Timing of Coronary Recanalization
Paradigms, Paradoxes, and Pertinence

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Benefit conferred by recanalization of a culprit infarct-related artery in patients with evolving myocardial infarction is incontrovertible.1-3 Nevertheless, the extent to which benefit depends on the interval between coronary occlusion and recanalization remains controversial. Disparate interpretations of available data can be readily reconciled, however, by a unifying concept encompassing the value of restoring infarct artery patency at specific intervals after the onset of an index infarct.

Importance of Early Recanalization

In hearts of experimental animals, irreversible myocardial injury occurs when perfusion is interrupted completely for intervals as brief as 20–60 minutes.4,5 The failure of reperfusion to salvage irreversibly injured tissue has been documented rigorously. For example, Reimer et al4 ligated coronary arteries in dogs for selected intervals and assessed necrosis morphologically. In contrast to the 55% of ischemic myocardium that remained viable when reperfusion was implemented after 40 minutes, less than 17% remained viable when reperfusion was implemented only after 6 hours (Figure 1). Similarly, in dogs with experimentally induced thrombotic coronary artery occlusion and subsequent thrombolysis induced with streptokinase, reperfusion within 2 hours salvaged approximately 50% of jeopardized myocardium as judged from positron emission tomograms.5 In contrast, late reperfusion (implemented after 6 hours) resulted in no significant salvage (Figure 2).

Despite the consistency of these results, extrapolation to human hearts is neither straightforward nor necessarily justified. In patients, the impact of thrombotic occlusion will be conditioned by the severity and extent of underlying atherosclerotic coronary artery disease and variable contributions of collateral flow to protection of myocardium.6 In addition, some favorable consequences of reperfusion may depend on mechanisms independent of salvage of jeopardized myocardium, as discussed below. Nevertheless, results of several controlled clinical trials of thrombolysis underscore the primacy of early restoration of patency as a major determinant of improved survival.7-9

In the Gruppo Italiano per lo Studio dello Streptochinasi nell-Infarto Miocardico (GISSI-I) trial of intravenous streptokinase compared with the then conventional treatment of myocardial infarction without fibrinolytic drugs, the most striking drug-dependent reduction in mortality (47%) was demonstrable in patients treated within 1 hour after the onset of symptoms.7 No significant reduction of mortality was evident in patients treated more than 6 hours after the onset of symptoms (Figure 3). A similar result was observed in the European Cooperative Study Group trial of intravenous tissue-type plasminogen activator (t-PA) compared with placebo.8 Overall reduction of 3-month mortality was 36%. However, among patients treated within 3 hours of the onset of symptoms, it was 59%. Similarly, in the International Study of Infarct Survival (ISIS-2) trial of intravenous streptokinase and/or aspirin compared with placebo, the most striking reduction of mortality was evident in those patients treated early. Thus, treatment with both aspirin and streptokinase led to overall reduction in 35-day mortality of 39%. The reduction was 56% in patients treated within the first hour after the onset of symptoms.

The concept that early reperfusion is critical in maximizing benefit in patients with evolving myocardial infarction, supported by these results, has influenced clinical practice. Recognition of the importance of diminution of the interval between the onset of ischemia and the onset of reperfusion has led to the adoption of intravenous rather than intracoronary administration of activators of fibrinolysis, the institution of treatment in emergency rooms and even in ambulances rather than exclusively in coronary care units, and the development and evaluation of novel dose regimens designed to maximize early recanalization.10-14

Possible Value of Late Recanalization in the Absence of Early Reperfusion

Some have suggested that prognosis improves with restoration of infarct artery patency regardless of when the patency is induced,15,16 even though it is not possible to exclude preceding intermittent recanalization in some or all of those who benefit. Retrospective analysis of outcome among patients who have not been treated with fibrinolytic agents has demonstrated a correlation between infarct artery patency documented angiographically relatively late after the index infarct and survival.17 Furthermore, a review of 776 patients studied...
in the first five Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trials showed that patients subjected to successful rescue angioplasty 90 minutes after failed initial treatment with fibrinolytic drugs, i.e., in whom recanalization was induced relatively (90 minutes or more) late after the onset of treatment, had a prognosis comparable to that in patients in whom thrombolysis had been initially successful. Although the incidence of reocclusion was lower and resting ejection fraction values were higher in patients who had responded initially to pharmacological thrombolysis, in-hospital mortality was not significantly better (5.9% for patients who required angioplasty compared with 4.6% for those who did not). After an average follow-up interval of 20 months, mortality among patients who had been discharged alive was 3% after angioplasty compared with 2% after thrombolysis alone. However, even though reperfusion was induced within a conventionally accepted therapeutic window of 6 hours in patients treated successfully, it was induced relatively late within the interval (>4.5 hours after the apparent onset of infarction) in terms of the maximal potential time-dependent benefit that could be anticipated, as discussed below. Thus, benefit might not have been optimal.

Judging from a meta-analysis of 33 relatively small, randomized trials of intravenous streptokinase or urokinase and of intracoronary streptokinase, Yusuf et al concluded that a significant reduction of mortality (22%) was demonstrable whether patients were treated within 12–24 hours compared with 6 hours after the onset of symptoms. Based in part on this report, the enrollment criteria for patients in the ISIS-2 study included pain within 24 hours (there was no requirement for a qualifying electrocardiogram). Among those patients presenting with symptoms of more than 5 hours’ duration, a reduction of mortality from 11.8% to 10% (17% reduction) was seen after streptokinase compared with placebo, and a reduction from 12% to 9.7% (21% reduction) was seen after aspirin. One cannot exclude the possibility, however, that the reduction in mortality in patients treated late with streptokinase or in patients treated with aspirin alone at any time after the onset of symptoms may have reflected prevention in patients in whom bona fide infarction was not yet evolving. This interpretation would explain the apparently equal efficacy of aspirin and streptokinase and the additive benefit with both.

One phenomenon touted as antithetical to the primacy of early patency as a determinant of efficacy of coronary thrombolysis is the marked reduction of mortality seen in some studies despite only a modest improvement in left ventricular function after thrombolytic drugs. In the Western Washington Study of intracoronary streptokinase, 12-month survival was significantly improved in patients in whom patency was demonstrable angiographically at the time of the index infarction. However, the lower mortality was not accompanied by a higher average ejection fraction in survivors who had a patent infarct-related artery. A similar dichotomy has been seen in other trials as well. In some, the reduction of mortality has been disproportional to improvement in left ventricular function.

Several factors may contribute to this paradox. Apparent improvement in global left ventricular function is dependent not only on the status of the jeopardized myocardium and its response to treatment but also on the compensatory augmentation of function of the noninfarct region, loading conditions, the intensity of neurohumoral simulation, diastolic compliance, and the timing of the assessment of function. Because evaluations of left
ventricular function cannot be performed in nonsurvivors and because survivors who would have died without treatment with a thrombolytic drug are likely to be those patients with the most markedly impaired ventricular function accompanying extensive infarction, average ejection fraction values are likely to be diminished in treatment compared with control groups.21

Several mechanisms have been postulated to account for putative beneficial effects of late reperfusion in the absence of salvage of substantial amounts of myocardium, including improved healing and remodeling of the infarct region, reduction of the incidence or severity of ventricular aneurysms, reduced late left ventricular dilatation and hence reduced wall stress, improved electro-physiological stability, enhanced development of collateral channels limiting subsequent ischemia or infarction in territories supplied by initially nonculprit vessels.15,16 In concert, these mechanisms are implied by the conventionally defined “open artery hypothesis,” which holds that a patent infarct-related artery enhances survival even when patency is restored only late after onset of myocardial infarction. Nevertheless, the benefit may depend wholly or in part on occult, early, transient or sustained, spontaneous recanalization that is undetected because of unavoidable limitation of study design.

Ambiguity of the Dependence of Benefits of Late Recanalization on Reperfusion in the Absence of Previous Occult Recanalization

Unfortunately, it is impossible to ascertain whether benefit does occur under conditions in which only late recanalization is induced. Patients exhibiting late infarct artery patency, with or without antecedent administration of an activator of the fibrinolytic system or angioplasty, may have manifested undetectable or undocumented intermittent recanalization in the course of evolving infarction analogous to the cyclic flow variation seen typically with thrombotic coronary occlusion in experimental animals.24 Intermittent, early reperfusion may, of course, protect or salvage myocardium. Consistent with this possibility are the results from a recent review of data from the TAMI studies by Ohman et al25 in which 810 patients presenting with acute myocardial infarction had been treated with t-PA, urokinase, and/or angioplasty. In-hospital mortality was 11.0% among those patients in whom the infarct-related artery was shown to be patent after 90 minutes but in whom reocclusion occurred before the performance of the 7-day follow-up angiogram. Among the patients in whom reocclusion occurred after initial recanalization, 44% underwent successful angioplasty or bypass surgery. Mortality in this group was significantly higher than that in patients in whom initially induced, early patency had been sustained (4.5% mortality). Nevertheless, the overall 11% mortality was considerably lower than that in patients in whom patency of the infarct-related artery was not demonstrable after either 90 minutes or 7 days (17.2% mortality). Accordingly, it appears that the fate of patients in whom only late reperfusion can be observed is parallel to that in patients with early reperfusion, reocclusion, and subsequent late reperfusion. A likely explanation is that early, transient, occult restitution of perfusion occurred in some patients with only late reperfusion despite the impossibility of its documentation. Thus, benefits assumed to accompany exclusively late reperfusion may reflect salvage of myocardium in some patients with late patency in whom early, unrecognized, intermittent reperfusion or collateral flow into the infarct zone has been present as well. Benefit in such patients could account for the overall increase in survival associated with documented late patency.

Unfortunately, definitive evaluation of the hypothesis that isolated late reperfusion is beneficial is virtually impossible. It would be neither ethical nor feasible to demonstrate persistent occlusion of an infarct-related artery by observation for as long as 24 hours and to restore blood flow only then, in a random assignment fashion, to define the impact of late reperfusion, per se, on long-term outcome.

A Unifying Hypothesis

Results that have supported the conventionally defined open artery hypothesis are not, in fact, contrary to the concept that early restitution of coronary blood flow is the prime determinant of benefit in patients treated with thrombolytic drugs for evolving myocardial infarction. In fact, the conventionally defined open artery hypothesis comprises two implicit and non–mutually exclusive components that are readily distinguishable as illustrated in Table 1. One component attributes benefit to treatment (or spontaneous recanalization) sufficient to induce significant myocardial salvage by either early and sustained recanalization or by later recanalization of an infarct-related artery that had manifested intermittent, occult patency earlier. We shall refer to this as the time-dependent open artery hypothesis component. A second component attributes benefit to late recanalization under conditions in which intermittent, early, spontaneous or drug-induced recanalization is unequivocally absent. Although limited myocardial salvage occurring with late reperfusion26,27 is not excluded by this component, its thrust is that benefit is not contingent upon salvage of myocardium per se nor necessarily reflected by improved left ventricular systolic function: We shall refer to it as the time-independent component.

Implications

Integration of these two complementary components appears to clarify interpretation of results of clinical trials and the nature of appropriate expectations regarding impact of treatment on individual patients. The curve in Figure 4 is a composite of results from laboratory studies shown in Figures 1 and 2 and results from the clinical study shown in Figure 3. Despite the purposeful admixture of results with diverse end points, conditions, and species, the composite depicts a nonlinear, time-dependent relation between the extent of benefit and the interval preceding reperfusion. The conformity of the data to a smooth curve is striking and suggests that the benefit reflected by reduction of mortality with very early reperfusion is indeed attributable to myocardial salvage. The shading in the figure represents the hypothetical magnitude of benefit implied by the time-independent component of the open artery hypothesis alone. The overall curve plus the shaded region represents the net benefit implied by both components implicit in the open artery hypothesis.
Consideration of Figure 4 suggests that the importance of immediate induction of treatment varies inversely with the duration of the interval after the onset of ischemia. As judged from the curve, a patient presenting within 2 hours after the onset of symptoms is likely to have the most to gain from prompt restoration of blood flow to jeopardized myocardium. Because of the nature of the steep portion of the curve, minimization of treatment delay is likely to be most crucial in such a patient. As indicated by the curve, both the potential for benefit and the attenuation of benefit by even brief delay are marked.

Conversely, consideration of the curve suggests that a patient presenting as late as 6 hours after the onset of symptoms may benefit from recanalization. Benefit may be dependent on late recanalization alone and attendant mechanisms for which it has been thought to be responsible or late reperfusion in hearts of some patients in whom occult early, transient or sustained, spontaneous recanalization has occurred but not been detected. Regardless, the magnitude of benefit associated with induction of late recanalization is likely to be modest. Furthermore, a given amount of additional delay is likely to be much less deleterious than it would be in a patient presenting early, as judged from the modest slope of the curve depicting events after the first few hours. Because the rapidity of initiation of treatment is less crucial in a patient presenting late, more methodical evaluation may be appropriate, including echocardiographic or angiographic assessment before initiation of treatment. The decision to proceed with attempts at revascularization by any means (thrombolysis, angioplasty, or surgery) in an individual patient seen with acute myocardial infarction only after 6 hours or more, is, unfortunately, ultimately a subjective one on the part of the physician. It should be based on the best estimate that can be made of the amount of viable myocardium that is in continuing jeopardy and the risk of the procedure contemplated.

Assuming that the risk inherent in the use of thrombolytic agents is of constant magnitude over the first 6 hours, the benefit/risk ratio is obviously greatest for patients who can be treated very early. For those presenting later, relative contraindications may carry more weight. Although the composite curve we have constructed permits generalizations, it cannot define the benefit/risk ratio a priori for an individual patient. The pertinent hypothetical curve applying to a given patient may be shifted upward and to the right if good collateral flow is present in jeopardized tissue or if myocardial oxygen demand has been limited by treatment with agents such as β-adrenergic blockers. It may be shifted to the left if tachycardia, systemic hypertension, increased wall stress, or other factors have increased myocardial oxygen demand or limited oxygen supply.

Despite these caveats, Figure 4 is applicable to subsets of patients in whom infarct artery recanalization occurs at specific intervals after the onset of infarction and to interpretation of results from trials comparing different treatment regimens. The figure suggests that the advantage of prompt recanalization of an infarct-related artery with a specific therapeutic regimen will be
most obvious in patients who can be treated very early and that when patency can be maintained, a significant improvement in survival can be anticipated with regimens that restore flow most rapidly. However, differences between regimens conferring rapid compared with less rapid recanalization are likely to be modest for patients who can be treated only late.

Conclusions

The two non–mutually exclusive, complementary components of the open artery hypothesis that we have delineated are implicit. Recanalization is most beneficial when it can be induced very early after the onset of ischemia. The importance of the rapidity of initiation of treatment is itself time dependent, in a nonlinear fashion. Patients presenting early have the most to gain by early treatment and by rapid induction of patency. Patients presenting late have less to gain from recanalization per se and less to lose from additional delay such as that accompanying slower induction of recanalization.

The inferences delineated here are consistent with results from previously published meta-analyses. They are consistent also with the established higher relative impact of early as opposed to late recanalization on survival. The potential value of late reperfusion in some patients, regardless of its mechanism of benefit, should not be ignored. However, inappropriate therapeutic strategies can result if the impact on survival of very early reperfusion is underestimated or if clinical implications of an open vessel are not considered in the context of the time of induction of recanalization.

References

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