Cardioreparation in Hypertensive Heart Disease
Karl T. Weber

Abstract—The normal myocardium is composed of a variety of cells. Cardiac myocytes, tethered within an extracellular matrix of fibrillar collagen, represent one third of all cells; noncardiomyocytes account for the remaining two thirds. Ventricular hypertrophy involves myocyte growth. Hypertensive heart disease (HHD) includes myocyte and nonmyocyte growth that leads to an adverse structural remodeling of the intramural coronary vasculature and matrix. In HHD, it is not the quantity of myocardium but rather its quality that accounts for increased risk of adverse cardiovascular events. Structural homogeneity of cardiac tissue is governed by a balanced equilibrium existing between stimulator and inhibitor signals that regulate cell growth, apoptosis, phenotype, and matrix turnover. Stimulators (eg, angiotensin II, aldosterone, and endothelins) are normally counterbalanced by inhibitors (eg, bradykinin, NO, and prostaglandins) in a paradigm of reciprocal regulation. To reduce the risk of heart failure and sudden cardiac death that accompanies HHD, its adverse structural remodeling must be targeted for pharmacologic intervention. Cardioprotective agents counteract the imbalance between stimulators and inhibitors. They include ACE and endopeptidase inhibitors and respective receptor antagonists. Cardioreparative agents reverse the growth-promoting state and regress existing abnormalities in coronary vascular and matrix structure. ACE inhibition has achieved this outcome with favorable impact on vasomotor reactivity and tissue stiffness. Today’s management of hypertension should not simply focus on a reduction in blood pressure, it must also target the adverse structural remodeling that begets HHD. (Hypertension. 2001;38[part 2]:588-591.)

Key Words: hypertrophy ■ fibrosis ■ myocardium ■ homeostasis

The myocardium is composed of various cell populations: (1) cardiac myocytes tethered within an extracellular scaffolding of fibrillar collagen and (2) noncardiomyocytes, which include endothelial and vascular smooth muscle cells of the intramural coronary circulation and fibroblasts located in interstitial and perivascular spaces.1,2 Ventricular hypertrophy is based on the growth of cardiac myocytes, which may or may not be accompanied by other iterations in tissue structure. In athletes, the growth of muscular and nonmuscular compartments of the heart are proportionate; tissue homogeneity is preserved. Myocardial mass that accompanies exercise training is comparable to that of left ventricular hypertrophy (LVH) seen in patients with essential hypertension of mild to marked severity.3 In hypertensive heart disease (HHD), however, tissue homogeneity gives way to heterogeneity and a disproportionate involvement of noncardiomyocyte cells, which accounts for a pathologic remodeling of tissue structure.2 Fibroblasts, for example, contribute to a perivascular fibrosis of intramural arteries and arterioles, which over time extends into contiguous interstitial space. Medial thickening of these vessels involves hypertrophy and/or hyperplasia of vascular smooth muscle cells.4 Microscopic scars replace myocytes lost to necrosis (apoptosis is not followed by fibrosis). These iterations in tissue structure are responsible for the pathologic hypertrophy of HHD5 and predisposition to enhanced risk of adverse cardiovascular events, including myocardial infarction, diastolic and/or systolic ventricular dysfunction, symptomatic heart failure, and arrhythmias.6,7 It is not the quantity but rather the quality of myocardium that distinguishes HHD from adaptive hypertrophy of the athlete.

Pathologic Remodeling: Tissue Homeostasis Gone Awry

Homeostasis refers to a state of equilibrium that exists between different yet interdependent elements or groups of elements (eg, salt and water balance in circulatory homeostasis). Tissue homeostasis represents a self-determination in cellular composition and structure based on cell differentiation, replication, and programmed cell death and a growth or regression in its structural protein scaffolding. Peptide, steroid, and/or amine molecules, produced locally, are involved in regulating these events. Circulating substances may also contribute (vide infra).

In the case of the heart, myocardial structure is governed by a balanced equilibrium between stimulator and inhibitor signals (Figure). These signals regulate cell growth, apoptosis, phenotype, and metabolic behavior (eg, collagen turn-


Cardiac Remodeling in HHD

<table>
<thead>
<tr>
<th>Regulation of Structure</th>
<th>Stimulators</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellular (± phenotype)</td>
<td>Growth</td>
<td>Apoptosis</td>
</tr>
<tr>
<td>Collagen (± Fb phenotype)</td>
<td>Synthesis</td>
<td>Degradation</td>
</tr>
</tbody>
</table>

remodeling (and/or cell phenotype). In HHD, an adverse structural remodeling is related to an imbalance in this equilibrium in favor of an absolute increase in stimulators or a relative increase secondary to a paucity of inhibitors.

over). Stimulators include both locally produced and circulating substances that gain access to interstitial fluid to create a state designed for growth that can lead to adverse structural remodeling. This includes growth of cellular elements and synthesis of structural proteins. Stimulators are normally counterbalanced by inhibitory signals with opposing effects on cells and matrix turnover. Stimulators include angiotensin (Ang) II, aldosterone, endothelins, and catecholamines. Inhibitors have opposing biologic actions. They include bradykinin, NO, prostaglandins, natriuretic peptides, and glucocorticoids. Through a biologic economy of action, stimulators not only contribute to tissue repair following injury, they also participate in preserving circulatory homeostasis.

Loss of reciprocal regulation that normally exists between stimulator and inhibitor production accounts for connective tissue remodeling (reviewed in Weber). As seen in the Figure, an excess of stimulators, due to either absolute stimulator overproduction or their relative overabundance secondary to a deficit in inhibitor formation, promotes fibrosis and thereby pathologic hypertrophy. For example, local overproduction of Ang II accompanies a large transmural anterior myocardial infarction. Based on its regulation of fibrogenic transforming growth factor-β expression (mRNA and protein), local Ang II contributes to formation of infarct scar and to interstitial fibrosis that appears in the interventricular septum and right ventricle remote to the infarct site. Cardiac fibrosis accompanies a paucity of inhibitors, such as that which appears with pharmacologic interference with NO formation and which is in turn prevented by AT1 receptor antagonists. A similar perivascular fibrosis of intramural coronary vessels appears in mice with genetically targeted interruption of their B1 bradykinin receptors.

Fibrosis of ventricles, atria, and systemic organs appears when these stimulators reach the circulation, such as that which occurs with chronic activation of the renin-angiotensin-aldosterone system (RAAS) in heart failure or unilateral renal artery stenosis or that which occurs when its effectors hormones are given intravenously. Organ fibrosis likewise accompanies chronic mineralocorticoid excess (plus salt) due to adrenal adenoma (reviewed in Weber and Brilla). Cardiac tissue homogeneity is preserved when myocyte growth that appears in response to ventricular pressure or volume overload is not associated with circulating RAAS activation. Such adaptive hypertrophy accompanies chronic anemia, small arteriovenous fistula, atrial septal defect, or hyperthyroidism.

Cardioprotective and Reparative Interventions

The adverse structural remodeling of cardiac tissue seen in HHD must be targeted for pharmacologic intervention to reduce adverse risk. In recognizing the differential regulation of myocyte and nonmyocyte compartments, posed respectively by hemodynamic and nonhemodynamic factors, it is possible to prevent adverse structure. A cardioprotective agent counteracts the disproportionate balance that exists between stimulators and inhibitors. ACE inhibitors, AT1 receptor antagonists, antagonists of ETₐ and ET₉ receptors, and aldosterone receptor antagonists represent such cardioprotective strategies. Agents that promote an overabundance of inhibitors to counterbalance stimulators include ACE and endopeptidase inhibitors.

Reparation of pathologic remodeling in HHD is based on reversing the growth-promoting state and regressing existing abnormalities in tissue structure. A cardioreparative intervention induces a relative excess of inhibitors to promote apoptosis of myofibroblasts and regression of adverse accumulation of matrix protein by proteolytic digestion. Such a pharmacologic intervention is intended to promote regression and perhaps even normalization of abnormalities in tissue structure and thereby to improve or even correct associated functional derangements. In HHD, this concept focuses on a regression in fibrous tissue accumulation with or without reversal of cardiac myocyte hypertrophy. It no longer should be acceptable to simply reduce arterial pressure or left ventricular mass in individuals having HHD. The cardioreparative concept has undergone experimental and clinical validation and this experience is reviewed below.

Validation of the Cardioprotection Concept

Type I collagen is the dominant fibrillar collagen of the normal myocardium and that found in HHD. Its tensile strength, which approximates steel, resists tissue deformation. Hemodynamic factors do not promote the appearance or contribute to the degradation of type I collagen. In the arrested heart, a distending pressure >100 mm Hg is required to break fibrillar collagen, whereas in the beating heart, an intraventricular pressure of >500 mm Hg is needed to induce ventricular rupture. A reduction in arterial pressure in systemic hypertension will not promote the regression of established fibrosis consisting predominantly of type I collagen. Biochemical degradation of fibrillar collagen is required. Active degradation of this fibrillar collagen by proteolytic enzymes, termed matrix metalloproteinases (MMPs), that normally reside in the myocardium in latent form is involved in cardioprotection.

The regression of established cardiac fibrosis was addressed in 14-week-old male rats with genetic spontaneous hypertension (SHR) in which established LVH with perivascular/intersitial fibrosis was present together with abnormal myocardial stiffness and impaired coronary vasodilator reserve to adenosine. Twelve-week treatment with an ACE inhibitor, given in either nondepressor or depressor dosages,
was examined. Comparisons were then made with 26-week-old gender-matched untreated SHR and untreated normotensive Wistar-Kyoto (WKY) controls. In treated SHR, the following was observed: normalization in arterial pressure and regression of LVH with depressor dosage only; regression of morphometrically assessed perivascular and interstitial fibrosis and normalization of myocardial stiffness with either dosage; and reversal of intramural coronary artery medial thickening with normalization in arterial pressure together with a restoration in vasomotor reactivity. This study demonstrated the feasibility of regressing established cardiac fibrosis in young adult SHR using an ACE inhibitor. Moreover, it provided further evidence as to the functional significance of fibrosis in HHD independent of myocyte hypertrophy.

It remained to be determined whether such treatment would also prove effective when cardiac fibrosis was more advanced and whether the regression in fibrosis involved MMPs. These questions were next addressed in 78-week-old male SHR with advanced HHD using 8-month treatment with an oral ACE inhibitor, given in depressor dosage. Comparisons were made with untreated age- and gender-matched SHR and with treated and untreated WKY controls. The following was observed in 110-week-old treated SHR: normalization in arterial pressure and complete reversal of LVH; a reduction in established cardiac fibrosis with improvement in diastolic stiffness and prevention of impaired systolic function that appeared in untreated SHR; and increase in tissue MMP-1 activity (collagenase) with treatment, which was not seen in untreated or treated WKY. This study further demonstrated the feasibility of cardioreparation, even in elderly rats with advanced HHD; the functional significance of fibrosis; and the regression of cardiac fibrosis occurred, at least in part, through enhanced collagenolytic activity. Several mechanisms can be invoked to explain such activity with ACE inhibitor treatment. An excess of inhibitors, such as bradykinin, NO, and prostaglandins, may serve to activate latent MMPs. Likewise a reduction in natural tissue inhibitors of MMPs could be contributory. This uncertainty notwithstanding, there exists the potential for a cardioreparative intervention to regress toward or to normalize adverse structural remodeling by fibrous tissue in HHD and to thereby reverse associated functional disturbances.

The cardioreparative concept has recently undergone clinical evaluation using a prospective randomized trial in patients with HHD. Featured were echocardiographic evidence of LVH with diastolic dysfunction and biopsy-proven left ventricular fibrosis documented by both morphometric and biochemical assays. No patient had angiographic evidence of coronary artery disease. In double-blind fashion, 35 patients were randomized to receive either an ACE inhibitor or a thiazide diuretic in addition to their preexisting antihypertensive regimen. The study’s primary end point focused on a regression in biopsy evidence of cardiac fibrosis. After 6 months’ treatment only individuals randomized to ACE inhibitor were found to have a regression in fibrosis. No reduction in LV mass was observed with either regimen. In keeping with the regression in fibrosis, a significant improvement in echocardiographic parameters of diastolic dysfunction were observed in ACE inhibitor–treated patients.

Conclusions

The potential exists for targeting adverse structural remodeling in human HHD using either cardioprotective or cardioreparative strategies. The potential to regress cardiac fibrosis by ACE inhibition and to reverse ventricular diastolic dysfunction is supported by experimental studies in rats with genetic hypertension and the recent clinical trial by Brilla et al in patients with HHD. The findings of these studies should set the stage for larger trials in which noninvasive detection of cardiac fibrosis in HHD could be used. These might include echocardiographic-based characterization of tissue structure and/or serologic markers of collagen turnover. Laviades and coworkers have reported that ACE inhibitor treatment normalizes such a marker of excess collagen synthesis in patients with HHD.

It is time to revisit the current management of HHD. The importance of pathologic structural remodeling, not simply the control of arterial pressure, needs to be addressed. Moreover, in recognizing that quality, not quantity, of myocardium in HHD is responsible for adverse cardiovascular events, management must no longer solely focus on a regression in left ventricular mass. Far more desirable is a regression of left ventricular mass and fibrosis with correction of ventricular dysfunction. Cardioprotective and cardioreparative interventions specifically target such remodeling with the view toward respectively preventing or regressing cardiac fibrosis in HHD and in so doing favorably influencing adverse risk.

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