increased cardiomyocyte apoptosis with diminished cardiomyocyte number has been found in HF of hypertensive patients.[16] Apoptosis may serve as one mechanism involved in the loss of contractile mass and function in HHD. Second, some mechanisms that are activated during the apoptotic process may also interfere with the function of viable cardiomyocytes before death.[17] In fact, caspase 3 cleaves cardiac myofibrillar proteins, resulting in an impaired force/calcium relationship and myofibrillar ATPase activity. In addition, the release of cytochrome C from mitochondria during apoptosis may impair oxidative phosphorylation and ATP production, thus leading to energetic compromise and 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 hypertensive myocardial remodeling. Excess myocardial collagen present in LVH is suggested to result from the combination of several alterations[18]: (1) increased procollagen synthesis by fibroblasts and phenotypically transformed fibroblast-like cells or myofibroblasts; (2) increased extracellular conversion of procollagen into fibril-forming collagen; (3) increased fibril assembly and cross-linking to form collagen fibers; and (4) unchanged or decreased collagen fiber degradation by matrix metalloproteinases. Fibrosis might contribute to the increased risk of adverse cardiac events in hypertensive patients with LVH through different pathways (Figure 3). First, a linkage between fibrosis and LV dysfunction/failure may be established.[19] Initially, the accumulation of collagen fibers compromises the rates of relaxation, diastolic suction, and passive stiffness, thereby 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 (defined as reduced coronary vasodilator response to different stimuli) associated with LVH might be related to several factors, including perivascular fibrosis.[20] In fact, the amount of perivascular collagen has been correlated inversely with coronary flow reserve in

hypertensive patients with LVH. Third, interstitial fibrosis may also contribute to ventricular arrhythmias in hypertensive LVH.[21] Thus, hypertensive patients with arrhythmias exhibited higher values of LVM and myocardial collagen than patients without arrhythmias, despite the finding that the ejection fraction and the frequency of coronary vessels with significant stenosis may be similar in the 2 groups of patients. Fibrosis, therefore, would induce conduction abnormalities, such as promoters of local re-entry arrhythmias. Finally, although the key role of ectopic foci in pulmonary veins as a trigger of atrial fibrillation has been recognized, structural remodeling, in particular, atrial fibrosis, has been identified as the main mechanism for atrial fibrillation persistence.[22] This suggests that atrial fibrosis in hypertensive patients, namely those with chronic HF, may be a part of more widespread changes in the myocardial collagen matrix, affecting the left ventricle and left atrium.

Hypertensive LVH is characterized by different structural alterations in the small intramyocardial vessels.[23] On the one hand, hyperplasia and/or hypertrophy, as well as altered alignment of vascular smooth muscle cells, promote encroachment of the tunica media into the lumen causing both an increased medial thickness:lumen ratio and a reduced maximal cross-sectional area of intramyocardial arteries. On the other hand, vascular density in LVH (vessel number per unit area) is relatively decreased. This seems to result from capillary rarefaction (ie, vessels actually missing or temporarily nonperfused or "recruited") and inadequate vascular growth (ie, impaired angiogenesis) in response to increasing muscle mass. These microcirculatory alterations, together with the increased arteriolar tone of hypertension, and endothelial dysfunction also contribute to decreased coronary flow reserve of hypertensive patients with LVH (Figure 3).[24]

In summary, histological abnormalities that develop in the myocardial parenchyma and intramyocardial vasculature of the hypertensive left ventricle provide structural support for those alterations of cardiac function, perfusion, and electric activity that characterize the clinical evolution of HHD.

Revisiting the Clinical Management of HHD

Time has come to revisit current management of HHD simply focused on detecting LVH and reducing LVM.[4] It is now necessary to develop new approaches aimed at early identification of hypertensive patients highly vulnerable to the development of LVH, with more accurate measurement of LV anatomy and function, noninvasive assessment of those microscopic changes responsible for myocardial remodeling, and correction of the molecular and cellular changes of the myocardium that alter its structure and function (Table 2). In so doing, the adverse risk associated with HHD should be reduced more effectively.

Early Detection

In most studies and meta-analyses, the relationship between changes in office pressure and LVM has been relatively weak (correlation coefficients: <0.50). Emerging evidence indicates that 24-hour monitoring of pressure may help identify those hypertensive patients highly predisposed to the development of LVH (ie, patients with early morning pressure rise
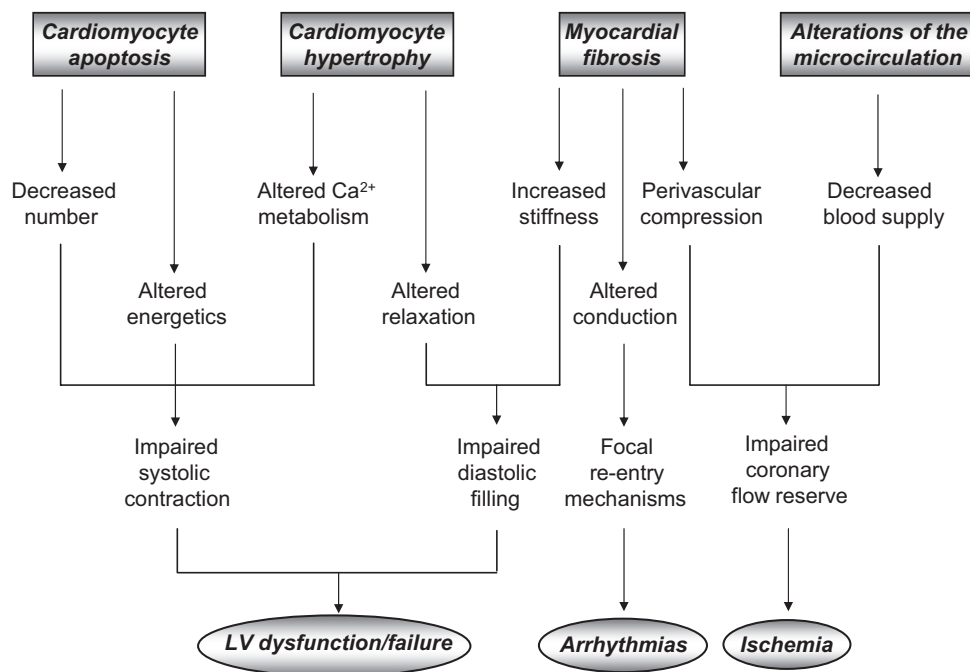
Figure 3. Pathways linking myocardial remodeling with clinical manifestations in hypertensive heart disease.

or with a nondipping profile) and more prone to benefit from the ability of some antihypertensive drugs to prevent it.[25]

As mentioned previously, LVM is a highly complex phenotype influenced by interacting effects of multiple genetic and hemodynamic factors. Genetic variation probably contributes to interindividual differences in LVM by virtue of effects on arterial pressure as well as other pathways not captured by pressure measurement. Identification of genes that influence LVM may enhance the detection of those patients requiring early treatment to prevent LVH development. In this regard, a meta-analysis of case-control and association studies has shown that the D allele of the insertion/deletion polymorphism of the angiotensin-converting enzyme (ACE) gene behaved as an LVH marker in untreated hypertensive patients.[26] In addition, recent findings suggest that the concomitant presence of the D allele of the insertion/deletion polymorphism of the ACE gene and the C allele of the A1166C polymorphism of the AT_1 receptor gene synergistically increased predisposition to diastolic dysfunction/failure in hypertensive patients.[27] Of interest, the C allele of the A1166C polymorphism of the AT_1 receptor gene has been found to be associated with enhanced LV chamber stiffness in HHD patients.[12]

Plasma concentration of cardiotrophin 1 (CT-1), a cytokine belonging to the interleukin 6 cytokine family that induces cardiomyocyte hypertrophy, is abnormally increased in hypertensive patients, especially those with echocardiographic LVH.[28] Thus, 31% of hypertensive patients without echocardiographic LVH already exhibited concentrations of CT-1 abnormally elevated,[28] suggesting that circulating levels of this cytokine increase early during the evolution of arterial hypertension and, thus, may be useful to identify those patients predisposed to the development of LVH.

Optimized Diagnosis
New 3D cardiac imaging techniques, including MRI and 3D echocardiography, can measure LVM and dimensions more accurately than conventional techniques and may, thus, offer an advantage.[29] Special ultrasound methodologies (ie, speckle tracking echocardiography aimed to assess LV strains) may be useful for the detection of myocardial remodeling, especially fibrosis.[30] MRI is another promising technique for characterizing the myocardial composition, particularly with the late gadolinium enhancement areas in the myocardium that probably represent fibrotic regions.[31] This methodology 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

Table 2. Proposed New Aims for the Clinical Handling of HHD

To identify patients prone to develop LVH
    24-h monitoring of blood pressure
    Insertion/deletion polymorphism of ACE gene
    Circulating cardiotrophin 1
To optimize the diagnosis of LVH
    3D echocardiography
    MRI
To detect noninvasively myocardial remodeling
    Speckle tracking echocardiography
    MRI
    Nuclear molecular imaging techniques
    ELISA of circulating biochemical markers
To provide therapeutic benefit beyond reduction of LVM
    Agents (i.e., antihypertensive and nonantihypertensive agents) that repair myocardial remodeling
    Antihypertensive agents that preserve cardiac function, electrical activity, and intramyocardial perfusion

spatial resolution. With regard to myocardial remodeling, molecular imaging is rapidly expanding to involve imaging and monitoring of apoptosis (ie, using ^{99m}Tc-labeled annexin A5 that binds to apoptotic cardiomyocytes)[32] and collagen synthesis (ie, using ^{99m}Tc-labeled peptides that bind to activated fibroblasts).[33]

Recent identification of biochemical markers of potential usefulness for clinical management of cardiac diseases evolving to HF has been a prolific field. However, for a circulating molecule can be considered a biochemical marker of hypertensive myocardial remodeling, it must fulfill several criteria.[34] Until now, several molecules have been proposed as biochemical markers of hypertensive myocardial remodeling that accomplish these criteria. For instance, plasma concentration of CT-1 has been correlated with LVM in untreated hypertensive patients,[28] suggesting that plasma CT-1 may be a potential marker for the assessment of cardiomyocyte hypertrophy and LVH in hypertensive patients. In addition, an association was found between antihypertensive treatment-induced decrease of plasma CT-1 and reduction of LVM in patients with LVH,[35] suggesting that this cytokine may be useful to assess the ability of antihypertensive drugs to reduce cardiomyocyte growth and decrease LVM. On the other hand, recent data suggest that some biochemical markers related to myocardial fibrosis (ie, serum carboxy-terminal propeptide of procollagen type I) or cardiomyocyte apoptosis (ie, plasma annexin A5) may provide information useful to assess these aspects of myocardial remodeling in hypertensive patients.[34]

The common negative aspect of these methodologies is the high cost that would have to be made available to the large hypertensive populations internationally. Indeed, to address their economic impact is a major issue for national health systems, as is the necessity to make present-day advanced technology cost-effective. However, the anticipated resultant reduction in morbidity and mortality with longer productive lives may tremendously offset those costs.

Effective Reduction of LVM

Antihypertensive drugs have been effective in reducing LVM. Mosterd et al[36] recently analyzed the Framingham Heart Study data and reported that the increasing use of effective antihypertensive therapy has decreased the prevalence of both hypertension and LVH. Many trials and meta-analyses have attempted to compare the effects of different antihypertensive agents on LVM, but flawed study designs and methodologic problems have limited their utility. Nevertheless, one meta-analysis including 80 double-blind, randomized, controlled trials with 146 active treatment arms and 17 placebo arms showed that, after adjustment for treatment duration and change in diastolic pressure, there was a significant difference among medication classes in decreasing LVM.[37] The decreased LVM (indexed by body surface area or LVM index) induced by the different classes was as follows: AT_1 receptor blockers>calcium antagonists>ACE inhibitors>diuretics>β-blockers. In paired comparisons, AT_1 receptor blockers, ACE inhibitors, and calcium antagonists were more effective at reducing LVM index than diuretics and β-blockers. Remaining questions about these

conclusions exist. Were the clinical status (including pretreatment pressures and the severity of hypertensive disease) and the accuracy of echocardiographic devices to assess LVM and dimensions similar to permit these comparisons? Furthermore, with conclusions about reduction of risk with treatment, was this outcome attributable to the decreased LVM or the result of reduced arterial pressure? Finally, with echocardiographically derived LVM, were the effects of the different pharmacological agents similar on the wall and chamber dimensions?

Antiremodeling Strategies

In recent trials in hypertension, development of HF was comparable with stroke.[38] Thus, physicians should be aware that HF still represents a frequent and deleterious consequence of hypertension. Also, recent Framingham Heart Study data suggest that causal classification may help to reduce syndromic heterogeneity, providing a disease pathogenesis–oriented approach to patients with HF (ie, hypertension facilitates HF with preserved ejection fraction).[39] These points underscore the necessity of addressing a new paradigm concerning HHD, its risk, and diagnostic and therapeutic approaches. Appropriate strategies to effectively fight the development of HF during its asymptomatic stages when early structural and functional cardiac abnormalities are identified should be applied to hypertensive patients with a high-risk profile (ie, patients with HHD). In this conceptual framework, beyond controlling pressure and reducing LVM, it is necessary, indeed essential, to pay attention to strategies focused on repairing myocardial remodeling.

Cumulating experimental evidence suggest that sodium loading exacerbates target organ damage associated with long-standing hypertension. In particular, sodium loading not only further increased arterial pressure and LVM in spontaneously hypertensive rats but also impaired LV and right ventricular diastolic functions and coronary flow reserve associated with enhanced interstitial and perivascular fibrosis.[15] The observation that AT_1 receptor blockade with low-dose candesartan failed to reduce the salt-induced rise in pressure but significantly attenuated LVM, myocardial fibrosis, and the development of LV diastolic dysfunction in spontaneously hypertensive rats[40] suggests that angiotensin II contributed to the pressure-independent remodeling effect of salt excess on the hypertensive myocardium. Therefore, salt restriction, shown previously to lower pressure and prevent hypertension, may also prevent myocardial remodeling and other target organ damage associated with hypertension. This possibility is supported in part by recent findings from the Trials of Hypertension Prevention Study showing that reduction in dietary sodium intake reduced long-term risk of cardiovascular complications.[41]

Available experimental data suggest that the goal of repairing myocardial remodeling is achievable in HHD using specific antihypertensive agents (Table 3).[42] Clinical studies provide important support to this possibility. Brilla et al[43] reported that, in patients with HHD, ACE inhibition regressed myocardial fibrosis, irrespective of LVM reduction, and it was accompanied by improved LV diastolic function. These effects were not observed in the patients treated with hydro-

Table 3. Experimental and Clinical Evidence-Based Effects of Antihypertensive Agents in HHD

Pharmacological Class	Decrease of Blood Pressure	Regression of LVH	Repair of Remodeling
Diuretics	Yes	Mild effect	Proven for torsemide
β-Blockers	Yes	Mild-moderate effect	Apparently not
α-Blockers	Yes	Mild effect	Untested
Calcium antagonists	Yes	Marked effect	Apparently not
ACE inhibitors	Yes	Marked effect	Yes
Angiotensin receptor blockers	Yes	Marked effect	Yes
Aldosterone antagonists	Yes	Mild-moderate effect	Apparently yes
Direct renin inhibitors	Yes	Marked effect	Untested

chlorothiazide despite similar pressure control. Long-term ACE inhibitor therapy has also promoted structural repair of coronary arterioles that was mainly characterized by the regression of periarteriolar fibrosis and marked improvement in coronary flow reserve in patients with HHD.[44] In addition, despite similar antihypertensive and antihypertrophic efficacy, an AT_1 receptor blocker, but not a calcium antagonist, reduced histologically proven cardiomyocyte apoptosis[45] and myocardial fibrosis[46] in patients with HHD. Reduction of myocardial fibrosis by the AT_1 blocker was associated with decreased LV chamber stiffness and the improvement of diastolic filling in hypertensive patients.[47] Recently, treatment with the loop diuretic torsemide, but not furosemide, was associated with a reduction of myocardial fibrosis and a trend toward improved LV function in patients with hypertensive HF.[48] Of interest, the diuretic and hemodynamic effects of the 2 compounds were similar. These data bring to mind 2 questions. On the one hand, the long-standing question remains as to the similarity of all pharmacological agents that are classified under the "label" of a same drug class. On the other hand, there is the question regarding the necessity of using drugs with a potential antifibrotic capacity to both prevent diastolic dysfunction that precedes HF in hypertensive patients and to treat hypertensive patients with HF and preserved ejection fraction.[49]

Current therapy of myocardial remodeling is presently based on targeting mechanical and humoral causative mechanisms. However, multiple and redundant signaling systems are involved in remodeling. Thus, novel therapeutic strategies may be necessary to reverse or even prevent myocardial remodeling. Recent insights from experimental studies have provided new targets for interventions.[50–53] The first insight is to act on those genetic mechanisms that intrinsically regulate the hypertrophic responses of the cardiomyocyte (ie, modulating activated osteoglycin-related pathways) or the profibrotic response of the fibroblast/myofibroblast (ie, inhibiting micro-RNA 29 or stimulating micro-RNAs 21 and 208). The second is to block the detrimental intracellular mechanisms activated by biomechanical stress on cardiomyocytes (ie, inhibiting intracellular renin activation and angiotensin II generation, superoxide anion generation by NADPH oxidase, and overstimulation of kinases, such as Rho-kinase, and phosphatases, such as calcineurin). Third is to prevent inhibition of negative signaling modulators and negative interacting proteins that are repressed by biomechanical stress in the cardiomyocyte (ie, increasing the availability and actions of cyclic GMP). Fourth is to preserve functioning cardiomyocytes (ie, through inhibition of apoptosis via poly [ADP-ribose] polymerase inhibition and/or preservation of cell survival mechanisms via insulin-like growth factor 1 activation) or to regenerate lost cardiomyocytes (ie, using stem cell therapy). Fifth is to restore normal turnover of the collagen network at the fibroblast and myofibroblast level (ie, modulating the synthesis and secretion of procollagen precursors, as well as of those enzymes controlling the extracellular processes of fibril and fiber formation, as well as degradation). Last is to stimulate the angiogenic activity of endothelial cells (ie, stimulating phosphatidylinositol 3-kinase-Akt-NO–mediated mechanisms).

Concluding Remarks

Classical conceptualization has considered HHD as the adaptive hypertrophy of LV wall to increased pressure. Recent findings in hypertensive animals and patients now challenge this paradigm by demonstrating that HHD also results from pathological structural remodeling of the myocardium in response to a mosaic of hemodynamic and nonhemodynamic factors altered in hypertension. We anticipate that this expanded view will benefit from the application of integrated "omic" methodologies aimed to reveal critical genes, pathways, and networks for LV growth and myocardial remodeling. The potential clinical relevance of this shift in paradigm is strengthened by the fact that it entails a new approach to HHD in terms of a more precise diagnosis and more demanding treatment. In addition, available information sets the stage for large and long-term clinical trials aimed at determining whether the diagnosis and reversal of myocardial remodeling in HHD are associated with greater benefit on the patient's cardiac function and prognosis than simply detecting and regressing LVH. This novel view of HHD may have tremendous epidemiological importance. In fact, the possibility that hypertensive patients predisposed to develop HHD may be detected before the appearance of clinical detectable LVH opens a new way to prevent cardiac complications associated with hypertension and its cardiac impact, especially HF.

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