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EDITORIAL COMMENT

Fibrosis

A Living Tissue and the Infarcted Heart*

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Heart failure has reached epidemic proportions among the elderly, in whom it is most often attributable to an ischemic cardiomyopathy (ICM) with previous myocardial infarction(s) (MIs). The infarcted heart is a "house divided" (1), its myocardium disrupted by the loss of necrotic cardiomyocytes, its structural syncytium interrupted by an infarct scar, and its remaining viable myocardium corrupted by an interstitial fibrosis. Multiple foci of replacement fibrosis, in combination with interstitial fibrosis, are reported to be the major cause of ventricular remodeling in the cardiomyopathic heart of ischemic origin, where it accounts for nearly 70% of fibrotic tissue; infarction (scar) comprises 30% (2).

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The electrical behavior of the infarcted heart and its function during systolic and/or diastolic phases of the cardiac cycle are each perturbed by the accumulation of fibrous tissue (3). An understanding of the pathobiology responsible for the fibrosis that appears remote to the infarct could forge new frontiers in identifying risk for such adverse structural remodeling and in so doing, prevent the onset of heart failure and thwart its progressive nature. What is known about fibrosis in the infarcted heart?

Collagen turnover after MI. Cleutjens et al. (4) studied the timeline of collagen degradation and synthesis in the infarcted rat heart. During the early days after left coronary artery ligation, the activity and expression of matrix metalloproteinases rose at the infarct site, only to be attenuated by day 7 with the up-regulation of their tissue inhibitors. Thereafter, collagen synthesis prevailed. Increased messenger ribonucleic acid expression of type I and III fibrillar collagens appears predominantly at, and to a lesser extent, remote to the infarcted left ventricle (LV), which includes the noninfarcted interventricular septum and right ventricle (RV) and where it was persistent for prolonged periods.

Cells responsible for fibrous tissue. Phenotypically transformed fibroblast-like cells, termed myofibroblasts because they express alpha-smooth muscle actin (SMA) microfilaments, express fibrillar collagens found at and remote to the infarct (5). The myofibroblasts arrive at the infarct site on days 3 and 4 post-MI and remain there for prolonged periods (months in rats and years in humans). Their ongoing activity creates a "living tissue" that imparts a dynamic nature to collagen turnover.

De novo angiotensin (Ang)II generation in the regulation of myofibroblasts collagen turnover. Various imaging techniques have been used to monitor the cellular and molecular biology involved in angiotensin peptide (AT) generation in the infarcted rat heart (5). Increased expression of angiotensinogen and renin, together with renin activity, and high-density angiotensin-converting enzyme (ACE) and AT_1 receptor radioligand binding are found on day 7 post-MI and localized to both macrophages and myofibroblasts. A progressive rise in ACE and AngII receptor binding densities are found at the infarct site at 2, 4, and 8 weeks after MI and are associated with myofibroblasts; macrophages gradually disappear beyond day 14. At week 2 and beyond, increased ACE and AngII receptor binding densities are also found remote to the MI and other sites of fibrous tissue accumulation, such as pericardial fibrosis. The ACE and AngII receptor binding at 4 weeks post-MI are shown in Figure 1. Displacement studies, using AT_1 and AT_2 receptor antagonists, identified AT_1 receptors to be the predominant subtype. Increased expressions of transforming growth factor (TGF)-β_1 and type I collagen were likewise found at the infarct site and attributed to myofibroblasts. In an auto/paracrine manner, myofibroblast-based AngII generation up-regulates the expression of the fibrogenic cytokine TGF-β_1 during tissue repair, with TGF-β_1 responsible for myoFb collagen synthesis. Treatment with an ACE inhibitor or AT_1 receptor antagonist attenuates the expression of TGF-β_1, type I collagen, and the appearance of fibrous tissue found at the various sites of healing, including the noninfarcted LV and RV (4,5).

Thus, tissue repair involving myofibroblasts and their de novo generation of AngII and TGF-β_1 serve to regulate collagen turnover at and remote to MI and to account for fibrous tissue formation. Fibrosis is a dynamic living tissue whose activity can be modified by an ACE inhibitor or AT_1 receptor antagonist.

Monitoring fibrosis in the infarcted heart. Interstitial fibrosis remote to the infarct is an important determinant of abnormal electrical and mechanical behavior of the infarcted heart. The approach to monitoring fibrosis might proceed along different yet complementary directions.

Myofibroblasts. In this issue of the *Journal*, van den Borne et al. (6) have addressed the utility of intravenous technetium 99m (^{99m}Tc)–labeled Cy5.5-RGD imaging peptide (CRIP), together with single-photon emission computed tomography, in monitoring myofibroblasts at and remote to MI in the open-chested mouse after left coronary artery

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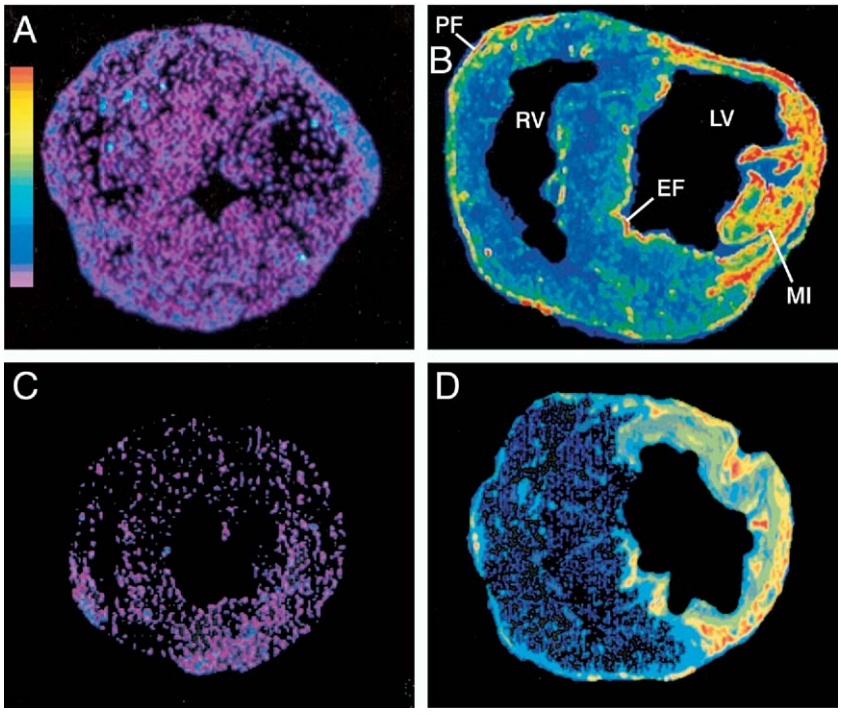

Figure 1 **Angiotensin-Converting Enzyme and Angiotensin II Receptor Binding**

Quantitative in vitro autoradiographic imaging of angiotensin-converting enzyme (ACE) and angiotensin (Ang)II receptor binding densities in coronal sections of the rat heart, revealing the right ventricle (RV) and left ventricle (LV). Binding densities are color-coded: **red** and **yellow** indicate the highest density and **purple** the lowest density binding. [^{125}I]351A, a tyrosyl derivative of lisinopril, was used to monitor ACE binding density. In the control rat heart **(A)**, ACE binding density is low; at week 4 after myocardial infarction (MI) **(B)**, binding density has increased throughout the heart, with the highest density seen at the infarct (MI) and sites remote to it, which include pericardial (PF) and endocardial fibrosis (EF) evident by histochemical staining and light microscopy (not shown). ^{125}I[Sar^{1},Ile^{8}]AngII, an Ang receptor antagonist, was used to monitor AngII receptor binding. In the control rat heart **(C)**, AngII binding density is low; at week 4 post-MI **(D)**, high-density binding is found at the infarct and remote sites that include pericardial and endocardial fibrosis. Displacement studies using angiotensin peptide $(AT)_1$- and AT_2-specific receptor antagonists identified AT_1 receptors as the predominant subtype in the infarcted rat heart (not shown).

ligation. The peptide binds to integrins, adhesion molecules expressed by these myofibroblasts as they attach to fibrillar collagen at the site of repair. Fluorescence microscopy identified probe uptake to localize with alpha-SMA–positive myofibroblasts, whose ultrastructure was confirmed by immunoelectron microscopy, and paralleled collagen fibrillogenesis. It was at its maximum at week 2 post-MI and remained increased at 4 and 12 weeks, with a time course similar to that in enhanced tissue labeling seen at sites remote to the MI. The CRIP uptake at 4 weeks post-MI was attenuated by captopril alone or in combination with losartan. This is a promising approach. The study was conducted in the infarcted mouse heart where, unlike in the rat, collagen expression and accumulation at the infarct site is low, thereby raising the propensity for rupture, which is even lower remote to the MI. Wound healing post-MI in mice is more rapid and associated with a disappearance of myofibroblasts compared with rats and humans, where they are more persistent. Additionally, a number of cells participating in tissue repair, including myofibroblasts and inflammatory and endothelial cells, have an up-regulated expression of adhesion molecules that could make CRIP binding less specific for myofibroblasts. Tissue binding of this radionuclide does not directly monitor myofibroblast activity or their turnover of collagen.

Monitoring ACE and AngII receptors. As noted above, radiolabeled ACE inhibitors, together with quantitative in vitro autoradiography, have identified increased ACE binding in the infarcted rodent and human heart, particularly at the site of infarction, while AngII receptors have been detected using radiolabeled Ang receptor blockers (5,7,8). Intravenous ^{99m}Tc-labeled losartan was used in a murine model of MI in which, at 1 to 6 weeks after coronary artery ligation, dense uptake was observed at the infarct site (8). To date, no reports have appeared on the use of these tracers in humans.

Serologic markers of collagen turnover. Monitoring various peptides, derived from the synthesis and degradation of type I and type III collagens, holds promise as a noninvasive tool regarding the extent of myocardial fibrosis and its pathobiology, as well as patient prognosis and response to therapy. The accumulating evidence, mainly obtained in patients with hypertensive heart disease, points to the carboxy-terminal propeptide of procollagen type I (PICP) as the only circulating molecule that meets the criteria required as a true biochemical marker of myocardial fibrosis (9).

PICP is cleaved from procollagen type I during the extracellular synthesis of fibril-forming collagen type I.

Increased serum concentrations of PICP have been reported in patients within the first days after MI (10–12). When patients were stratified according to PICP values at presentation or at 3 months post-infarction, those presenting with the highest values developed progressive LV dilatation, reduced ejection fraction, and impaired diastolic filling (10–12). In addition, change in serum PICP proved to be an independent predictor of cardiac death or heart failure during follow-up (12). Therefore, serum PICP concentration is related to the development of LV remodeling and dysfunction after MI, and provides prognostic information.

In summary, fibrosis appears at and remote to MI. At remote sites, it represents the major component to the adverse structural remodeling in the failing heart of ischemic origin. Fibrosis is a living tissue. It includes a population of myofibroblasts whose ongoing collagen turnover is related to their de novo generation of AngII and its auto/paracrine regulation of TGF-β_1. By examining tissue repair after MI, including the pathobiology and dynamic nature of cardiac fibrosis, novel insights into predicting the risk of such adverse structural and geometric remodeling, preventing the onset of ventricular dysfunction, and interfering with the progressive nature of heart failure can be gained.

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