From Myocardial Salvage to Patient Salvage in Acute Myocardial Infarction: The Role of Reperfusion Therapy*

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The outlook for patients with acute myocardial infarction has improved dramatically. During the 1960s, the widespread introduction of coronary care units led to a marked reduction in the mortality due to primary ventricular arrhythmias. In the 1970s, the use of antiarrhythmic drug therapy and efforts to reduce myocardial oxygen consumption with use of hemodynamic monitoring further reduced the risk during the acute phase of infarction (1). In the decade of the 1980s reperfusion therapy, predominantly with intravenous thrombolytic agents, was disseminated and a dramatic reduction in short-term and long-term mortality has been observed (2,3). Careful examination of these data has led to new questions about the mechanisms by which reperfusion therapy reduces mortality and about clinical practices that may enhance the short and long term effects of thrombolytic agents.

Acute Reperfusion Therapy

A carefully constructed scientific argument in favor of reperfusion therapy was developed from multiple experiments performed in the basic laboratory. The rationale for this approach was based on the demonstration that early reperfusion of an artery after a transient period of occlusion led to a smaller infarct size than that obtained with a permanently occluded artery (4). These experiments also provided important evidence that myocardial infarction progresses over time from the subendocardium toward the epicardium in a “wavefront of ischemic cell death” (5). Importantly, the time frame for this process in models thought to represent the human situation is quite short, on the order of 3 to 4 h. Thus, the clinical rationale for myocardial reperfusion was based on the concept that very early reperfusion would lead to better patient outcome because myocardium at risk would survive. Data from clinical studies had demonstrated that the most powerful determinant of survival after acute infarction was left ventricular ejection fraction (6). Thus, shifting a patient downward on the ejection fraction curve should lead to a lower risk of death (Fig. 1).

Effect on prognosis. Initial expectations that acute reperfusion would alter the prognosis of patients with acute myocardial infarction have been met. The majority of trials have demonstrated a striking reduction in early mortality after thrombolytic therapy with streptokinase, recombinant tissue plasminogen activator (rt-PA) and anisoylated plasminogen streptokinase activator complex (APSAC) (2,7–11). Furthermore, both global and regional left ventricular function have consistently been improved in patients treated early with thrombolytic therapy. In patients with cardiogenic shock, the benefit of acute reperfusion has been dramatic and appears to have markedly changed the natural history of the syndrome (12). However, the magnitude of the effect on ejection fraction has been relatively small, and a consistent benefit has been shown only in patients treated early with thrombolytic therapy. In patients with cardiogenic shock, the benefit of acute reperfusion has been dramatic and appears to have markedly changed the natural history of the syndrome (12). However, the magnitude of the effect on ejection fraction has been relatively small, and a consistent benefit has been shown only in patients treated early after the onset of symptoms (13–19). Furthermore, in the few angiographic studies that have assessed coronary patency in relation to mortality, the benefit occurred only in patients with reperfusion of the infarct-related artery: the earlier the artery is open, the greater the benefit to the patient (20–22).

Mechanisms of mortality reduction. The experimental model of reperfusion and infarct salvage, which is sound and reproducible, has been supported by clinical studies and trials. Nonetheless, the manner in which this valid experimental postulate has been replicated in its clinical application is not as clear as a cursory examination of the data might suggest. Evidence is accumulating that the effects of reperfusion in acute infarction may be the consequence of other mechanisms in addition to salvage of the ischemic myocardium. These possible mechanisms are listed in Table 1.

The benefit in terms of mortality is apparent in subgroups of patients who achieve reperfusion at a time when myocardial salvage would not be expected. Pooled results from the randomized trials of intravenous thrombolytic therapy in the
Figure 1. Relation between left ventricular ejection fraction at the
time of hospital discharge and 2 year survival after acute myocardial
infarction. The major issue is whether thrombolytic therapy moves
the patient to a different portion of the same curve (A) because of
reduction of infarct size or whether reperfusion places the patient on
a different curve that is shifted down to the left (B) by altering the
influence of other factors on long-term survival. This figure is
adapted with permission from Morris KG, Palmeri ST, Califf RM, et

1970s (2) demonstrated a significant reduction in mortality in
patients treated between 6 and 24 h from symptom onset.
More recently, the ISIS 2 trial (2) found a persistent benefit
of aspirin and streptokinase in patients treated between 6
and 24 h after the onset of symptoms.

It is becoming increasingly apparent that the long-term
improvement in the outcome of patients with sustained
patency of the infarct-related artery exceeds the expecta-
tions based on improvement in left ventricular function
(23-26). The Western Washington trial (20), the first to
carefully examine long-term survival in relation to patency
of the infarct-related artery, found improved survival at 1
year of follow-up in patients with adequate perfusion of the
infarct-related territory even though left ventricular function
in the treated group was not improved over that in the
control group. In multivariable analysis perfusion of the
infarct-related artery was more closely related to outcome
than was left ventricular function.

Effect of Reperfusion on Infarct Expansion,
Healing and Remodeling

Infarct "remodeling" refers to the processes of early
expansion and thinning of the infarcted segment that in turn
(in addition to volume overload and hypertrophy) appears to
be a major determinant of subsequent, progressive dilation
of the noninfarcted segments of the left ventricle (27,32). The
latter is a powerful predictor of subsequent congestive heart
failure, ventricular arrhythmias and mortality (33,34). The
correlation between the extent of infarct expansion and
subsequent remodeling and infarct size is well documented,
although the relation is widely variable (35,38). The potential
for successful perfusion to favorably affect these pathologic
processes is obvious. In patients entered into the TIMI I trial
(39), successful reperfusion was associated with less dila-
tion. Whether reperfusion of the infarct-related artery can
alter the process of healing and remodeling by mechanisms
other than a simple reduction in the mass of infarcted tissue
is an important issue currently under investigation.

Pathophysiology. In the experimental animal and in au-
topsy studies, expansion is a function not only of infarct size
but also of the extent of transmural necrosis. Experimental
reperfusion has been shown to limit expansion by reducing
the extent of transmurality, presumably by preserving an
epicardial rim of myocardium (40,41). In a study on rats (42),
large but only focally transmural infarcts did not show
evidence of expansion. Hochman and Choo (43) documented
in the rat preparation that late perfusion was associated with
less expansion, independent of any effect on either myocar-
dial infarct salvage or transmurality. The mechanisms

Table 1. Possible Mechanisms for Mortality Reduction in Acute
Myocardial Infarction After Reperfusion Therapy

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<tr>
<th>Possible Mechanisms</th>
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<tr>
<td>Reduction in infarct size</td>
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<tr>
<td>Mechanical factors</td>
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<td>Improved healing</td>
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<tr>
<td>Less expansion</td>
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<tr>
<td>Less aneurysm formation (arrrhytmia, thrombus)</td>
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<td>Lower wall stress</td>
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<td>Improved diastolic function</td>
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<td>Prevention of rupture</td>
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<td>Scaffolding</td>
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<td>Electrophysiologic function</td>
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<td>Arrhythmia protection</td>
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<td>Preservation of sympathetic fibers</td>
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<td>Collateral flow provision</td>
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<td>Ancillary therapies</td>
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whereby this effect can be achieved are speculative and include the possibility that reperfusion accelerates the rate of healing of the infarcted segment and that the tensile strength and scar thickness of nonperfused and reperfused infarct scars are different (44-46).

Several studies (44,47) have shown that reperfusion causes increased hemorrhage, cell swelling and edema which, by increasing the stiffness of the vessel wall, could reduce the extent of systolic bulging or expansion. A reduction in diastolic infarct expansion after late reperfusion, unrelated to the extent of myocardial salvage, was noted by Force et al. (48). In contrast, however, a recent study by Kurnik et al. (49) showed that reperfusion reduced diastolic stiffness only in conjunction with an improvement in systolic function.

Clinical results of reperfusion therapy. Clinical evidence supporting the potential for reperfusion to favorably affect remodeling, independent of infarct salvage, is tenuous but tantalizing. Jeremy et al. (50), using serum enzyme levels as an index of infarct size (in patients not receiving thrombolytic therapy), found that the degree of perfusion of the infarct-related artery at predischarge angiography was an important predictor of subsequent left ventricular dilation, independent of infarct size. No such correlation was found, however, by Warren et al. (51) in their study of patients undergoing thrombolysis relatively late (5 h after the onset of symptoms).

Several recent clinical studies reported in a preliminary fashion (52-54) offer some evidence of benefit from reperfusion independent of infarct size. Nolan et al. (52) documented a reduction in the extent of infarct expansion after administration of rt-PA, even though ejection fraction and thallium defects were similar on day 1 in patients randomized to placebo or rt-PA. A study by Hamano et al. (54) documented a reduction in the development of left ventricular aneurysm, even among patients who received thrombolytic therapy 4 to 10 h after the onset of symptoms. The possibility that reperfusion can favorably influence the healing of the myocardial infarct, independent of the effect on myocardial salvage, has important implications for the timing of treatment and size of the patient pool likely to benefit from reperfusion. This area remains a critical topic for investigation because the data to date are far from conclusive but certainly provocative.

Marino and colleagues (54) in a report from GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico) in this issue of the Journal have examined the effects of streptokinase on preservation of cavity size and function, duly noting that, compared with conventional therapy, reperfusion therapy led to a 10% to 15% smaller ventricular cavity size without better ejection fraction. There are a few caveats to bear in mind in interpreting this important study. First, the improvement in regional wall motion, rather than reperfusion alone, likely contributed to preserved cavity size. Second, there was no significant evidence of cavity dilation between the predischarge and 6 month evaluation. This observation differs from other published data (50,51) that have emphasized the occurrence of late cavity dilation in many patients. The lack of progressive dilation over time in the GISSI echocardiographic substudy (54) is likely due to the substantial 30% dropout rate from the subacute phase to follow-up, with the patients lost to follow-up constituting the highest risk group for further infarct expansion. Third, the lack of a central echocardiographic laboratory in this multicenter, unblinded study is conspicuous, as such a laboratory would have undoubtedly improved reliability and permitted more direct analysis of infarct expansion such as the end-systolic anterior to posterior endocardial segment length ratio. Fourth, there is excessive subgroup analysis, which predisposes toward the potential for spurious results. In perspective, the study provides further cogent evidence for an effect of reperfusion therapy on cavity preservation independent of functional improvement. This phenomenon is likely a key explanation for the discordance of mortality versus left ventricular function results in large scale thrombolytic trials (12,13).

Preservation of the epicardial rim, even in the absence of salvage of a large amount of myocardium, may provide sufficient tensile strength of the infarct to prevent myocardial rupture. Intriguing data from another GISSI substudy (55) demonstrated that the risk of rupture after the first 24 h after treatment was markedly reduced by streptokinase therapy.

Electrophysiologic Effects and Mortality

The predominant mechanism of death after hospital discharge in patients treated without reperfusion therapy has been sudden cardiac death. Although the precise mechanism for such death remains unresolved, a consensus has been reached that patients at high risk are those with markedly impaired left ventricular function, multivessel coronary disease or an unstable electrical milieu as demonstrated by Holter ambulatory electrocardiographic (ECG) monitoring, electrophysiologic study or signal-averaged ECG (56-58). That ischemia may precipitate the penultimate electrical event is suggested by the careful autopsy studies of Javies and Thomas (59), which documented plaque fissuring in patients with coronary artery disease and sudden death.

Effect of reperfusion on arrhythmias and sudden death.

Recent human studies have suggested that a change in the risk of sudden death may account for a substantial proportion of the improvement in outcome after reperfusion therapy. The first careful study implicating revascularization in reduction of sudden death was the multicenter Coronary Artery Surgery Study (CASS) (60). In this trial a profound effect on sudden death rates was observed in patients with chronic ischemic heart disease treated with coronary artery bypass graft surgery, particularly in patients with markedly
impaired rest left ventricular function. These results were observed despite the predominant belief at the time that revascularization would not help patients with "chronically scarred" myocardium. Although this study did not involve patients with acute myocardial infarction, it provided important clues about protection from sudden death. Subsequent studies (61) have demonstrated that after revascularization in acute myocardial infarction, abnormal afterpotentials often return to normal on the signal-averaged ECG and fewer patients have prognostically important arrhythmias induced on electrophysiologic testing. In one interesting study (62) of 32 patients with a large anterior wall infarction (half of whom had received thrombolytic therapy), incidence of inducible ventricular tachycardia and subsequent sudden cardiac death was strikingly reduced in patients treated with thrombolytic therapy, despite a similar degree of left ventricular dysfunction.

In a study of 62 patients by Kersschott et al. (63), sustained ventricular arrhythmias were less commonly induced in patients with early reperfusion after thrombolysis than in patients without reperfusion. This study, however, did not attempt to distinguish between the differential effects of arterial patency and ventricular function. In contrast, using the induction of ventricular tachycardia as a marker of electrical stability (rate of inducibility 22%), McComb et al. (64) were unable to distinguish between patients with and without successful reperfusion. Cardiac mortality was only 1% in both groups over a follow-up period of 30 ± 16 months. The conclusions of this study, regarding the effects of reperfusion on electrical stability must be tempered by the investigators' use of antiarrhythmic therapy in patients who had inducible ventricular tachycardia and the relative lack of specificity of electrophysiologic testing when performed as early as 7 to 25 days after infarction.

Recent observations from Cedars Sinai (65) are intriguing in that the strongest explanation with a persistently occluded infarct-related artery was the presence of late potentials, as assessed by the signal-averaged ECG. In a multivariable analysis, a powerful independent predictive variable was the presence of late potentials followed by the ejection fraction. This finding points strongly toward a beneficial effect of reperfusion on electrical stability in addition to the preservation of left ventricular function.

Other Factors in Improved Mortality

A third possible explanation is that the improved mortality is unrelated to scar formation or the electrophysiologic environment. Perhaps a reduction in mortality in a subset of patients with ongoing ischemia accounts for all of the improvement in survival in patients treated late. Perfusion of the infarct area could have further benefits over time engendered by the provision of collateral flow to other areas of myocardium when they become jeopardized. For example, a patient with an anterior wall infarction from left anterior descending artery occlusion might have a better outcome with subsequent right coronary occlusion if the left anterior descending artery was patent to provide collateral flow. Finally, multiple ancillary therapies in these patients, including beta-adrenergic blockade, aspirin use and risk factor modification, may account for the unexpected overall reduction in mortality and sudden death after thrombolytic therapy.

Although the startlingly low late mortality after thrombolytic therapy may be attributed to a number of potential pathophysiologic interactions, more mundane explanations need to be considered. Two critical issues are the baseline characteristics of patients receiving thrombolytic therapy and the influence of subsequent revascularization procedures.

Role of baseline clinical characteristics. The decision to initiate thrombolytic therapy introduces an element of bias because patients over the age of 70 to 75 years have been excluded in most trials. Similarly, high risk patients with a prior history of cerebrovascular disease and other life-threatening conditions including gastrointestinal bleeding, recent cardiopulmonary resuscitation, significant hypertension, prior coronary bypass surgery or prosthetic valve replacement have been excluded.

The majority of the trials to date and all of those that have evaluated the role of coronary angioplasty in conjunction with lytic therapy required the presence of ST segment elevation for inclusion. The distribution of coronary artery disease in patients with these ECG features, however, may differ from that in patients presenting with ST segment depression. A comparison between the coronary anatomy in recent trials of patients undergoing thrombolytic therapy with that in a series of patients undergoing predischarge angiography at Johns Hopkins Medical School between 1974 and 1978 highlights these differences (66). The latter patients did not receive thrombolytic therapy and approximately a third had a non-Q wave infarction. In this group, predischarge angiography documented triple vessel disease in 50% of patients, double vessel disease in 23% and single vessel disease in 27%. In contrast, in the TIMI-2a (26) and TAMI I (67) trials, the incidence of triple vessel disease was 11% and 10%, respectively, and that of double vessel disease 24% and 32%, respectively (Fig. 2). In a Mayo Clinic series (24) of 160 patients with acute infarction undergoing coronary angioplasty with or without associated thrombolytic therapy, triple vessel disease was present in only 19%, double vessel disease in 31%, but single vessel disease in 50%. In a multivariable analysis of late outcome in survivors of acute infarction (66), the site of coronary obstruction, the number of vessels diseased and left ventricular function were identified as the major determinants.

Influence of subsequent revascularization procedures. Finally, studies using aggressive revascularization strategies to
maintain the perfusion status of patients with clinical evidence of instability have experienced extremely low mortality rates in long-term follow-up. Patient series from Duke University (23), the Mayo Clinic (24) and the University of Michigan (12) employing emergency angioplasty have reported extremely low mortality rates in out of hospital follow-up of patients discharged with a patent infarct artery. In the TAMI trials (22), an intermediate strategy of rescue angioplasty when thrombolytic therapy failed to achieve patency and deferred revascularization in patients with a patent vessel after thrombolytic therapy resulted in similarly low long-term mortality rates. Preliminary results from the TIMI trials (25,26) have demonstrated that excellent long-term outcome can be achieved when angioplasty and surgical revascularization are used liberally only in the subset of patients with recurrent ischemia or hemodynamic instability during the convalescent phase. In comparison, studies (2,3) with more conservative revascularization strategies have experienced follow-up mortality rates similar to the rates observed in the 1960s and 1970s.

The high incidence of revascularization procedures (coronary bypass surgery, coronary angioplasty, or both) in many studies of thrombolytic therapy needs to be addressed. In TIMI-2a (a trial of early versus delayed angioplasty) (26), almost 25% of patients underwent coronary bypass surgery before discharge; in the TAMI trials (68), 19% underwent bypass surgery before discharge and 6% during the subsequent 2 years. In the Mayo Clinic series of patients undergoing coronary angioplasty with or without lytic therapy, almost 30% of patients underwent coronary bypass surgery either before hospital discharge or during an average follow-up period of 2 years. Thus, the patients currently receiving lytic therapy appear to be a relatively low risk group, and many undergo coronary revascularization before discharge. These factors may significantly contribute to the low late mortality rate.

Clinical Implications

If the benefits of reperfusion occur for reasons beyond the traditional model of acute myocardial salvage, the implications for current treatment and development of future treatment strategies are profound. Many of the recommendations for current therapy are based on the concept that treatment should be limited to patients in whom infarct is not "complete," although the definition of the term "complete" is not as clear as previously assumed. Development of risk/benefit models based solely on changes in left ventricular function as characterized by ejection fraction would lack a significant component reflecting other effects of an open infarct-related artery. A broader spectrum of patients would need to be treated and more effective methods of achieving and sustaining myocardial salvage would be needed so that the 10% to 25% of patients currently discharged from the hospital with a closed infarct-related artery despite thrombolytic therapy would not be deprived of the benefits of persistent perfusion. Better definition of other factors relating to scar formation and the potential for an arrhythmogenic substrate is needed.

An important patient group in which these concepts can be explored comes to medical attention after the infarct is "complete" by the traditional definition of symptom onset >6 hours, Q wave formation and resolution of symptoms. If reperfusion in these patients results in better outcome, then the contribution of other factors can be examined in the absence of the confounding effect of myocardial salvage. Confirmation of a benefit might lead to a multifaceted approach to the treatment of acute myocardial infarction that would seek to obtain early perfusion for myocardial tissue salvage and persistent reperfusion together with careful control of the hemodynamic state to achieve myocardial shape salvage and a favorable electrophysiologic substrate.

Conclusion

The concept of acute reperfusion in evolving myocardial infarction has motivated an exciting era of investigation with demonstrable success in the clinical arena. The initial results of this therapeutic approach have fulfilled its promise and further advances in management are forthcoming. An improved understanding of the complexity of the effects of reperfusion therapy has unveiled the potential for further benefits aside from salvage of ischemic myocardium. These findings provide an exciting challenge to reach the goal of increased patient salvage in addition to myocardial salvage.

References


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