Ventricular Remodeling After Infarction and the Extracellular Collagen Matrix: When Is Enough Enough?

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Ventricular Remodeling After Infarction and the Extracellular Collagen Matrix

When Is Enough Enough?

Bodh I. Jugdutt, MD

Left ventricular (LV) remodeling after myocardial infarction (MI) contributes significantly to LV dilation and dysfunction, and disability and death. Two paradigms, pertinent to antiremodeling therapy after MI (Figure 1), have evolved over the last 3 decades. Paradigm 1, LV remodeling is a major mechanism for disability and death,1,2 has received a great deal of attention. In contrast, paradigm 2, remodeling of the extracellular collagen matrix (ECCM) plays a major role in LV remodeling,3–7 whereby decrease, disruption, and/or defective composition of the ECCM promote LV dilation and rupture,4–7 has received little attention. A host of clinical trials showed that angiotensin-converting enzyme (ACE) inhibitors (ACE-Is) with or without aldosterone antagonists, angiotensin II (AngII) type 1 (AT1) receptor blockers (ARBs), β-adrenergic blockers or reperfusion improve outcome in survivors of MI.8–10 Concurrent evidence has underscored the importance of preserving the ECCM during healing after MI.2–7 However, the antifibrotic action of ACE-Is, aldosterone antagonists and ARBs on ECCM in the infarct zone (IZ) and noninfarct zone (NIZ),6,7,9,11 and the reperfusion-induced damage to the ECCM in the IZ,5,7,12 remain unreconciled with the benefits.8–10,13 Nevertheless, excessive ECCM, as in dilated ischemic cardiomyopathy after remote MI,14,15 can contribute to LV diastolic dysfunction and poor outcome,5 suggesting that antifibrotic drugs that target excess ECCM might be a logical therapeutic approach. This review focuses on the role of the ECCM in the evolution of LV remodeling after MI and the potential impact of therapies that target the ECCM.

Ventricular Remodeling After MI and the Role of ECCM

Five points merit emphasis. First, the LV remodeling process after MI is complex, dynamic, and time dependent, and progresses in parallel with healing over months,1,2,7,16 Notably, it involves differential changes between the IZ and NIZ with respect to the following: (1) LV structure, shape, and topography1,2 (Figure 1); (2) cell type, such as myocytes and nonmyocytes (Table 1);6,7,17–22; (3) proteins, cytokines, and growth factors2,24,25; and (4) the ECCM.5,7,13–17,19–23 Differential regional remodeling of the ECCM contributes significantly to global LV structural remodeling after MI (Figure 2)7,9,26 and plays a pivotal role in paradigm 1,3,6,7

Second, the post-MI heart shows remarkable capacity to adapt to the rather sudden development of an IZ and a NIZ. Thus, MI results in time-dependent damage to myocytes, nonmyocytes, and the ECCM in the IZ; ventricular dysfunction followed by volume overload and progressive dilation; reactive hypertrophy with interstitial fibrosis and increased collagen in the NIZ; gradual reparative fibrosis in the IZ7; and vascular remodeling in the IZ and NIZ.7

Third, several endogenous molecules that affect collagen synthesis and are upregulated after MI, and several agents that are used therapeutically for MI, affect collagen turnover (Table 2, Figure 3) and exert an antifibrotic effect.2,7,9,10,28 This can potentially alter ECCM remodeling in the IZ9,28 and impair healing,29 and thereby promote adverse remodeling and outcome, depending on their timing relative to pathophysiological stages of healing (Table 3).

Fourth, a fine balance, between matrix metalloproteinases (MMPs) that degrade ECCM and endogenous tissue inhibitors of MMPs (TIMPs) that inhibit MMPs,30–32 maintains normal remodeling and function, and an imbalance can result in adverse remodeling.24,25,30,33,34

Fifth, although a 2- to 3-fold increase in myocardial collagen above the normal level results in increased LV stiffness and mild dysfunction,35 a very small decrease in collagen below normal can lead to drastic consequences,36,37 including LV dilation3,22,34 and rupture.33,38 In reperfused MI, decreased or damaged ECCM in the IZ5,12,39 is associated with cardiac rupture.5,39

Key Points to Remember About Pathobiology of Cardiac ECCM

First, nearly 75% of the cells in the healthy heart are nonmyocytes, which include fibroblasts38,21 that account for 90% to 95% of nonmyocyte cell mass17,20,21 (Table 1). Myocardial cells are supported by a matrix (Table 4) consisting of a macromolecular network of fibers36 with intricate 3D organization11 that largely determines the structural and functional integrity of the heart.7

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Second, fibroblasts and myofibroblasts (myoFbs) produce most of the matrix macromolecules, including collagen, the principal structural protein. Third, the collagen molecules consist of a central core of long, stiff, triple-stranded helices in which chains wind around each other to form a superhelix. Of the many collagen types (Table 5), the major fibrillar collagens are types I and III, which constitute the bulk of cardiac ECCM. Thus, ≈85% of total collagen is type I, which is associated mainly with thick fibers that confer tensile strength and resistance to stretch and deformation, whereas ≈11% of total collagen is type III, which is associated with thin fibers that confer resilience. The other matrix components also mediate important functions (Table 4).

Fourth, collagen biosynthesis involves enzymatic steps, including intracellular synthesis of pro-α chains, hydroxylation, glycosylation, formation of procollagen triple helices, secretion into extracellular space, conversion into less soluble molecules, assembly into fibrils, and aggregation into fibers. The key enzyme, prolyl-4-hydroxylase (P4H), catalyzes the hydroxylation of proline to yield stable protocollagen molecules that are secreted into the ECCM. P4H requires several cofactors, including ascorbic acid (vitamin C). Other factors also influence collagen synthesis and include growth factors, such as transforming growth factor-β1 (TGF-β1), insulin growth factor and connective tissue growth factor (CTGF), cytokines such as tumor necrosis.

**TABLE 1. Myocytes and Nonmyocytes in the Myocardium**

<table>
<thead>
<tr>
<th>Group</th>
<th>By Cell No.</th>
<th>By Cell Volume</th>
<th>By Cell Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiomyocyte</td>
<td>25%§</td>
<td>~75%</td>
<td>~90%</td>
</tr>
<tr>
<td></td>
<td>30–35%</td>
<td>~67%</td>
<td>~90%</td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td>67%</td>
<td>...</td>
</tr>
<tr>
<td></td>
<td>33%</td>
<td>80%</td>
<td>...</td>
</tr>
<tr>
<td>Nonmyocyte</td>
<td>75%*</td>
<td>~33%</td>
<td>~10%</td>
</tr>
<tr>
<td></td>
<td>65–70%</td>
<td>33%†</td>
<td>(90–95%)</td>
</tr>
<tr>
<td></td>
<td>67%</td>
<td>20%</td>
<td>(13% vascular)</td>
</tr>
</tbody>
</table>

*Connective tissue nuclei.
§Includes lumen (volume fraction).
†Mostly fibroblasts.
‡Fibroblasts as % of nonmyocyte fraction.
factor-α (TNF-α) and interleukin-1 (IL-1), and various hormones and enzymes (Table 2, Figure 3).

Fifth, the orderly degradation of ECCM, critical for growth, remodeling and repair, is mediated mainly by MMPs (Table 5) (30,31). The collagenases (MMP-1, -8, and -13) are highly specific and primarily cleave fibrillar collagens at specific sites, thereby destroying structural integrity with the minimum amount of proteolysis. The gelatinases (MMP-2 and -9) degrade the denatured fibrillar collagens, other collagen types, and elastins.42 Once MMPs bind to collagen fibrils and begin their attack, they could continue to act until all collagen is degraded unless they are inhibited by the TIMPs, which provide an essential inhibitory mechanism against uncontrolled degradation by MMPs.40,42

Sixth, the net proteolytic activity of MMPs depends on their transcription, activation, and inhibition.7 Transcription from MMP genes to pro-MMPs is stimulated by several factors including IL-1, platelet-derived growth factor (PDGF), and TNF-α, and inhibited by others, including TGF-β, retinoids, heparin, and corticosteroids. Activation of latent pro-MMPs to active MMPs is stimulated largely by the urokinase plasminogen activator (uPA)/plasmin system, expressed in several cells including monocytes and macrophages, and inhibited by TIMPs. The uPA system, with its specific receptor uPAR and its inhibitors plasminogen activator inhibitor [PAI] 1 and 2, localizes the proteolytic activity. Inhibition of activated MMPs by TIMPs and drugs, such as tetracyclines, anthracyclines, synthetic TIMP inhibitors, regulate the proteolysis of ECCM.

Seventh, myocardial MMPs and TIMPs are coexpressed and secreted by several cell types including fibroblasts, endothelial cells, and inflammatory cells, and their gene expression is tightly controlled at the transcription level.32 Several cytokines, polypeptide growth factors, hormones, steroids, and phorbol esters modulate the synthesis and secretion of pro-MMPs and TIMPs. The fibrotic effect of TGF-β, may be due not only to stimulation of ECCM formation but also to decreased MMP and increased TIMP levels or to a decreased MMP/TIMP ratio.

Eighth, chronic LV pressure overload, leading to concentric hypertrophy, is associated with increased ECCM and LV diastolic dysfunction, thus providing the basis for antifibrotic therapy. Chronic LV volume overload, leading to eccentric hypertrophy, is associated with increased ECCM, collagen cross-linking, and fibronectin.7 In human end-stage heart failure from ischemic cardiomyopathy, collagen, cytoskeletal proteins, and CTGF are increased, but collagen cross-links are decreased, thus favoring LV dilation.7 In human end-stage

Figure 2. Temporal changes during healing after MI. Schematic showing pathways leading to formation of the infarct scar. R indicates receptor, and RAAS, renin-angiotensin-aldosterone system. Other abbreviations as in text.
MI, total collagen and the type I/III ratio are increased in the IZ scar and border areas but not in the NIZ, suggesting that the NIZ remains susceptible to dilation. Thus, antifibrotic agents might be useful in some but not all patients with chronic LV volume overload.

Ninth, several studies have provided proof that ECCM dissolution promotes dilation. An important finding is that a mild reduction of only \( \approx 20\% \) in 4-hydroxyproline content is sufficient to reduce the melting temperature of collagen helices below the physiological level of 37°C, thereby decreasing the physical stability of collagen, its resistance to proteolysis, its secretion with the ECCM, and its ability to interact with other matrix components. This implies that lowering collagen below normal might facilitate remodeling and narrow the therapeutic window with collagen-lowering agents after acute MI.

Tenth, the rate of collagen synthesis, at 0.56% per day, is slow compared with 7.2% per day for noncollagen protein, and the 80- to 120-day half-life of collagen is \( \approx 10 \) times longer than that for noncollagen protein. This implies that ECCM replacement after degradation is fairly slow, thus providing a window of potential vulnerability for adverse remodeling in conditions associated with increased ECCM degradation such as acute MI.

**TABLE 2. Endogenous Factors and Drugs That Might Affect Myocardial Collagen Turnover**

<table>
<thead>
<tr>
<th>Endogenous Factors (( \downarrow ) synthesis)</th>
<th>Drugs</th>
</tr>
</thead>
</table>
| Collagen synthesis inhibitors (\( \downarrow \) synthesis) | • Bradykinin,
| | • Nitric oxide,
| | • TNF-\( \alpha \), IL-1,2,12,41,44,45
| | • Interferon-\( \gamma \)
| | • Parathormone
| | • Thyroid hormone
| | • Glucocorticoids
| | • Steroid hormones
| | • P4H inhibitors
| | • MMP inhibitors
| | • Anti-TGF-\( \beta \); TGF-\( \beta \) inhibitors
| | • ACE inhibitors
| | • ARBs
| | • Bradykininase inhibitors
| | • Endothelin antagonists
| | • Chymase inhibitors
| | • Vasopeptidase inhibitors
| Collagen breakdown promoters (\( \uparrow \) breakdown) | • MMPs
| | • Bradykinin
| Collagen synthesis promoters (\( \uparrow \) synthesis) | • MMP inhibitors
| | • TGF-\( \beta \), stimulate myofibroblasts
| | • Angiotensin II, aldosterone, ACE, chymase, endothelin
| | • CTGF, PDGF, EGF, TGF-\( \alpha \), bFGF, IGF
| | • Growth hormone
| | • Ascorbic acid (vitamin C)
| Collagen breakdown inhibitors (\( \downarrow \) breakdown) | • TIMPs
| | • Recombinant TIMP
| | • Phenytoin
| | • Retinoids (vitamin A)
| | • MMP inhibitors

EGF, epidermal growth factor; TGF-\( \alpha \), transforming growth factor-\( \alpha \); bFGF, basic fibroblast growth factor; IGF, insulin-like growth factor. Other abbreviations as in text.
cular cells, as well as proinflammatory cytokines; growth factors; and endocrine, autocrine, paracrine and intracrine factors, participate in the ECCM and LV remodeling (Figures 1 and 2). Inflammatory cells, which are increased in very early and early stages,2,27 produce MMPs25 that modulate ECCM remodeling. Mast cells may lead to MMP activation, collagen degradation, and LV dilation. MMP-9, localized to neutrophils early after reperfused MI,7 mediates ECCM degradation. Proinflammatory cytokines, expressed by cardiomyocytes, fibroblasts, macrophages, and other nucleated cells, orchestrate the inflammatory responses, thereby modulating healing. The expression of proinflammatory cytokines and MMPs has also been colocalized to cardiac fibroblasts,37 and several cytokines, such as IL-1β and TNF-α, which are elevated in the IZ during early healing and in the NIZ during later stages after MI, activate MMPs and regulate the activity of TIMPs,7 thereby contributing to LV remodeling.24 MMPs also regulate cytokine activity.25 In heart failure, as is often the case after MI, overexpression of proinflammatory cytokines initially results in MMP activation, loss of fibrillar collagen, LV dilation, myocyte loss through apoptosis, and progression of heart failure.25 However, long-term stimulation by proinflammatory cytokines results in increased TIMPs, decreased MMP/TIMP ratio, and increased fibrillar collagen25 and induces ongoing diffuse microinflammation, scarring, and long-term remodeling.

Contrary to common belief, the IZ scar is a living, dynamic structure.47 The fibrogenic cytokine TGF-β1 and the proinflammatory cytokines TNF-α and IL-125 induce phenotypic remodeling of cardiac fibroblasts into myoFbs.17 These myoFbs contain α-smooth muscle actin and mediate scar contraction.7,17 They appear early after MI, mainly in and

### TABLE 3. Stages of Healing and Remodeling After MI for Timing of Therapy

<table>
<thead>
<tr>
<th>Stage/Timing</th>
<th>Pathophysiologic Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very early (≈first 24 hours)</td>
<td>Acute evolution and completion of MI; edema, ↑ glycosaminoglycans; necrosis, apoptosis; acute inflammation, neutrophils predominating; cytokine activation, ↑ MMPs, enhanced ECCM degradation</td>
</tr>
<tr>
<td>Early (≈first 2 weeks)</td>
<td>Early IZ healing, before the collagen plateau; chronic inflammation with macrophages peaking after ≈48 hours, and mononuclear cells; fibroblasts predominating after ≈1 week; ↑ MyoFs; increased P4H activity after ≈5 days; ↑ TGF-β, CTGF; collagen deposition in IZ, 5-fold or more</td>
</tr>
<tr>
<td>Late (≈3 to 6 weeks)</td>
<td>Late IZ healing to scar formation after the collagen plateau; little cellular infiltration; MyoFs</td>
</tr>
<tr>
<td>Very late (≈1.5 months to 1 year or more)</td>
<td>Late IZ scarring and NIZ fibrosis, with continued ECCM remodeling; MyoFs</td>
</tr>
</tbody>
</table>

Information derived in part from Jugdutt.7
around the IZ, and persist throughout healing and beyond, having been found in human MI scars for up to 17 years.7 Endothelin and AngII receptors on the myoFbs and regulatory signals, such as AngII, TGF-β1, and ACE, modulate MMP activity and ECCM remodeling.7,11 MyoFbs not only produce collagen types I and III after MI, but their persistence, together with continued expression of AngII, TGF-β1, and ACE in later stages, is accompanied by low-grade collagen turnover in mature IZ scars.7,47

Remodeling of the IZ and NIZ after MI depends on the 3D organization of the ECCM besides the amount and type of collagen.6,7 Increases in the amount of collagen by up to 12-fold in the IZ scar during early and late healing phases, and by 2 to 3-fold in the NIZ during late and very late stages,27,28 contribute resistance to distension.48 Although collagen types I and III in the IZ increase during early healing, the new collagen, being immature and mostly thin type III, remains susceptible to stretch even by 15 weeks. As a result, the infarcted left ventricle is more distensible in the early 2-week window after MI48 but remains distensible in the later stage. Subsequent collagen maturation, involving development of intermolecular cross links (Figure 2), loss of water and ground substance, and replacement by type I, results in increased collagen type I/III ratio and greater resistance to distension. Greater increase of cross-link formation in the IZ than NIZ by 13 weeks contributes tensile strength. The mature IZ scar, apart from being alive, is anisotropic and trilayered and shows a different 3D orientation of each layer.7 Taken together, the data suggest that ECCM remodeling during healing after MI is an attempt to restore mechanical

TABLE 4. Main Components and Function of Myocardial Extracellular Matrix

<table>
<thead>
<tr>
<th>Component</th>
<th>Main Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagen fibrils (types I and III)</td>
<td>● Structural support, maintain shape</td>
</tr>
<tr>
<td></td>
<td>● Transmission of force</td>
</tr>
<tr>
<td></td>
<td>● Tensile strength (type I); resilience (type III)</td>
</tr>
<tr>
<td>Elastin</td>
<td>● Resilience; vessel wall stretch; cardiac wall stretch and relaxation</td>
</tr>
<tr>
<td>Cells</td>
<td></td>
</tr>
<tr>
<td>Fibroblasts</td>
<td>● Produce fibrillar collagens</td>
</tr>
<tr>
<td></td>
<td>● Convert to myoFbs after injury</td>
</tr>
<tr>
<td>Macrophages</td>
<td>● Phagocytosis; inflammatory response</td>
</tr>
<tr>
<td></td>
<td>● Monocytes</td>
</tr>
<tr>
<td>Plasma cells</td>
<td>● Immune defense</td>
</tr>
<tr>
<td>Other cells</td>
<td>● Endothelial cells; smooth muscle cells; pericytes; neurons</td>
</tr>
<tr>
<td>Gel matrix (ground substance)</td>
<td>● Viscous gel-type fluid; bath cells and fibrils</td>
</tr>
<tr>
<td>Glycoproteins</td>
<td></td>
</tr>
<tr>
<td>Integrons (matrix receptors)</td>
<td>● Myocyte-fibroblast interactions; matrix remodeling</td>
</tr>
<tr>
<td>Fibronectin and laminin</td>
<td>● Mainly noncollagen adhesive fibrous proteins</td>
</tr>
</tbody>
</table>

TABLE 5. MMPs and Potential Relevance in Myocardial Remodeling

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>MMP</th>
<th>Enzyme (kDa Latent/Active)</th>
<th>Substrate</th>
<th>Remodeling*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagenases</td>
<td>MMP-1</td>
<td>Interstitial collagenase (52/42)</td>
<td>Collagen type I, II, III, VII, and X; gelatins; proteoglycans; entactin</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>MMP-8</td>
<td>Neutrophil collagenase (85/64)</td>
<td>Collagen type I, II, and III</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>MMP-13</td>
<td>Collagenase-3 (52/42)</td>
<td>Collagen type I, II, and III</td>
<td>+</td>
</tr>
<tr>
<td>Gelatinases</td>
<td>MMP-2</td>
<td>Gelatinase A (72/66), type IV collagenase</td>
<td>Gelatins (type I), collagen type I, II, III, IV, V, VII, and XI; fibronectin; laminin; elastin; proteoglycans</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>MMP-9</td>
<td>Gelatinase B (92/84), type V collagenase</td>
<td>Gelatins (type I and V), collagen type I, II, III, IV, V, and VII; elastin; entactin; proteoglycans</td>
<td>+</td>
</tr>
<tr>
<td>Stromelysins</td>
<td>MMP-3</td>
<td>Stromelysin 1 (57/45)</td>
<td>Gelatins (type I, III, IV, and V), collagen type III, IV, IX, and X; collagen telopeptides; proteoglycans; fibronectin; laminin; MMP activation</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>MMP-10</td>
<td>Stromelysin 2 (54/44)</td>
<td>Collagen type IV; proteoglycans; laminin; fibronectin</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>MMP-11</td>
<td>Stromelysin 3 (64/46)</td>
<td>Furin cleavage</td>
<td>–</td>
</tr>
<tr>
<td>Membrane type</td>
<td>MMP-14</td>
<td>MT1-MMP (66/54)</td>
<td>Collagen type I, II, III, and IV; gelatin; fibronectin; laminin; activation of proMMP-2 and proMMP-13</td>
<td>+</td>
</tr>
<tr>
<td>Others</td>
<td>MMP-7</td>
<td>Matrilysin, PUMP-1 (28/19)</td>
<td>Proteoglycans, fibronectin, gelatins, collagen type IV, elastin, entactin</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>MMP-12</td>
<td>Metalloelastase (54/22)</td>
<td>Elastin (macrophage elastase)</td>
<td>?</td>
</tr>
</tbody>
</table>

*Role in cardiac remodeling was classified as documented (+), probable (?), or not known (–).
strength and resistance of both IZ and NIZ of the infarcted ventricle to distension.

The importance of the cytokine AngII in fibrosis during tissue repair, the local production of tissue AngII after injury, the presence of AngII receptors on cardiac myocytes and fibroblasts, and their roles in ECCM turnover have been reviewed. Local ACE, which is markedly elevated in high-turnover sites including the IZ, contributes local AngII. AngII stimulation of AT1 receptors, which are upregulated during healing after MI, induces fibrosis. AngII type 2 (AT2) receptors, which are re-expressed after MI and upregulated in heart failure, are more abundant in human than in rat hearts, are expressed in fibroblast-like cells, and mediate fibrosis, and AT2 loss prevents collagen deposition and causes cardiac rupture.

### Antiremodeling Therapies After MI: Lessons About Timing From Long-term Studies

The aim of antiremodeling therapy after MI is to prevent, limit, or reverse adverse structural remodeling and thereby interrupt the sequence of LV dilation, LV dysfunction, disability, and death. An important aspect of this goal is to protect the ECCM during remodeling after MI.

Longitudinal studies suggested that timing and duration of therapy are critical. Sequential changes during LV remodeling after MI (Figure 1) span the phases of acute MI, healing, and repair over weeks to months (Figure 2) and beyond. Because mechanical deformation forces and increased wall stress act on the IZ and NIZ throughout these phases, thereby promoting progressive LV dilation and stimulating fibrosis, early and prolonged antiremodeling therapy is favored.

However, several of the antiremodeling strategies currently used after MI exert pleiotropic effects that can potentially affect ECCM turnover in both the IZ and NIZ (Table 2 and Figure 3). Thus, ACE-Is, ARBs, and aldosterone blockers decrease ECCM and aldosterone antagonist spironolactone decreases collagen turnover. ARBs also decrease P4H. Reperfusion disrupts ECCM, increases MMPs and collagen degradation, decreases IZ collagen, accelerates healing, decreases cross-links, and increases ruptures.

Unloading with the LV assist device results in downregulation of MMPs, increased TIMPs, decreased collagen damage, and increased collagen cross-links. β-Blockers decrease MMPs. Nitrates preserve IZ collagen and prevent the decrease in collagen after reperfusion. Digoxin increases P4H activity, although digoxin does not alter IZ collagen. Endothelins increase collagen synthesis and decrease MMPs, whereas endothelin blockade impairs healing after MI. Bradykinin increases MMPs and decreases collagen. Agents such as adenosine, which elevate cAMP, NO, and cGMP, decrease fibrosis.

Several studies suggested potentially harmful effects with some therapies after MI, supporting caveats against hypotension with vasodilators very early after MI, or impairing healing with powerful anti-inflammatory drugs during early healing. Other post-MI studies demonstrated progressive LV enlargement over 1 year or 3 years despite therapy, and morbidity and mortality remain high. In addition, cardiac rupture remains a major cause of death after reperfused MI, and the number of post-MI patients needing the LV assist device or awaiting transplantation is increasing, suggesting that protection against LV dilation, adverse ECCM remodeling, decreasing IZ collagen, and impairing healing is needed.

### Caveat With the Use of Antifibrotic Agents After MI

A major aim of antifibrotic therapy is to inhibit or reverse cardiac fibrosis and its adverse effects on LV function. Potential approaches include long-term suppression of ACE, TGF-β and CTGF, P4H, and MMPs; inhibition of TGF-β-stimulated collagen synthesis and profibrotic cytokines with pirfenidone; PDGF inhibition and enhancement of adenosine with pentoxifylline; and breaking excessive cross-links due to advanced glycation end products by 4,5-dimethylthiazolium chloride (ALT-711). Although MMP inhibitors may reduce MMP activation acutely, they may reduce ECCM in the long term.

Antifibrotic therapy may be beneficial for noninfarcted hearts with chronic LV pressure overload and possibly for ischemic cardiomyopathy and the NIZ after remote MI. However, caution might be advisable in idiopathic dilated cardiomyopathy without MI because of increased MMPs, decreased TIMPs, and reduced cross linking. Collective evidence emerging from experimental and clinical studies using antiremodeling strategies after MI suggest that careful attention should also be given to timing (Figure 2), especially because antifibrotic agents exert global actions that can affect both the IZ and NIZ (Figure 3). Experimental data on the temporal evolution of healing and ECCM remodeling suggest that these agents could potentially enhance adverse ECCM remodeling in the IZ during the highly vulnerable periods of very early and early stages of healing after MI (Figure 3; Table 3). Pending further safety data, it might also be prudent to exercise caution during the phase beyond scar formation.

### Protecting the ECCM of the IZ After MI

Although the importance of ECCM remodeling in paradigm 1 is widely acknowledged, little has been done to protect the ECCM in the IZ. Although growth hormone was shown to stimulate post-MI repair, increase IZ scar collagen, and reduce LV aneurysm formation, such approaches have not been actively pursued. Strategies to protect the ECCM after MI, especially in the IZ, might further lower post-MI mortality and limit morbidity. Several factors, as shown in Figure 3, could be targeted. In contrast to global approaches that target both the IZ and the NIZ with systemic delivery of adjunctive agents, regional strategies could be applied to selectively protect the IZ against adverse ECCM remodeling.

Monitoring using several markers could be systematically applied to detect potentially adverse ECCM and LV remodeling after MI during therapy.

### Summary

Prevention of adverse remodeling after MI remains a therapeutic challenge. Current antiremodeling therapy is clearly not ideal, as many ventricles continue to enlarge after MI, and mortality and morbidity remain significant.
despite therapy. Collective evidence indicates that the ECCM plays a major role in healing and remodeling after MI. Antifibrotic agents targeting excessive ECCM might be beneficial in selected patients without MI. After MI, however, the situation is complicated by the development of an IZ and a NIZ with differential pathophysiological responses. Because one aim of therapy is to maximize benefits and minimize unwanted, often delayed adverse effects, failure to address protection of the ECCM in the IZ as well as the NIZ in the long term seems to deal with only half the problem. Protecting the ECCM in post-MI survivors should be a future priority.

Acknowledgments

All worthy papers could not be cited because of space limitations.

References


**Key Words:** collagen / angiotensin / metalloproteinases / enzymes / drugs