Editorials

Myocardial Reperfusion, Limitation of Infarct Size, Reduction of Left Ventricular Dysfunction, and Improved Survival

Should the Paradigm Be Expanded?

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For nearly a decade, it has been appreciated that 1) thrombotic occlusion of an epicardial coronary artery is usually the proximate cause of acute myocardial infarction; 2) after sudden and sustained total occlusion of such a vessel, the course of myocardial necrosis is generally rapid and relentless (in most cases, the process is completed within 3 or 4 hours of the coronary occlusion, in 6 hours at a maximum); 3) infarct size is a critical determinant of left ventricular function; and 4) left ventricular function, in turn, is the most important determinant of early (in-hospital) and long-term (postdischarge) survival.

Major efforts have been devoted to the development of techniques designed to interfere with the sequence of events summarized above. Considerable attention has been directed to achieving timely reperfusion of occluded coronary arteries to interrupt the infarction with the hope that the resultant limitation of infarct size will improve ventricular function and thereby patient survival.1 Many techniques to achieve reperfusion have been used, including emergency coronary artery bypass surgery, emergency percutaneous transluminal coronary angioplasty (PTCA), and the intracoronary and intravenous administration of a variety of thrombolytic agents; the last of these approaches is particularly attractive because its simplicity makes it applicable to a large proportion of patients with acute myocardial infarction. In some instances, combinations of these techniques, such as intravenous thrombolytic therapy followed by PTCA, have been used.

These efforts to treat acute myocardial infarction have been notably successful, as reflected in an improvement in survival noted in controlled randomized trials.2–6 Also, the absolute mortality rates achieved in some recent trials of reperfusion therapy (3–5%) are far lower than those noted previously in comparable patients with acute myocardial infarction.6,7 The finding that thrombolytic therapy is associated with a reduction of left ventricular dysfunction8–13 supports the concept that salvage of reversibly damaged, ischemic myocardium is responsible for the salutary effect of myocardial reperfusion in acute myocardial infarction. The concepts embodied in the sequence of events leading to mortality and heart failure in acute myocardial infarction and the mechanism responsible for their interdiction by reperfusion have become so widely accepted that they might be termed a paradigm.

Inconsistent Observations

However, several groups of observations suggest that the situation may actually be more complex than it was initially believed to be and that, therefore, this paradigm may have to be expanded.

First, one group of observations involves some patients not treated actively with reperfusion at all (i.e., patients with Q wave infarction who exhibit spontaneous reperfusion—presumably consequent to normal intrinsic thrombolytic mechanisms). Because these mechanisms ordinarily do not come into play sufficiently early (i.e., within the first 3 or 4 hours after coronary occlusion) to salvage substantial quantities of myocardium, it is difficult to understand why left ventricular function is frequently superior in patients with Q wave infarction and an open infarct-related artery demonstrated at coronary arteriography compared with patients in whom the infarct artery has remained occluded.14–16

The second group comprises the discrepancies between the effects of reperfusion on left ventricular function and survival. In the Western Washington trial comparing intracoronary streptokinase with placebo carried out in 1981–1982, patients were treated relatively late in the course of their infarcts, achieving reperfusion an average of 5 hours after the onset of symptoms.17 Despite the achievement of successful reperfusion in the majority of actively treated patients, this was not associated with improved global or regional left ventricular function or infarct size measured 2 months after the acute

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event, presumably because of the relatively late onset of therapy. However, at the time of these measurements, patients who were treated demonstrated a lower mortality than those who were not. Patency of the infarct-related coronary artery proved to be an important independent predictor of survival. For example, the mortality at 1 year of patients with anterior wall infarcts treated with streptokinase with complete perfusion of the infarct-related artery was only 5% compared with a mortality of 36% in patients with partial or no reperfusion. Similarly, in the TIMI I trial, thrombolytic therapy commenced relatively late (an average of 4½ hours after the onset of symptoms) so that the pretreatment status of the infarct-related vessel could be assessed angiographically. Patency of the artery had only minor beneficial effects on the left ventricular ejection fraction or regional wall motion, but it appeared to improve long-term (1 year) survival.

Similar observations have been made by other investigators using other thrombolytic agents. In the German multicenter trial of anisoylated plasminogen streptokinase activator complex (APSAC), mortality was reduced from 12.6% in the control (heparin-treated) patients to 5.6% in the APSAC-treated patients without an effect on global or infarct-related ejection fraction. Van de Werf et al reported that mortality was reduced from 5.8% in placebo-treated patients to 2.7% in those receiving t-PA, yet left ventricular ejection fraction was only 2.2% higher, which would not appear to be sufficient to account for the marked reduction of mortality. If mortality in patients with acute myocardial infarction treated with thrombolytic agents is reduced simply by salvage of ischemic myocardium, why is it not regularly accompanied by easily detectable and substantial reduction of left ventricular dysfunction?

Third, patients were entered into the ISIS-2 trial, which evaluated the effectiveness of streptokinase and aspirin—singly and together—as late as 24 hours after the onset of symptoms of acute infarction. Although treatment with streptokinase was most effective when it was begun within the usually accepted time window for thrombolytic therapy (i.e., under 4 hours), a significant and substantial reduction in mortality was also observed in patients treated as late as 12–24 hours after the onset of symptoms. Although a detailed description of these patients is not yet available, if it is assumed that a large fraction actually had acute myocardial infarction, it seems unlikely that sufficient quantities of myocardium could have been salvaged at this time to prevent the development of left ventricular failure and subsequent mortality.

Finally, animal experiments have demonstrated that late coronary reperfusion carried out after significant quantities of myocardium could no longer be salvaged nevertheless reduced the resultant dilatation of the left ventricle, limited wall thinning, and aneurysm formation and improved healing. These observations provide quantitative morphologic confirmation of the hypothesis that a patent coronary artery perfusing necrotic myocardium may influence favorably the subsequent size and shape of the left ventricle.

### Possible Explanations

What is emerging from these observations, taken together, is the concept that an open infarct-related artery may be beneficial, both in terms of preventing left ventricular dilatation and improving survival by mechanisms other than limiting infarct size and the associated deterioration of left ventricular function. How could such salutary effects be achieved?

One possibility stems from the well-established fact that on the basis of animal experiments, acute myocardial infarction is followed by a profound remodeling of the left ventricle. This remodeling results from infarct expansion, which involves thinning and dilation of the infarct zone, presumably caused by slippage of myocytes and stretching of myocardial fibrils. Infarct expansion may cause volume overload and dilatation of the remaining viable myocardium and lead to a more spherical shape of the left ventricle. Elevated end-diastolic pressure and volume increase ventricular wall stress, which in turn leads to expansion of both the infarcted and noninfarcted portions of the ventricle. When this process is unchecked, the ventricle may continue to enlarge, leading sometimes to a vicious cycle (ventricular dilatation begets more dilatation), which may culminate in left ventricular failure and death.

Late reperfusion of the infarct-related coronary artery may prevent or limit this left ventricular remodeling by a variety of mechanisms. It has been suggested that reperfusion causes hemorrhage, contraction band necrosis, cell swelling, and edema, changes that increase the stiffness of the infarct, limiting its expansion and the secondary dilatation of the remaining ventricle. It is also possible that the open, blood-filled, infarct-related artery and vascular bed provide a scaffolding that limits expansion of the necrotic myocardium.

Another possibility is that coronary reperfusion may improve the electrical stability of the heart. It has recently been demonstrated for any degree of left ventricular dysfunction thrombolytic therapy is associated with a decreased induction of ventricular tachyarrhythmia by electrophysiologic stimulation and with a reduction of spontaneous life-threatening arrhythmias. Thrombolysis also appears to reduce the incidence of ventricular late potentials and of early ventricular fibrillation. Animal experiments have demonstrated that reperfusion carried out too late to limit infarct size nonetheless reduced ventricular arrhythmias. In a manner not yet defined, the open infarct-related artery may allow more homogeneous activation of the ventricles; perhaps this results from the salvage of small islands.
of chronically ischemic myocardium at the boundary between the viable and necrotic myocardium or from the aforementioned effect on ventricular remodeling. Reduced formation of ventricular aneurysm, which can occur with reperfusion without myocardial salvage,\textsuperscript{25} may reduce foci responsible for electrical instability.

A final possibility is that an infarct-related artery that has been opened after the completion of the infarct might provide collateral vessels to viable portions of the ventricle and protect them from ischemic damage in the event of occlusion of other coronary arteries.

**Implications**

Regardless of the mechanism(s) involved, evidence is emerging that patency of infarct-related arteries may provide substantial clinical benefit. In the TIMI II pilot study, in which all patients were treated with t-PA followed when possible by PTCA, the 6-week survival rate was very high (95%), and the prognosis after hospital discharge was excellent. Stack et al\textsuperscript{44} treated patients with acute myocardial infarction with a thrombolytic agent followed by angioplasty. The mortality between hospital discharge and 1 year was only 2.6%,\textsuperscript{45} far lower than would be expected from previous observational studies of acute myocardial infarction\textsuperscript{46,47} or from trials of thrombolytic therapy in which mechanical revascularization was very rarely used (GISSI-2 and ISIS-2),\textsuperscript{25} in which the mortality between hospital discharge and 1 year was approximately equal to the in-hospital mortality.

Thus, there is a growing body of information that suggests that it is important to achieve a patent infarct-related artery, even beyond the time period when that patency may be expected to salvage myocardium. Furthermore, a widely patent artery achieved by mechanical revascularization could prove to be more beneficial than the usually stenotic patent artery achieved by thrombolysis alone. Admittedly, the evidence to support these suggestions, though substantial and growing, is still circumstantial. However, it is sufficient to call for a thorough reexamination of the width of the “time window” during which reperfusion therapy is likely to be beneficial. It now seems possible, indeed likely, that this interval is longer than the commonly accepted 4–6 hours so that the present indications for reperfusion therapy might be greatly expanded in the future.

Obviously, these potentially broadened indications for reperfusion require careful prospective assessment. It is not appropriate to discard the widely accepted paradigm relating the late improvement in ventricular function and survival to salvage of reversibly injured ischemic myocardium because there is no doubt that this sequence of events occurs. Nor should efforts be relaxed to minimize the time interval between the onset of the clinical manifestations of acute myocardial infarction and reperfusion therapy. Instead, it may be useful to allow for expansion of the paradigm and consider seriously the possibility that the clinical benefits of reperfusion may result both from myocardial salvage and some other, not yet fully defined mechanism(s) dependent on reestablishing and maintaining patency of the artery to infarcted myocardium.

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