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.

See p 1388

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 disproportionate 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

Concepts of Cardioprotection and Reparation

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The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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(Circulation. 2000;102:1342-1345.)
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Circulation is available at http://www.circulationaha.org

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accompany a paucity of inhibitors, such as occurs with an experimental interference with nitric oxide formation and which, in turn, can be prevented by the pharmacological blockade of angiotensin II type 1 receptors.8 In mice with a genetically targeted interruption of their B2 bradykinin receptors, progressive perivascular fibrosis occurs in the intramural coronary vessels.10

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 non-hemodynamic 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 cardiopreparative 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 cardiopreparative concept undergone experimental validation? Is it possible to regress fibrous tissue?

**Cardiopreparation: 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.11 An 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 cardio-reparation (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 latent MMPs, and is the expression of MMPs and their natural tissue inhibitors involved? This uncertainty notwithstanding, the potential exists for a cardio-reparative intervention to regress or to normalize the adverse structural remodeling by fibrous tissue in HHD and, thereby, to reverse associated functional disturbances.

The cardio-reparative concept has now been demonstrated in man15 using a prospective, randomized trial of 35 patients with HHD. In this trial, echocardiographic evidence of LVH with diastolic dysfunction and biopsy-proven left ventricular fibrosis was documented by both morphometric and biochemical assays. No patient had angiographic evidence of coronary artery disease. In a double-blind fashion, patients were randomized to receive either an ACE inhibitor or a thiazide diuretic for 6 months in addition to their preexisting antihypertensive regimen. The study’s primary end point focused on regression of cardiac fibrosis, as determined by biopsy. Only individuals randomized to the ACE inhibitor had 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 the echocardiographic parameters of diastolic dysfunction was observed in ACE inhibitor–treated patients.

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 cardio-reparative 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 structure16,17 and/or serological markers of collagen turnover.18–20 In this connection, Laviades and coworkers18 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 of left ventricular mass. Far more sensible are cardio-reparative interventions that specifically target such remodeling with the view toward regressing the same and, in so doing, reducing adverse risk.

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**Key Words:** Editorials | hypertrophy | hypertension | fibrosis | collagen | angiotensin
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Circulation. 2000;102:1342-1345
doi: 10.1161/01.CIR.102.12.1342
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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World Wide Web at:
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