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. 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. 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. 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. 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 HHD and predisposition to enhanced risk of adverse cardiovascular events, including myocardial infarction, diastolic and/or systolic ventricular dysfunction, symptomatic heart failure, and arrhythmias. 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

Regulation of Structure

<table>
<thead>
<tr>
<th>Stimulators</th>
<th>Inhibitors</th>
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<td>Growth</td>
<td>Apoptosis</td>
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Cellular (± phenotype)

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<tr>
<th>Synthesis</th>
<th>Degradation</th>
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Collagen (± Fb phenotype)

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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 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. 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.

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 ET_A and ET_B 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 Cardioreparation 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 cardiopreparation.

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 normoten-
sive Wistar-Kyoto (WKY) controls. In treated SHR, the
following was observed: normalization in arterial pressure and regression of LVH with depressor dosage only; regres-
sion of morphometrically assessed perivascular and intersti-
tial fibrosis and normalization of myocardial stiffness with
either dosage; and reversal of intramural coronary artery
medial thickening with normalization in arterial pressure
gether with a restoration in vasomotor reactivity. This study
demonstrated the feasibility of regressing established cardiac
fibrosis in young adult SHR using an ACE inhibitor. More-
over, it provided further evidence as to the functional signifi-
cance 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. Compar-
isons 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: nor-
malization 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. Sev-
eral 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 notwith-
standing, there exists the potential for a cardioprotective
intervention to regress toward or to normalize adverse struc-
tural remodeling by fibrous tissue in HHD and to thereby
reverse associated functional disturbances.

The cardioprotective concept has recently undergone clin-
ical evaluation using a prospective randomized trial in pa-
tients with HHD. Featured were echocardiographic evi-
dence of LVH with diastolic dysfunction and biopsy-proven
left ventricular fibrosis documented by both morphometric
and biochemical assays. No patient had angiographic evi-
dence 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 antihy-
pertensive 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 improve-
ment in echocardiographic parameters of diastolic dysfunc-
tion were observed in ACE inhibitor–treated patients.

Conclusions
The potential exists for targeting adverse structural remodel-
ing in human HHD using either cardioprotective or car-
dioreparative 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 myo-
cardium 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 correc-
tion of ventricular dysfunction. Cardioprotective and car-
dioreparative interventions specifically target such remodel-
ing with the view toward respectively preventing or
regressing cardiac fibrosis in HHD and in so doing favorably
influencing adverse risk.

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