Targeting Pathological Remodeling
Concepts of Cardioprotection and Reparation

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The myocardium is composed of cardiac myocytes, which are tethered within an extracellular scaffolding of fibrillar collagen. Myocytes are large; they occupy a major portion of tissue space. However, they number only a third of all cells in the myocardium; noncardiomyocytes constitute the remaining two-thirds of cells and 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. Such adaptive hypertrophy contributes to enhanced cardiac performance.

The myocardial mass that accompanies exercise training is comparable to the 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 because the disproportional involvement of noncardiomyocyte cells accounts for the pathological 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. This perivascular/interstitial fibrosis is based neither on myocyte growth nor necrosis; it represents reactive fibrosis. Medial thickening of these vessels involves hypertrophy and/or hyperplasia of vascular smooth muscle cells. Microscopic scarring (a reparative fibrosis) replaces myocytes lost to necrosis (apoptosis is not followed by fibrosis). Together with the hypertrophy of left ventricular myocytes, these iterations in tissue structure in HHD create a pathological hypertrophy that predisposes to an 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.

Targeting Pathological Remodeling
Homeostasis can be defined as a state of equilibrium that exists between different yet interdependent elements or groups of elements in a living organism (eg, salt and water balance in circulatory homeostasis). Tissue homeostasis relates to 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 can also participate (vide infra).

The structural homogeneity of normal adult myocardium is governed by a balanced equilibrium between stimulator and inhibitor signals (Figure 1) that, respectively, regulate cell growth (and apoptosis) and phenotype and metabolic behavior (eg, collagen turnover). Stimulators include both locally produced and circulating substances that gain access to interstitial fluid to create a state designed for growth, which can result in the adverse structural remodeling of cardiac tissue. This remodeling can include the growth of cellular elements and the synthesis of structural proteins. Stimulators are normally counterbalanced by inhibitory signals, which have opposing effects on cells and matrix turnover.

Stimulator overproduction is invoked after tissue injury and initially contributes to circulatory homeostasis; its effects include platelet aggregation, coagulation, vasoconstriction, increased heart rate, enhanced contractility, and urinary sodium retention. Stimulators include angiotensin II, aldosterone, endothelins, and catecholamines. Inhibitors have opposing biological actions. They include bradykinin, nitric oxide, prostaglandins, natriuretic peptides, and glucocorticoids. Through the biological economy of action, stimulators are involved in the subsequent phases of tissue repair (inflammation and fibrogenesis).

Loss of the reciprocal regulation that normally exists between stimulator and inhibitor production (Figure 2) accounts for connective tissue remodeling (reviewed in Reference 7). An excess of stimulators, due either to absolute stimulator overproduction or a relative overabundance due to a deficit in inhibitor formation, can promote fibrosis and, thereby, pathological hypertrophy. Local overproduction of angiotensin II, for example, accompanies a large, transmural anterior myocardial infarction and, through its regulation of fibrogenic transforming growth factor-β expression, it contributes to infarct scar formation and to an interstitial fibrosis that appears remote to the infarct site. Cardiac fibrosis can...
Figure 1. 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 hypertensive heart disease, adverse structural remodeling is related to an imbalance in this equilibrium.

Fibrosis of the heart, including the ventricles and atria, and the systemic organs accompanies long-term elevations in circulating effector hormones of the renin-angiotensin-aldosterone system. This occurs when renal perfusion is impaired by heart failure or unilateral renal artery stenosis. Organ fibrosis likewise accompanies chronic mineralocorticoid excess (plus salt) due to adrenal adenoma or exogenous treatment with aldosterone or deoxycorticosterone (reviewed in Reference 2). Cardiac tissue homogeneity is preserved when the myocyte growth that appears in response to ventricular pressure or volume overload is not associated with the activation of the circulating renin-angiotensin-aldosterone system. Such adaptive hypertrophy accompanies chronic anemia, small arteriovenous fistula, atrial septal defect, and hyperthyroidism.2

Targeted Interventions: Protective and Reparative

The adverse structural remodeling of cardiac tissue seen in HHD represents a targeted goal of pharmacological intervention. In recognizing the differential regulation of myocyte and nonmyocyte compartments posed by hemodynamic and nonhemodynamic factors, respectively, it is possible to prevent adverse structural remodeling. A cardioprotective agent counteracts the disproportionate balance that exists between stimulators and inhibitors. Such cardioprotective strategies include the use of angiotensin-converting enzyme (ACE) inhibitors, angiotensin II type 1 receptor antagonists, antagonists of endothelin A and B receptors, and aldosterone receptor antagonists. Those agents that promote an overabundance of inhibitors to counterbalance stimulators include ACE and endopeptidase inhibitors.

Reparation of pathological remodeling in HHD is a concept based on specifically targeting such remodeling with a pharmacological intervention that will reverse the growth-promoting state and regress existing abnormalities in tissue structure. A cardioreparative intervention induces a relative excess of inhibitors to promote the apoptosis of myofibroblasts and the regression of the adverse accumulation of matrix protein by proteolytic digestion. Such a strategy is intended to promote the regression of, and perhaps even normalize, abnormalities in tissue structure, thereby improving or even correcting associated functional derangements. In HHD, this concept focuses on a regression in fibrous tissue accumulation, with or without a reversal of cardiac myocyte hypertrophy. In achieving this end point, it may be possible to reduce the risk of adverse cardiovascular events. In the 21st century, it may not be tenable to simply reduce arterial pressure in individuals having HHD. Has the cardioreparative concept undergone experimental validation? Is it possible to regress fibrous tissue?

Figure 2. Reciprocal regulation between stimulator and inhibitor production creates a balanced equilibrium that maintains stability in tissue structure. PG indicates prostaglandin; ET, endothelin; BK, bradykinin; Ang, angiotensin; TGF, transforming growth factor; NO, nitric oxide; and ALDO, aldosterone. Reproduced with permission from Weber KT. Angiotensin II and connective tissue: homeostasis and reciprocal regulation. Regul Pept. 1999;82:1–17.

Cardioreparation: Proof of Concept

Type I collagen is the dominant fibrillar collagen of the myocardium. Its tensile strength, which approximates that of steel, resists tissue deformation. Active degradation of this fibrillar collagen by proteolytic enzymes, termed matrix metalloproteinases (MMPs), which normally reside in the myocardium in latent form, is involved in the appearance of such pathological deformations as infarct expansion, ventricular aneurysm, and myocardial rupture.1 Pathophysiological elevations in diastolic or systolic pressure alone will not physically disrupt fibrillar type I collagen. In the arrested heart, a distending pressure >100 mm Hg is required to break fibrillar collagen.1 A intraventricular pressure >500 mm Hg is needed to induce ventricular rupture in the beating heart.12

A reduction in arterial pressure in systemic hypertension will not promote the regression of established fibrosis, which consists predominantly of type I collagen. Biochemical degradation is required. Can this be accomplished by pharmacological intervention?
This question was addressed in 14-week-old male rats with genetic hypertension (SHR) and in which established LVH with perivascular/interstitial fibrosis was present, together with abnormal myocardial stiffness and impaired coronary vasodilator reserve to adenosine.13 Twelve weeks of treatment with an ACE inhibitor, given in either nondepressor or depressor dosages, was undertaken. Comparisons were then made with 26-week-old, sex-matched, untreated SHR and untreated, normotensive Wistar-Kyoto (WKY) controls. The following were observed in treated SHR: normalization of arterial pressure and regression of LVH with depressor dosage only; regression of morphometrically assessed perivascular and interstitial fibrosis with either dosage and normalization of myocardial stiffness; 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 using an ACE inhibitor in young adult SHR. It also provided further evidence regarding 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 addressed in 78-week-old male SHR with advanced HHD using 8 months of treatment with an oral ACE inhibitor that was given in depressor dosage.14 Comparisons were made with untreated age- and sex-matched SHR and with treated and untreated WKY controls. The following were 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 the impaired systolic function that appeared in untreated SHR; and an 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 (in this case) in elderly rats with advanced HHD, the functional significance of fibrosis, and the regression of cardiac fibrosis, at least in part, through collagenolytic activity. Many questions remain as to the underlying mechanisms by which regression of fibrillar collagen occurs with ACE inhibition. Is it indeed an excess of such inhibitors as bradykinin, nitric oxide, and prostaglandins that activates natural tissue inhibitors involved? This uncertainty notwithstanding, the potential exists for a cardioreparative strategy. It supports experimental studies in rats with genetic hypertension showing the potential to regress cardiac fibrosis by ACE inhibition and to reverse ventricular diastolic dysfunction. The study used biopsy tissue to assess cardiac fibrosis directly; this is an invasive methodology with obvious limitations for wide-scale application. Nonetheless, the study findings set the stage for larger trials wherein noninvasive measures of cardiac fibrosis could prove useful. These might include echocardiographic-based characterization of tissue structure and/or serological markers of collagen turnover.18–20 In this connection, 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 pathological structural remodeling must be addressed instead of simply focusing on controlling arterial pressure. In recognizing that the quality, not quantity, of myocardium in HHD is responsible for adverse cardiovascular events, management must not only focus on regression in left ventricular mass. Far more sensible are cardioreparative interventions that specifically target such remodeling with the view toward regressing the same and, in so doing, reducing adverse risk.

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Overview

This clinical trial by Brilla et al,15 despite its limited size, underscores the potential for targeting adverse structural remodeling in human HHD using a cardioreparative strategy. It supports experimental studies in rats with genetic hypertension showing the potential to regress cardiac fibrosis by ACE inhibition and to reverse ventricular diastolic dysfunction. The study used biopsy tissue to assess cardiac fibrosis directly; this is an invasive methodology with obvious limitations for wide-scale application. Nonetheless, the study findings set the stage for larger trials wherein noninvasive measures of cardiac fibrosis could prove useful. These might include echocardiographic-based characterization of tissue structure and/or serological markers of collagen turnover.18–20 In this connection, Laviades and coworkers have reported that ACE inhibitor treatment normalizes such a marker of excess collagen synthesis in patients with HHD.

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