Editorial

Renin-Angiotensin System and Cardiac Rupture After Myocardial Infarction

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Of all the mechanical complications after acute myocardial infarction (MI), cardiac rupture remains the most devastating, dramatic, and deadly. Continued improvements in the care of patients with acute MI have decreased the incidence of cardiac rupture over the past decade to under 3% in patients receiving reperfusion therapy, although autopsy evaluation of patients who died suddenly with acute MI has suggested a higher incidence. Without extremely prompt surgical intervention, patients with cardiac rupture rarely survive.

Cardiac rupture in humans generally occurs after transmural MI. Patients who rupture the free wall of the left ventricle typically develop hemopericardium and cardiac tamponade, whereas septal rupture leads to ventricular septal defect. Rupture can occur as early as the first day after infarction, although it most often occurs later in the first week in the setting of myocardial necrosis and neutrophilic infiltration. A combination of factors, both pathological and physiological, make the infarct region most vulnerable within the first 7 to 10 days. This is when cardiac tissue in the involving infarct region is weakest and most friable. As ventricular enlargement and infarct thinning commence, regional wall stress can increase precipitously. While prompt reperfusion therapy is thought to lower the incidence of rupture, delayed reperfusion may be associated with an increased risk of rupture. Treatment with steroids or nonsteroidal antiinflammatory agents may also be associated with an increased risk of rupture.

While the initial phases of acute infarction are characterized pathologically by neutrophil infiltration and myocyte necrosis, the healing phase of acute MI, beginning after the first week, is typified by mononuclear cell and fibroblast infiltration and the absence of polymorphonuclear leukocytes. Resorption of necrotic myocytes often precedes scar formation, which occurs over the ensuing weeks, with accumulation of fibrillar collagen into an increasingly organized network. The complete healing process usually takes 5 to 6 weeks and ultimately results in a stable scar absent of cellular infiltration. The tensile strength of the scar that is formed exceeds that of steel, making the even thinned infarct region stable and less vulnerable to mechanical disruption.

Healing and remodeling after MI are intertwined, and the renin-angiotensin system is involved in both of these processes. Angiotensin-converting enzyme (ACE) inhibitors, which have been effective in attenuating remodeling, reduce fibrous tissue formation and perivascular fibrosis after angiotensin II (Ang II) infusion. Ang II itself increases collagen synthesis in the heart and inhibits collagen breakdown by collagenase. Both ACE inhibitors and angiotensin receptor antagonists suppress fibroblast and macrophage infiltration in infract zones. Indeed, activated macrophages and myofibroblasts that infiltrate the infarct region have demonstrated ACE activity, and ACE activity from infarcted tissue exceeds that of normal myocardium. Thus, local upregulation of ACE activity in infarcted tissue and the resulting increase in local production of Ang II has been proposed as one of the mechanisms of tissue repair after MI, possibly through induction of transforming growth factor-β1 by Ang II which, in turn, stimulates fibrogenesis.

Stimulation of the Ang II subtype 1 receptor (AT1) by Ang II is responsible for the majority of effects we typically ascribe to angiotensin, both traditional, such as vasoconstriction and sympathetic activation, and nontraditional, such as cell growth and proliferation. The relative importance of the angiotensin subtype 2 receptor (AT2) in the healing and remodeling process has been less clear, although this subtype may be the predominant form in human myocardium. The AT2 receptor is thought to mitigate many of the effects of the AT1 receptor and may serve as a “counterregulatory” receptor to many of the effects of Ang II on the AT1 receptor, possibly through stimulation of nitric oxide pathways.

The AT2 receptor is particularly prominent during fetal development. Although mice lacking this receptor appear to develop normally, these animals demonstrate a number of physiological impairments, including mildly elevated blood pressure, decreased thirst, and an exaggerated response to Ang II infusion. This receptor is normally downregulated during adult life, but is upregulated under certain pathological conditions, such as ventricular hypertrophy, infarction, and heart failure. The increased presence of the AT2 receptor in
infarcted myocardium may explain, in part, some of the beneficial effects of AT1 receptor blockade in animal models that could be abolished with either blockade of the AT2 receptor directly or by inhibition of the bradykinin B2 receptor or cyclooxygenase, suggesting a role for these intermediates in the AT2 receptor pathway.14 Indeed, attenuation of ventricular remodeling by AT1 receptor blockade in rats is abolished by AT2 receptor blockade,19 suggesting that at least part of the protective effect of AT2 receptor blockade is dependent on functional AT2 receptor pathways.

In this issue of Circulation, Ichihara et al20 further enhance our understanding of the role of the AT2 receptor. In mice lacking the AT2 receptor gene, a strain that fails to develop hypertrophy in response to aortic banding or hypertension, experimental MI was associated with an increased risk of myocardial rupture (28% in knockout Agr2−/− mice compared with 6% in wild type animals). This propensity to rupture coincided with elevations of Prostaglandin E2 and intermediates in the AT2 receptor pathway.18 Indeed, attenuation of ventricular remodeling by AT2 receptor blockade in rats is abolished by AT2 receptor blockade,19 suggesting that at least part of the protective effect of AT2 receptor blockade is dependent on functional AT2 receptor pathways.

Another factor that may limit the immediate relevance of these findings to myocardial rupture in humans is the fact that while rupture is most common within the first week after MI, significant collagen deposition does not occur until later in the course of healing. In contrast, the pathological processes in infarction are significantly accelerated in the mouse. Thus, deficiencies in collagen metabolism cannot be readily implicated in mechanisms underlying rupture in humans.

Although the mechanisms of rupture in this mouse model may differ considerably from those in humans, these experiments may provide insight into potential therapies in patients. If stimulation of the AT2 receptor is important in the healing of MI in humans, then therapies that allow this receptor to be naturally stimulated, such as AT2 receptor blockade, which leaves Ang II available to stimulate the AT2 receptor, may prove protective in humans. Two major trials of AT1 receptor blockade in patients with acute MI will soon generate clinical outcomes data to determine whether this theoretic benefit translates into an actual benefit.23,24 Likewise, future selective agonists of the AT2 receptor that may themselves provide benefit can be envisioned. However, since rupture in humans rarely occurs after the first week, therapies directly targeting the AT2 receptor will more likely affect the overall late remodeling process than the incidence of ventricular rupture following MI.

The most effective present strategy to lower the incidence of rupture after MI is to reduce infarct size with prompt reperfusion therapy, avoid agents that may interfere with healing, such as steroids and nonsteroidal antiinflammatory agents, and reduce wall stress with therapies that lower blood pressure and attenuate neurohormonal activation. β-blockers and ACE inhibitors, two therapies that have been shown to reduce early as well as late mortality after MI, may do so in part by reducing the risk of rupture, although only limited data are available to directly support this hypothesis.25 Finally, by adding to our understanding of the healing process after MI, experiments like those reported by Ichihara et al20 may ultimately lead to novel therapies that reduce morbidity and mortality by directly bolstering the structural integrity of the myocardium.

References


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