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.5 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

Homogeneity in myocardial structure is preserved by a balanced equilibrium between stimulators and inhibitors that respectively regulate cell growth and death (or apoptosis) and fibroblast (Fb) collagen turnover (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 Weber8). 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 interventions 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.9,10 A similar perivascular fibrosis of intramural coronary vessels appears in mice with genetically targeted interruption of their B1 bradykinin receptors.11

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 effector hormones are given intravenously.12 Organ fibrosis likewise accompanies chronic mineralocorticoid excess (plus salt) due to adrenal adenoma (reviewed in Weber and Brilla).13 Cardiac tissue homogeneity is preserved when myocyte growth that appears in response to ventricular pressure or volume over-
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.

References
6. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med. 1990;115:345–352.
10. Tomita H, Egashira K, Ohtara Y, Takemoto M, Koyanagi M, Kato M, Yamamoto H, Tamaki K, Shimokawa H, Takeshita A. Early induction of transforming growth factor-β via angiotensin II type 1 receptors con-
Cardioreparation in Hypertensive Heart Disease
Karl T. Weber

Hypertension. 2001;38:588-591
doi: 10.1161/01.HYP.38.3.588

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/38/3/588

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/