The Quest for the Ideal Reperfusion Strategy Continues

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Reperfusion therapy of evolving myocardial infarction has significantly improved its short- and long-term prognosis and is now the cornerstone of myocardial infarction management. Despite the remarkable progress, major deficiencies remain. First, a significant proportion of infarct arteries are not opened by thrombolytic therapy. Second, the time needed to open the infarct artery, 40–50 minutes, is too long; during that period considerable amounts of viable myocardium are lost to necrosis.4

Third, a significant proportion of the opened infarct arteries reocclude.5 Fourth, the opened infarct artery is usually severely stenotic, limiting myocardial blood supply and contributing to reocclusion.5 Fifth, routine angioplasty intended to correct the residual stenosis, whether performed immediately after thrombolytic therapy6 or days later,7 has proven to be hazardous. Sixth, serious bleeding may complicate thrombolytic therapy.1 The risk of serious bleeding prevents physicians from using thrombolytic agents in their most effective dosages and from treating a great number of patients with evolving myocardial infarction who could otherwise benefit from thrombolytic therapy. Seventh, reperfusion therapy is in general initiated with too much delay and is, therefore, less effective than it could be in reducing mortality and morbidity.6,9

Perspectives

Research to increase the efficacy and safety of reperfusion therapy is conducted along several lines:

1) Currently available plasminogen activators are optimized in terms of dosage and mode of administration.10

2) Plasminogen activators with complementary11 or synergistic12 properties are combined.

3) The molecular structure of plasminogen activators is modified (mutants)13 or portions of molecules of two activators are combined (chimers).14

4) The affinity of plasminogen activators for thrombi is increased by linking activators to fibrin-specific antibodies.15

5) Antiplatelet agents16 capable of disaggregating the platelet component of thrombi are added to plasminogen activators.

6) Selective inhibitors of thrombin17 with powerful antiplatelet and anticoagulant effects appear very promising for the prevention of reocclusion and the enhancement of thrombolysis.

7) Methods to lyse occlusive thrombi without lysing hemostatic plugs and other ways of preventing major bleeds are being explored.18

8) The feasibility of initiating thrombolytic therapy safely at the patient’s home or during transportation to a medical center is being investigated.19

The Present Study

The hypothesis of the study by Califf et al20 in this issue of Circulation is that reperfusion therapy and its clinical impact can be improved 1) by using a combination of tissue-type plasminogen activator (t-PA) and urokinase for thrombolytic therapy and 2) by using rescue angioplasty to open infarct arteries that had failed to open in response to thrombolytic therapy.

Combination Thrombolytic Therapy

Califf et al20 found that at the first diagnostic angiogram the infarct artery patency was highest after combination therapy; however, at the last diagnostic angiogram the patency rates following t-PA, urokinase, or combination therapy became more similar. It is not clear to what extent the trend toward equalization was due to continued lysis or to the mechanical effect of repeat injections. Because in clinical practice patients receiving thrombolytic therapy do not routinely undergo angiography with repeat intracoronary injections of contrast, it cannot be ruled out that in practice the difference between the effects of combination therapy and monotherapy would be more pronounced. It is also possible that the difference between the effects of combination therapy and the effects of the monotherapies would have been greater in this study had angiography been limited to a single injection. The higher initial patency rate following combination therapy may have been the result of the higher first-hour dose of t-PA.
alone, the greater cumulative fibrinolytic potency, or the cumulative systemic lytic effect of the two activators. Studies using intracoronary streptokinase or t-PA suggest that the lysis of occlusive thrombi is enhanced by progressive depletion of fibrinogen and by rising levels of fibrinogen degradation products. Collen et al observed a significantly greater breakdown of fibrinogen after t-PA administration in patients with successful recanalization, whereas in patients with persistent occlusion of the infract artery, the same time they found no correlation between the plasma concentration of t-PA and recanalization. In a study by Califf et al using t-PA, the nadir fibrinogen values were lower and the peak fibrinogen degradation product levels were higher in patients in whom the infract artery was patent at the 90-minute angiography.

Another beneficial effect of the combination therapy was the reduction in the rate of reocclusion; it was the lowest after combination therapy and the highest after t-PA administration. Califf et al attributed the lower reocclusion rate to the larger residual lumen, due to more complete lysis of the occlusive clot, and to the cumulative systemic lytic effect of urokinase and the larger first-hour dose of t-PA. The systemic lytic effect leads to a reduction of blood viscosity by depleting fibrinogen and exerts a strong anticoagulant and antiplatelet influence by releasing fibrinogen degradation products.

The recognition that a systemic lytic state enhances thrombolysis and prevents rethrombosis requires revision of our prior belief that a systemic lytic effect is a generally undesirable event.

**Rescue Angioplasty**

The second major objective of the study was to assess the potential role of rescue angioplasty after unsuccessful thrombolysis. In the study, angiography was performed in all patients of the aggressive strategy group to identify, in the absence of acceptable indicators of reperfusion, those patients whose infract artery had failed to open after thrombolytic therapy. At angiography the infract artery was found to be occluded in 69 of the 287 patients studied; two patients were sent directly to emergency coronary bypass surgery and 15 were treated conservatively because of unsuitable anatomy or a small area at risk. Sustained infract artery patency was established in 37 (71%) of the 52 patients in whom rescue angioplasty was attempted, or in 55% of the 67 patients in whom it was either attempted or considered. The overall 55% patency rate is only slightly higher than patency rates resulting from spontaneous reperfusion. Spontaneous reperfusion of the initially totally occluded infract artery was observed by Verheught et al in 48% and by Rentrop et al in 45% of patients at the follow-up angiograms performed 6 and 2 weeks, respectively, later. In both studies patients were receiving heparin until the time of the follow-up angiography.

The median time delay from the onset of symptoms to rescue angioplasty in the study by Califf et al was 331 minutes, the longest delay being 606 minutes. Clearly, in many of the patients the angioplasty must have been performed too late to achieve significant myocardial salvage. The global left ventricular function was not better in the aggressive than in the conservative strategy group. The function in the infract zone was slightly better, and ischemic events and heart failure tended to be less frequent in the aggressive strategy group. However, the aggressive strategy was associated with a higher mortality rate. Although the difference was not statistically significant in this relatively small population of patients, the excess mortality associated with the aggressive strategy must be viewed with concern because it was observed in previous trials of acute angioplasty.

Patients with TIMI grade 0 or grade 1 perfusion were considered to be candidates for rescue angioplasty. However, in the Western Washington trial, patients with partial infract artery perfusion, including those with sluggish degrees of TIMI grade 2 perfusion (W.J. Kennedy, personal communication), had the same high 1-year mortality as did patients with complete occlusion of the infract artery. It seems, therefore, justifiable to consider in the future those patients with sluggish degrees of TIMI grade 2 perfusion (for instance, those requiring 10 or more cycles for clearing of contrast) to be candidates for rescue angioplasty.

As already discussed, in the study by Califf et al, recanalization by rescue angioplasty was probably performed too late to result in significant myocardial salvage in many if not most patients. In light of the morbidity, and possibly mortality as well, associated with the aggressive strategy and in view of the high rate of spontaneous reperfusion, it would seem preferable to limit the performance of rescue angioplasty to within 4 hours after onset of symptoms or to unstable patients whose life is in imminent danger (for instance, patients in cardiogenic shock). Stable patients should receive heparin for several days to enhance endogenous thrombolysis and spontaneous reperfusion.

**Angioplasty for Recurrent Ischemia**

In the study by Califf et al as well as in numerous previous studies, urgent angiography was considered to be indicated in patients with recurrent chest pain and ST segment and T wave changes not relieved by standard nitrate therapy. Recurrence of ischemia not responsive to nitroglycerin almost certainly indicates reocclusion by thrombosis. In my experience and in that of others, such episodes usually respond promptly to a repeat course of thrombolytic therapy. Urgent angiography may not be necessary and is not feasible in the great majority of medical centers. Moreover, there is no evidence that the aggressive approach is preferable.
Conclusion

Califf et al\(^2\) have demonstrated that the combination of t-PA and urokinase, as used in their study, is superior to either t-PA or urokinase applied alone in preventing rethrombosis of the infarct artery and its clinical consequences. There is also suggestive evidence that the combination therapy is more effective in opening infarct arteries. However, the case for routine performance of rescue angioplasty is less convincing.

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Circulation. 1991;83:1818-1821
doi: 10.1161/01.CIR.83.5.1818

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/83/5/1818.citation

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