Potential Benefits of Late Reperfusion of Infarcted Myocardium
The Open Artery Hypothesis

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The salvage of severely ischemic myocardium by means of thrombolytic therapy represents a major advance in the management of acute myocardial infarction (AMI). Reperfusion was initially studied in canine models of evolving infarction with the temporary mechanical occlusion of a coronary artery and its subsequent release.\(^1\)-\(^3\) As shown by Reimer et al\(^4\) and Reimer and Jennings,\(^5\) such occlusion is followed by a wave front of myocardial necrosis spreading from endocardium to epicardium, with an inverse relation between the time to reperfusion and the ultimate size and extent of transmurality of the infarct. They and Kloner et al\(^6\) demonstrated in the dog that a rim of subepicardial myocardium could be salvaged when reperfusion occurred within 6 hours of coronary occlusion. In 1980, DeWood et al\(^7\) identified thrombotic occlusion of an epicardial coronary artery as the usual proximate cause of AMI in patients. Shortly thereafter, thrombolytic agents and other measures to restore reperfusion were developed to treat patients with this condition (see Reference 8 for review of early studies).

Subsequently, numerous placebo-controlled trials in patients with AMI confirmed the beneficial effects of thrombolytic therapy.\(^9\)-\(^14\) When tissue-type plasminogen activator (t-PA), streptokinase (SK), and anisoylated plasminogen-streptokinase activator complex (APSAC) were administered during the early phases of AMI, mortality was reduced significantly. Early in the thrombolytic era, it became clear that, as had been observed in the case of myocardial salvage in the canine model, benefit was greatest when such therapy was initiated within 1 hour of symptom onset.\(^8\),\(^10\),\(^13\),\(^15\)

As originally conceived, thrombolytic therapy was intended to interrupt the progression from myocardial ischemia to necrosis that resulted from occlusion of the infarct-related artery (IRA) (Fig 1). This measure would limit the size of the infarct and preserve left ventricular function,\(^16\) both these parameters having been shown to be powerful predictors of early and late outcome after AMI.\(^17\),\(^18\) Indeed, in several clinical trials, thrombolytic agents were shown to have salvaged ischemic myocardium, as reflected in modestly improved global left ventricular function (expressed in terms of left ventricular ejection fraction [LVEF]).\(^19\)-\(^21\) This modest improvement in LVEF induced by reperfusion is due to the preservation of regional myocardial function in the distribution of the IRA.\(^21\) Like patient survival, the extent to which thrombolysis preserves left ventricular function depends on the time interval between the onset of symptoms and commencement of treatment.\(^19\)-\(^25\)

The sequence described above, ie, early reperfusion of an occluded IRA \(\rightarrow\) myocardial salvage \(\rightarrow\) preservation of regional function \(\rightarrow\) preservation of global left ventricular function \(\rightarrow\) improved patient survival, is supported by many experimental and clinical studies and has become so widely accepted that it could be called a "paradigm." A key aspect of this paradigm is that the time of opening of the IRA is of central importance to the benefit achieved. Stated in another way, the effects of reestablishing an open artery may be considered to be "time dependent."

Challenges to the Paradigm

However, several findings have recently come to light that are not consistent with this paradigm, raising questions about whether the benefits of reperfusion are entirely (or even in large measure) secondary to myocardial salvage. These observations suggest that late reperfusion of an occluded coronary artery, ie, that achieved after the period of time generally considered necessary to achieve myocardial salvage, favorably affects clinical outcome.\(^26\)-\(^29\) These effects may be considered to be the "time-independent" effects of an open IRA.

The purpose of this article is (1) to review these observations, (2) to discuss mechanisms other than myocardial salvage that might account for the benefits accrued from successful late reperfusion, and (3) to review the growing evidence in favor of expanding the paradigm.

Discrepancy Between Improvement in Survival and Left Ventricular Function

One important challenge to the paradigm derives from the observation that, although thrombolytic therapy clearly enhances survival,\(^9\)-\(^16\) this benefit is, in fact, not consistently associated with significant improvement in left ventricular function.\(^20\),\(^21\),\(^25\),\(^27\),\(^28\) For example, in a trial of AMI patients randomized to APSAC or intravenous heparin, Meinertz et al reported that the APSAC-treated group had a 28-day mortality of 5.6% compared with 12.6% in the heparin-treated group.
However, left ventricular angiography performed 2 to 3 weeks after infarction revealed essentially identical LVEFs in the two groups: 53% in the APSAC-treated group and 54% in the heparin-treated group in patients with anterior myocardial infarction (MI) and 60% versus 61% in those with inferior infarction.29 In the Western Washington Intracoronary Streptokinase in Myocardial Infarction Trial,29,30 the 30-day mortality rates were 3.7% in the SK-treated group and 11.2% in the control group, respectively, while radionuclide ventriculography revealed that the two groups had identical mean LVEFs.29 In the TIMI-I trial, the 12-month mortality in patients with an open IRA at 90 minutes was 8.1% compared with 14.8% in patients with a closed IRA, despite the similarity of predischarge LVEFs in the two groups (47% and 49%, respectively).31,32

Fortin and Califf33 analyzed data from several trials of thrombolytic therapy and found only a small difference in LVEF between the groups receiving thrombolysis and those given placebo, a difference that these authors considered to be too small to account for the increase in survival (approximately 20%) associated with thrombolytic therapy. If, according to the paradigm, the benefit of thrombolytic therapy is due entirely, or even principally, to myocardial salvage, ie, to a time-dependent benefit of reestablishing patency of the IRA, then left ventricular function should be substantially better in those treated with thrombolysis than in placebo-treated patients, and this improvement might then translate into improved survival in a minority of patients.

**Improved Survival Despite Depressed Left Ventricular Function**

A second, related group of observations that are not consistent with the paradigm are the differences in the relation between LVEF and survival noted in the prethrombolytic era compared with the thrombolytic era. In studies carried out before the advent of reperfusion therapy, the LVEF before hospital discharge was inversely related to subsequent mortality.37 If, as would be dictated by the paradigm, the benefit of thrombolysis was attributable to the improvement in left ventricular function, the relation between LVEF and survival should not be altered by thrombolytic therapy (although both ventricular function and survival would be expected to be more favorable in patients so treated). However, in the TIMI-II trial, in which all patients received thrombolytic therapy, often followed by mechanical revascularization, 1-year mortality was surprisingly low (5.3%) in those with a predischARGE LVEF below 40%,38 whereas in the prethrombolytic era, the 1-year mortality among patients with similar ejection fractions exceeded 15% to 20%. Thus, at any level of LVEF, survival after thrombolytic therapy appears to be greater than that reported during the prethrombolytic era. Thrombolytic therapy thus appears to confer a greater survival benefit than can be accounted for by the improvement in left ventricular function.

**Beneficial Effects of Late Reperfusion**

Another major challenge to the paradigm is the survival benefit observed in patients with AMI in whom reperfusion was achieved after substantial myocardial salvage was no longer possible, ie, the time-independent effect of reestablishing an open IRA. In the prethrombolytic era, spontaneous reperfusion (which usually occurs many hours or even days after the onset of AMI) was found to be associated with improved left ventricular function. There is considerable evidence that non-Q-wave MI is associated with late spontaneous reperfusion and better left ventricular function than Q-wave AMI.39,40 In a study by Verheugt et al,41 left ventricular function was better after AMI in patients with patent IRAs than in those whose vessels were persistently occluded. During the 2 weeks after the AMI, LVEF increased by an average of 15 ejection-fraction units on radionuclide ventriculography in patients with spontaneous reperfusion compared with a reduction of 4.8 units in those with persistently occluded IRAs. Similarly, Jeremy et al42 studied 40 patients with a first AMI who did not receive thrombolytic therapy and noted that at 30 days, left ventricular dilatation (defined as an increase of >20% in end-diastolic volume) occurred in all 14 patients with persistently occluded IRAs compared with only 2 of 26 patients with patent IRAs. Pfeffer et al43 reported that in patients experiencing a first anterior MI, a persistently occluded left anterior descending coronary artery was an independent risk factor for subsequent left ventricular enlargement.

Thrombolytic therapy administered relatively late in the course of AMI also appears to improve survival. Data pooled from the early, small, randomized trials showed a 22% reduction in mortality among patients who received thrombolytic therapy 12 to 24 hours after the onset of symptoms—long after the time when significant myocardial salvage could be expected. The ISIS-2 trial also included patients who presented relatively late in the course of their AMI. Subgroup analysis showed that the odds of vascular death at 5 weeks was reduced by 20% in those given SK and aspirin 13 to 24 hours after the onset of symptoms.
hours after the onset of symptoms. A meta-analysis also revealed a significant improvement in survival among patients treated with thrombolytic agents 6 to 24 hours after symptom onset. In all instances, however, benefit was greater with earlier treatment.

The LATE trial specifically addressed the use of thrombolytic therapy in patients who presented 6 to 24 hours after the onset of symptoms of AMI. 5711 patients were randomized to either t-PA or placebo. At 35 days, there was a 26% reduction in mortality in the t-PA–treated patients who presented 6 to 12 hours after the onset of symptoms; however, patients who received thrombolytic therapy 13 to 24 hours after the event derived no benefit in terms of survival. In the EMERAS trial, in-hospital mortalities were nearly identical among 3600 patients with AMI who presented between 6 and 24 hours after the onset of symptoms and were randomized to SK or placebo (11.9% versus 12.4%, respectively [P=NS]). Although not statistically significant, there was a 14% reduction in mortality in patients treated with the thrombolytic agent between 6 and 12 hours.

Evidence is therefore accumulating that, like the effects of late occurrence of spontaneous recanalization of the IRA, thrombolytic therapy given more than 6 hours after the onset of symptoms may improve ventricular function and survival even though little if any salvage of myocardium occurs beyond that time. When thrombolytic agents have been administered >12 hours after the onset of symptoms, the results have been ambiguous, perhaps because these drugs are relatively ineffective in establishing coronary patency when clots are long-standing. However, late reperfusion, whether achieved spontaneously (see above) or by means of angioplasty (see below), appears to improve clinical outcome.

The “Open-Artery Hypothesis”

The concept that a patent IRA and myocardial reperfusion confer a benefit above and beyond that resulting from myocardial salvage has given rise to what has been called the “open-artery hypothesis,” for which there is now considerable support. This hypothesis ascribes hemodynamic and clinical benefits both to time-dependent and time-independent effects of coronary artery reperfusion. Cigarroa et al analyzed retrospectively the course of 179 patients who did not receive thrombolytic therapy after their infarction and who were found by coronary arteriography to have single-vessel disease. Although left ventricular volumes and global ejection fractions were similar in the two groups initially, at a mean follow-up of 47 months, none of the 64 patients with partial or complete antegrade blood flow in the IRA had died, compared with 21 deaths among the 115 patients in whom flow in the IRA was absent or minimal (Fig 2). In addition, the incidence of congestive heart failure was significantly lower in the patients with patent than in those with occluded IRAs (6% versus 17%).

These findings are complemented by those of Trappe et al, who studied 214 patients with single-vessel coronary artery disease, three fourths of whom had had an AMI; an occluded coronary artery was associated with a much higher incidence of subsequent sudden death than was a patent IRA that exhibited high-grade stenosis (15% versus 3%, respectively). In a study of 172 patients with single-vessel coronary artery disease who experienced a first Q-wave MI, patency of the IRA was found to be an independent predictor of survival on multiple logistic regression analysis. In the SAVE Trial, post-MI patency of the IRA was also identified as an independent predictor of a lower incidence of a combined clinical end point (cardiovascular death, severe heart failure, recurrent infarction, or marked deterioration of LVEF). At an average follow-up of 3.5 years, 36% of the patients with a patent IRA had reached one of these clinical end points, compared with 51% in those with an occluded IRA.

Trials of thrombolysis have also shown that IRA patency correlates strongly with improved survival, both short-term and long-term (Fig 3). For example, in the Western Washington Trial, mortality at 1 year was 2.5% in SK-treated patients with patent IRAs, compared with 15.0% in those with occluded vessels (P=.008). Low mortality with sustained IRA patency was also observed in the TIMI-I trial. In both of these trials carried out early in the thrombolytic era, thrombolytic therapy was begun relatively late, i.e., an average of 4.5 hours after the onset of symptoms. Recanalization did not occur for yet another 45 minutes, and it is unlikely that such delayed therapy salvaged much myocardium. Nevertheless, survival correlated with the presence of a patent IRA. Powerful support for survival benefit from an open IRA comes from the recently completed GUSTO trial, in which there was a close relation between coronary artery patency and survival among the various therapeutic regimens studied. Other studies of patients who received thrombolytic therapy have also demonstrated that patency of the IRA is an independent predictor of survival.

Whereas successful reperfusion and sustained patency of the IRA appear to lead to improved survival, reclosure of the IRA in patients with AMI is associated with a much poorer prognosis. In their review of the TAMI trials, Ohman et al noted that the failure to achieve IRA patency, the return of patency followed by reclosure, and early and sustained patency resulted in in-hospital mortality rates of 17.2%, 11.0%, and 4.2%, respectively.
respectively. When IRAs became reoccluded after thrombolytic therapy, the failure of angioplasty to restore patency was associated with a higher mortality (26.7%) than in patients in whom mechanical reperfusion was successful (12.1%).

Mechanisms Responsible for the Potential Benefit of the Open IRA

Mechanisms by which an open IRA confers benefit other than by salvaging ischemic myocardium are not clear, but there is evidence for several possibilities that are not mutually exclusive.

Improved Healing of Infarcted Tissue and Prevention of Ventricular Remodeling

It has been demonstrated in both animal experiments and patients that infarct expansion and left ventricular remodeling contribute to the late detrimental effects of myocardial infarction. In the hours after AMI, lateral slippage of muscle fibers occurs, causing thinning and then bulging of the infarcted region. This change in the shape of the ventricle sometimes leads to the formation of left ventricular aneurysm. Stroke volume and ejection fraction often are maintained through hyperfunction of the nonischemic, noninfarcted regions of the ventricle, and the hemo-
dynamic burden on the residual viable myocardium resulting from the combination of the loss of contractile tissue and of infarct expansion causes it to become dilated and remodeled into a more spherical, hypertrophied chamber.

The early formation of a firm myocardial scar reduces both infarct expansion and ventricular remodeling. The healing process commences with the influx of inflammatory cells into the infarct, followed by the proliferation of fibroblasts, deposition of collagen, and strengthening of the infarcted segment. When blood flow to regions of necrotic myocardium is restored, even when such restoration occurs after significant myocardial salvage would be possible, the influx of inflammatory cells increases. The importance of the early inflammatory reaction to scar formation is supported by studies in which glucocorticosteroids and nonsteroidal anti-inflammatory agents administered within hours of experimentally induced myocardial infarctions inhibited the inflammatory process, allowed greater infarct expansion, and resulted in thinner scars.

Late reperfusion after an AMI is also associated with intramyocardial hemorrhage, cellular edema, and calcium-induced contraction-band necrosis. These consequences of myocardial reperfusion, even when they occur too late to salvage jeopardized myocardium, might be expected to accelerate scar formation, with stiffening of the infarcted tissue, and to reduce infarct expansion, ventricular remodeling, and dilatation. On the other hand, Honan et al. have shown that the myocardial hemorrhage resulting from late thrombolytic therapy (>12 hours after the onset of symptoms) may increase the likelihood of cardiac rupture. However, despite the risk of this complication, a meta-analysis revealed that survival was improved with late treatment (6 to 20 hours).

Prevention of Infarct Expansion and Ventricular Remodeling

In 1960, Salisbury et al. showed that an "erec
tile force" provided by a blood-filled coronary vascular bed can reduce myocardial compliance. In accord with this observation, we have suggested that a blood-filled coronary vascular bed perfusing necrotic myocardium may provide a "scaffold" that supports the surrounding necrotic myocardium, maintains structural integrity, and limits infarct expansion and ventricular dilatation.

Results of animal experiments strongly support the concept that late reperfusion reduces infarct expansion, left ventricular dilatation, and aneurysm formation. In their seminal study in rats, Hochman and Choo found that reperfusion achieved too late to salvage myocardium still significantly reduced the degree and extent of infarct expansion (Fig 4). Infarct expansion was far more extensive in rats with permanent coronary occlusion than in those in which reperfusion was carried out.
ventricular remodeling and impairment of left ventricular function in patients as well. In TIMI I, LV end-diastolic and end-systolic volumes rose significantly more in patients with occluded versus those with patent IRAs. In TAMI-6, patients were randomized to treatment with t-PA or placebo 6 to 24 hours after the onset of symptoms of AMI. At 6 months of follow-up, left ventricular end-diastolic volume had increased from a mean of 127 mL to 159 mL in the placebo-treated group (P=.006) compared with 149 and 146 mL, respectively, for the t-PA–treated group. Coronary angioplasty of occluded IRAs 48 hours after the onset of symptoms resulted in an improved LVEF over that in patients who did not receive this procedure; however, this improvement in systolic function was not maintained at the 6-month follow-up. In a study of patients with AMI divided into early reperfusion (<6 hours from the onset of symptoms), late reperfusion (>6 hours), or no reperfusion, end-systolic and end-diastolic volumes were lower in both reperfusion groups compared with the persistent occlusion group. Leung and Lau studied patients with a first AMI with obstruction limited to the left anterior descending coronary artery who received thrombolytic therapy. Left ventricular end-systolic and end-diastolic volumes and ejection fractions were similar at 7 to 10 days in patients with patent and occluded IRAs. However, over the course of 1 year, patients with occluded IRAs showed significantly greater increases in ventricular volumes and reductions in LVEF than did patients with patent IRAs (Fig 6). Schroder et al reported that in patients with infarcts of comparable size, those with a patent IRA 1 month after AMI had significantly better left ventricular function than those with an occluded vessel; when the IRA was the left anterior descending artery, the LVEF was 52% when the vessel was patent compared with 36% when it was occluded.

Aneurysm formation after AMI is uncommon in patients who have good collateral circulation or a patent IRA. An abnormally shaped ventricle and aneurysm formation, in turn, are associated with a high risk for death. Thus, Meizlish et al have reported 1-year mortality rates of 61% and 9%, respectively, among AMI patients with and without severe left ventricular distortion. Late opening of the IRA, ie, after 6 hours, was found to be associated with reduced wall motion abnormalities when patients were evaluated 3 months later. Hirai et al reported that after a first AMI, left ventricular aneurysm developed in only 1 of 15 patients with successful reperfusion of the IRA compared with 7 of 12 patients whose vessel was persistently occluded; the other 5 patients either experienced late spontaneous reperfusion or had collateral filling of the IRA.

In addition to preserving systolic function, patency of the IRA may also improve left ventricular diastolic function, presumably by improving compliance of the affected ventricular wall. In the MITI trial, patency of the IRA correlated with improvement in the peak early ventricular filling rate.

Perfusion of “Hibernating” Myocardium
A markedly stenotic but patent IRA or the presence of collaterals perfusing severely ischemic tissue may allow sufficient blood flow to sustain viability of the involved regions of the myocardium but not to maintain
normal contractile function. The presence of so-called hibernating rather than infarcted myocardium might improve clinical outcome by reducing left ventricular dilatation, aneurysm formation, and electrical instability, three major complications of large infarctions.

This view is supported by three recent studies. In the first, Montalescot et al. reported that, in patients with Q-wave MI and a patent but markedly stenotic IRA, angioplasty performed >6 weeks after MI improved wall motion in the peri-infarct region. This finding indicates that myocardial viability must have been sustained for weeks after AMI by a patent though markedly obstructed IRA. In the second, Sabia et al. showed that perfusion of the peri-infarct region through collateral vessels can also preserve myocardial viability; in patients with coronary collaterals, angioplasty of an occluded IRA carried out an average of 12 days after MI resulted in an improvement of ventricular function. In a third, nonrandomized study carried out on patients with a persistently occluded IRA after AMI, the 3-year mortality was 7% in patients who were revascularized 6 to 24 days after AMI compared with 20% in those who were not. These three investigations, taken together, provide strong evidence that even very late increases in flow through an IRA can restore myocardial function in chronic, severely ischemic, noncontracting but viable myocardium in the peri-infarct zone. Thus, effects of late revascularization of hibernating myocardium provide yet another example of the benefits of a patent IRA.

**Increased Electrical Stability**

Patency of the IRA appears to be associated with greater electrical stability and thus fewer instances of tachyarrhythmias. Most likely, it is reduction of ventricular remodeling that accounts for this beneficial effect. Dilated hearts display more arrhythmogenicity and greater dispersion of refractory periods than do normal hearts. Since left ventricular aneurysms in particular are associated with a high incidence of ectopic activity, prevention of aneurysm formation by restoring IRA patency would be expected to reduce the likelihood of such arrhythmias.

There is clinical evidence that thrombolytic therapy reduces the late incidence of ventricular fibrillation as well as experimental evidence that this reduction may be independent of myocardial salvage.
Also, electrophysiological studies indicate that inducible, sustained ventricular tachycardia occurs much less frequently in patients with AMI who have received thrombolytic therapy (and who may be presumed to have a higher incidence of open IRAs). Kersschot et al.\textsuperscript{104} reported inducible, sustained ventricular arrhythmias in 10 of 21 patients randomized to SK compared with 15 of 15 patients randomized to treatment without a thrombolytic agent (P<.001). In another report on patients with recent anterior infarctions complicated by aneurysm formation, the rate of inducibility was 8% in those who had received thrombolytic therapy compared with 88% in the placebo-treated control group (P<.001).\textsuperscript{105} (Fig 7). Horvitz et al.\textsuperscript{106} studied a group of postinfarct patients in whom a cardioverter-defibrillator had been implanted to reverse life-threatening tachyarrhythmias; at 1 year, 73% of those with an open IRA had experienced no arrhythmias that necessitated automated firing, compared with 41% of those with a closed vessel.

Signal-averaged ECG to detect late potentials generated by asynchronous conduction through ischemic and/or fibrotic myocardium is also helpful in identifying postinfarct patients at increased risk for future arrhythmias. Late potentials have been reported to occur in approximately one third of patients with AMI who do not receive thrombolytic therapy.\textsuperscript{107,108} Vatterott et al.\textsuperscript{109} found that in post-AMI patients, a closed IRA was the most powerful independent predictor of late potentials and that they occurred in a lower fraction of patients given thrombolytic therapy. Lange et al.\textsuperscript{110} also reported late potentials in 8% and 40% of patients with open and closed IRAs, respectively. The presence of late potentials in patients receiving thrombolytic agents appears to correlate with persistent occlusion of the IRA.\textsuperscript{109,111-113} Conversely, the absence of late potentials was associated with persistently viable, presumably hibernating myocardium in patients in whom patency of the IRA had been achieved by angioplasty an average of 12 days after AMI.\textsuperscript{114,115} In a substudy of the LATE trial,\textsuperscript{45} Steinberg et al.\textsuperscript{116} found that t-PA treatment 6 to 12 hours after the onset of symptoms resulted in a small but significantly shorter total QRS duration (the most powerful signal-averaged ECG predictor of adverse events) than did placebo treatment.

**Implications for the Future**

The enormous benefits of establishing patency of the IRA within 1 or 2 hours of coronary occlusion result primarily from myocardial salvage. Vigorous efforts to achieve reperfusion as early as possible after the development of severe myocardial ischemia must be continued and indeed intensified.\textsuperscript{115} In addition, reocclusion after successful reperfusion is associated with a poor outcome, so efforts must be made to maintain patency once the IRA is opened by thrombolytic therapy. New adjunctive drugs such as novel new antiplatelet agents and specific antithrombins such as hirudin,\textsuperscript{117} designed to prevent reocclusion, are being actively investigated. The substantial benefits of myocardial reperfusion—i.e., prevention of infarct expansion, reduction of ventricular remodeling, and improvement of electrical stability—all appear to accrue when IRA patency occurs >6 hours and perhaps even days after the onset of AMI. Therefore, attempts should be made to restore vessel patency in AMI beyond the traditional 6-hour "window" after the onset of symptoms. Thrombolytic therapy might be appropriate for up to 12 hours, whereas at a later time when thrombolytic agents are no longer as effective, primary mechanical revascularization, generally by means of angioplasty, may be more appropriate.

The case for angioplasty for failed thrombolysis ("rescue angioplasty") appears to be growing. Preliminary studies indicate that clinical outcomes and mortality rates are improved in patients who were successfully reperfused by means of angioplasty after failed thrombolysis and are similar to those of patients in whom patency was achieved by primary thrombolysis.\textsuperscript{118-120} However, if rescue angioplasty or retreatment with a thrombolytic agent for failed thrombolysis\textsuperscript{21} is to be more widely used, we need accurate, noninvasive methods to ascertain the status of the IRA. Coronary angiography is the gold standard for determining vessel patency, but routine early catheterization after thrombolytic therapy is not practical for most patients with AMI.

Fortunately, a number of promising noninvasive techniques are emerging. Continuous ST segment monitoring may provide a useful marker of successful reperfusion and patent IRAs after thrombolytic therapy\textsuperscript{122-124}; such monitoring may also detect reocclusion early in the post-MI period. A second noninvasive technique involves use of the creatine kinase (CK) MM and MB isoenzyme subforms, which have been identified and separated electrophoretically into the two types found in cardiac muscle, MB\textsubscript{2} and MM\textsubscript{2}. After they are released into the serum, these forms are converted by the enzyme carboxypeptidase N to the serum forms MB\textsubscript{1} and MM\textsubscript{1}. CK-MB\textsubscript{2} and CK-MM\textsubscript{2} are released more rapidly if reperfusion has occurred than if the artery remains occluded. An elevated ratio of MB\textsubscript{2}/
MB₁ and a rapid rate of rise in the concentration of MM₁ both appear to correlate with vessel patency on angiography.¹²⁵,¹²⁶

Imaging with ⁹⁹mTc-labeled somatostatin may also allow the success of thrombolytic therapy to be assessed noninvasively. Somatostatin rapidly accumulates in viable myocardial cells proportional to their perfusion; however, unlike thallium, it does not redistribute significantly as a function of time. Therefore, somatostatin has been used to define myocardium at risk during the early (pretreatment) phase of AMI and subsequently to determine myocardial perfusion and salvage after thrombolytic therapy.¹²⁷,¹²⁹

It is hoped that the use of such noninvasive markers of vessel patency (perhaps in combination) as well as others now being developed will identify those patients with AMI who do not respond to thrombolytic therapy initially or in whom reocclusion has subsequently occurred. In such cases, angioplasty or retreplant can be considered to restore coronary patency.

As the open-artery hypothesis continues to be examined, it is clear that the original paradigm on which reperfusion in AMI was based must be expanded. Although substantial evidence suggests that it is beneficial to achieve (and maintain) late patency of the IRA, such evidence is still not strong enough to warrant radical changes in the care of patients with AMI. These changes would be expensive and resource intensive, involving the frequent use of rescue angioplasty for selected patients suspected of having failed thrombolytic therapy, as well as coronary arteriography before hospital discharge for all AMI patients who have received treatment with a thrombolytic followed by mechanical revascularization in patients with occluded vessels. This strategy would not be without risk, since coronary angioplasty in this setting could damage the non–infarct-related artery and lead to a reduction of collateral flow. However, in view of the importance and magnitude of the problem of management of patients with AMI and occluded coronary arteries, it is now appropriate to initiate a prospective, randomized trial to determine whether establishing late patency of the IRA will affect clinical outcome in such patients.

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