Wound model of myocardial infarction

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ISCHEMIC HEART DISEASE is the major etiology for heart failure today (3). The initial event is frequently a large or recurrent myocardial infarction. Acute myocardial infarction starts with thrombotic occlusion of a coronary artery, develops during several hours, and terminates when necrosis has reached its ultimate extension, which is defined by the boundary of the infarct-associated vascular bed and potential collateral flow. Therapy of acute myocardial infarction is reasonably standardized and consists of prevention of fatal arrhythmias and early reperfusion, for instance, by vessel dilation and stent implantation, to limit infarct size. If reperfusion is established too late, large transmural infarction may develop that results in a reduction of left ventricular function and is followed by “remodeling” of the heart (Fig. 1). Remodeling is closely related to “infarct expansion,” which may continue after the necrosis has extended to its ultimate size; the left ventricle dilates, probably because of increased wall stress on the basis of La Place’s law (1). The increase in global left ventricular volume indicates and quantifies remodeling of the heart, which may ultimately result in heart failure, arrhythmias, and sudden death (8). Standard therapy today tries to prevent remodeling and its prognostic consequences by reducing cardiac preload and afterload and preventing hypertrophy and fibrosis in residual surviving myocardium with the use of angiotensin-converting enzyme inhibitors or angiotensin II type 1 receptor antagonists. Thus clinical research has focused on strategies for an optimal reperfusion therapy during the first hours of developing myocardial infarction or long-term prevention of remodeling. However, despite standard therapy, prognosis remains serious in patients with large infarctions and severe left ventricular dysfunction (20). This may be due to the fact that the “first hours” have mostly elapsed before patients receive reperfusion therapy, and a large myocardial defect or cardiac aneurysm (Fig. 1) may not respond well to therapy.

Infarct expansion occurs after the first hours of developing myocardial infarction and precedes remodeling, hypertrophy, and fibrosis of residual myocardium. In fact, it occurs predominantly during healing of the “cardiac wound” when the normal collagen structure has been destroyed and the scar is formed. If the infarct heals without expansion, the heart maintains its shape and prognosis is good. Infarct expansion has been studied in some detail, and mechanical determinants have been defined. Physical exercise begun early after a myocardial infarction has promoted left ventricular dilatation and thinning of the infarct in animal experiments (9). In contrast, mechanical unloading by nitroglycerin or captopril has prevented infarct expansion and thinning in dogs and humans, especially when combined with reperfusion (17, 18). Thus the infarct scar mostly has been considered from a biophysical point of view. However, the cellular, biochemical, and molecular characteristics of the infarct wound as “a living tissue,” which may be even more important for healing, infarct expansion, and the development of arrhythmias, so far have been more or less neglected. The time course of morphologic and histological changes of infarcted myocardial tissue was recently reviewed in some detail (4). Inflammatory cells invade the infarct and, somewhat later, myofibroblasts appear in the wound. Inflammatory cells release proteases and contribute to removal of necrotic tissue; myofibroblasts participate in the reconstruction of a new collagen network. The actions of the myofibroblasts are admirably systematic and are essential for the organization of scar formation.

Obviously, it would be highly desirable to influence healing of the cardiac wound by more targeted interventions. While research to improve traumatic and surgical wound healing has quite a tradition back to ancient medicine, current research on myocardial infarction is limited to cell transplantation into the infarct wound. It is attractive to compare wounds of various organs to detect general principles of wound healing. However, discrepancies are more obvious than similarities between skin wounds and myocardial infarcts. The myocardial infarct develops during hours, remains ischemic if it is not reperfused, and faces the stress of rhythmic cardiac contraction. In addition, the paracrine and autocrine milieu is probably quite different between cutaneous and cardiac tissue even when wounded. Nevertheless, a number of similar steps of healing may be observed in wounds and appear to be general characteristics of healing, like the influence of gender, age, diabetes, and certain factors perhaps essential for wound healing (Table 1). Indeed, some cutaneous phenomena are related to cardiovascular abnormalities: 1) the occurrence of keloid and certain types of hypertension; 2) synthesis of collagen in skin fibroblasts and the occurrence of varicose veins in patients; and 3) an impaired ability to synthesize collagen in vitro of fibroblasts isolated from venous ulcers. Thus a genetic defect was assumed to transmit varicose vein pathology, a weakness of venous wall, and, in general, a systemic biochemical defect of the extracellular matrix affecting the entire body structure. Holbrook and Byers (13) defined skin as a window on heritable disorders of connective tissue. A single factor, “secretory leukocyte inhibitory protein,” was recently identified by Ashcroft et al. (2) to be essential for cutaneous wound healing. So far, no such factor has been related to infarct healing. In humans, deficient wound healing is observed in certain hereditary diseases. Osteogenesis imperfecta, Ehlers-Danlos syndrome, and other genetically transmitted deficiencies in connective tissue could be rare but representative models for general states of deficient wound healing.

Attempts were undertaken to stimulate reparative processes following experimental myocardial infarction by the group of Sigmundur Gudbjarnarsson and Richard Bing (10) in the 1960s but did not reach clinical application. Their limitation was a lack of methods for a detailed analysis of cellular and molecular biology. Some indirect evidence about a potential modification of healing of the myocardial infarct wound may be
deducted from available data. Animal experiments have suggested that late reperfusion of myocardial infarction after completion of cardiomyocyte death may prevent further infarct expansion and thinning (5, 6, 11, 12, 16), possibly by an interference with collagen and matrix metalloproteinase metabolism. Angiotensin-converting enzyme inhibition delayed maturation of the infarct scar as indicated by reduced collagen content (23). Targeted deletion of angiotensin II type 2 receptor reduced collagen volume fraction and scar thickness in experimental infarcts and caused cardiac rupture (15). Angiotensin-converting enzyme inhibitors and even more angiotensin II type 1 receptor antagonists reduced the inflammatory infiltrates into the infarct zone and prevented accumulation of type I myocardial collagen in noninfarcted myocardium (22). Left ventricular dilatation was aggravated by the use of endothelin A receptor antagonists early after myocardial infarction. Early initiation of the selective endothelin A receptor blocker LU 135252 resulted in scar expansion, reduction of scar collagen, and a particular unfavorable outcome. This was most likely caused by an activation of myocardial tissue metallopro-teinases (7, 14, 19, 21). However, others reported a reduction of metalloproteinase activity by another endothelin A receptor antagonist (21). Nevertheless, principles inhibiting the renin-angiotensin system have been used successfully in patients with myocardial infarction. However, a large trial in which an angiotensin converting enzyme inhibitor was used intravenously early after myocardial infarction failed and was stopped because of a tendency toward increased mortality in a subgroup of patients. Thus, today, clinically established or developing therapeutic approaches already have the potential to interfere with cellular, biochemical, and molecular processes during healing of the infarct wound. These processes, therefore, urgently need to be analyzed with modern techniques of cell and molecular biology and genetics. They may offer new therapeutic options. However, they have to avoid weakening of the scar and an eventual aneurysm and rupture.

In conclusion, while the current conventional concepts of pathophysiology and myocardial infarction therapy consider coronary occlusion, development of necrosis, and remodeling of residual myocardium, the concept of wound healing focuses on the cellular, biochemical, and molecular changes of the myocardial wound after ultimate extension of necrosis and before scarring. Reperfusion, mechanical factors, hormones, and neurohumoral and other factors may influence wound healing. General acquired or inherited deficiency of wound healing may be important for infarct healing but has not been defined in depth, so far. Interventions to improve wound healing may open a new time window between the few hours

Table 1. Factors that may influence infarct healing

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<td>Reperfusion</td>
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<td>Mechanical load</td>
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<td>Neurohumoral factors, cytokines, and growth factors</td>
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<td>Drugs</td>
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Fig. 1. A large anterior myocardial infarction (MI) followed by deficient wound healing, infarct expansion, and a large apical aneurysm was the sequence of events leading to heart failure and terminal arrhythmia in the patient from whom this tissue was taken.

Anteroapical Aneurysm
that may be used to limit necrosis by reperfusion and an irreversible cardiac scar or aneurysm. It is conceivable that therapeutic concepts to improve wound healing (collagen generation, hypertrophy) differ fundamentally from the therapy of remodeling (prevention of fibrosis and hypertrophy). Because healing and remodeling are closely related but have a different time course, differential therapy may be designed.

REFERENCES


