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Angioplasty or thrombolysis in acute myocardial infarction: dilate or dissolve?

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For a patient with an acute myocardial infarction, seconds count: the sooner perfusion can be restored, the better the patient's chance for survival. Although thrombolysis has become the standard of care, there are theoretic and practical reasons why immediate angioplasty may be better. In this Cardiology Dialogue, Dr. Bernard J. Gersh, who is the W. Proctor Harvey Teaching Professor of Cardiology, Chief of the Division of Cardiology, and Professor of Medicine at Georgetown University Medical Center, presents the case for thrombolysis; Dr. Eric J. Topol, Chairman of Cardiology, The Cleveland Clinic Foundation, defends primary angioplasty.

THE CASE FOR THROMBOLYSIS

DR. GERSH: Primary angioplasty is the treatment of choice for patients in cardiogenic shock or who have pulmonary edema, contraindications to thrombolysis, or an equivocal electrocardiogram with angiographic evidence of thrombosis. However, thrombolysis, given promptly and efficiently, is unquestionably superior for the routine treatment of acute myocardial infarction. I base this on a number of studies, most notably the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial.[1] It would be difficult to improve upon a mortality rate of only approximately 6% in acute infarction.

The lesson from the Myocardial Infarction, Triage, and Intervention (MITI) registry is that the sooner the patients are treated, the lower the mortality rate. Weaver and colleagues[2] found that patients treated with thrombolysis within 70 minutes had a mortality rate of approximately 1%, and those treated between 70 minutes and 180 minutes had a mortality rate of approximately 3%. In GUSTO, those treated with tissue plasminogen activator (t-PA) within 2 hours had a mortality rate of 4.3%.[1]

Further, thrombolytic agents will continue to improve. Whereas patency at 90 minutes is the current benchmark, new agents will establish reperfusion within 30 minutes. Angioplasty will also get better from a technical standpoint, but it will not get faster: a certain amount of delay is unavoidable.

Is thrombolysis actually better than angioplasty? The randomized trials show no difference in survival between the two therapies, but an average of 210 minutes elapsed between the onset of symptoms and

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This series is based on the Cleveland Clinic Heart Center's "Controversies in Cardiology" conferences, at which a visiting clinician-professor and a Cleveland Clinic Heart Center clinician give contrasting perspectives on the application of a current technology or the management of a cardiologic disease.

the initiation of thrombolysis or angioplasty. After that much time it may not matter which therapy is given. This is why I think the third International Study of Infarction Survival (ISIS-3)[3] and the *Gruppo Italianao per lo Studio della Sopravvivenza nell'Infarto Miocardico* (GISSI-2)[4] never showed a difference between t-PA and streptokinase, and why GUSTO was so successful.[1,5] In the Mayo Clinic randomized trial, which compared intravenous t-PA with primary angioplasty, the primary end point was myocardial salvage. This was identical between the two groups, treated on an average approximately 3.5 hours after the onset of symptoms, which is consistent with routine clinical practice.[6]

In the Dutch trial,[7] the Brazilian trial,[8] and the Primary Angioplasty in Myocardial Infarction (PAMI) trial,[9] in patients with inferior or anterior infarcts, primary angioplasty resulted in a lower mortality rate, a lower incidence of stroke, and a lower incidence of recurrent ischemia. However, the PAMI results were troubling: the rates of death and myocardial infarction in thrombolysis-treated patients were much too high, beyond the 95% confidence level in the large, multicenter Thrombolysis in Myocardial Infarction (TIMI) trial.[10] The incidence of stroke with thrombolytic therapy in the PAMI trial was approximately 2%, which also seems high. The stroke rate with angioplasty in their trial was 0%. These results were probably due to small numbers: patients who underwent thrombolysis did very badly and patients who underwent angioplasty did unrealistically well.

Primary angioplasty patients in these trials tended to incur lower in-hospital costs than thrombolysis patients, but the trend did not achieve statistical significance. Critics point out that costs are higher for thrombolysis-treated patients because many of them need to undergo angiography. Tissue-plasminogen activator is also expensive. However, the crucial issue is the cost of establishing cardiac catheterization units in thousands of hospitals across the country that do not have them now.

The investigators in the PAMI trial,[9] our trial,[6] and others[8] had enormous experience with elective angioplasty. This will not be the case in most community hospitals that do not perform many angioplasties. Primary angioplasty will never be feasible for most patients.

What treatment would you want if you had an infarct? If it were midday and the catheterization lab were open, primary angioplasty might be preferable. However, in the middle of the night, a patient may have to wait for angioplasty, whereas thrombolytic therapy could be started almost immediately. Making a patient wait for angioplasty would be unethical.

Finally, as demonstrated by Weaver and colleagues,[2] when angioplasty works it works well, but when it does not, it may harm the patient. Angioplasty triggers catecholamine release and hemodynamic changes. Of patients with blood pressure greater than 100 mm Hg and a heart rate less than 100, nearly 20% died if primary angioplasty failed, and every study shows this trend. One could argue that the mortality rate was high because these patients were sicker to begin with, and this may be true. Nonetheless, I worry about it.

DR. TOPOL: Let me cite some pathophysiologic arguments for thrombolysis that you did not mention. A patient with an acute myocardial infarction already has a ruptured and fissured plaque, platelet aggregation, a fibrin clot, and an occluded artery. Angioplasty recreates the crime: it dilates the vessel, ruptures the plaque some more, creates new fissures, and perhaps makes it worse. It is surprising that angioplasty works so well.

DR. GERSH: Do you think there is a difference between primary angioplasty and angioplasty after thrombolytic therapy?

DR. TOPOL: That is an important point. The prothrombotic effects of thrombolysis have been underestimated. Thrombolysis releases soluble thrombin, leading to a further aggregation of platelets and the procoagulant response. Certain patients have a refractory thrombosis syndrome that angioplasty makes worse. Fortunately, this vicious cycle does not happen often. These patients eventually need thrombolytic therapy after the angioplasty, but several randomized trials combining thrombolytics and angioplasty have indicated that this is not a good mix.

It may have been premature to pronounce primary angioplasty the treatment of choice. Fewer than 1000 patients have been involved in randomized trials of angioplasty. In contrast, nearly 200 000 patients have been involved in thrombolytic trials over the last decade. The confidence intervals with angioplasty have been wide because the numbers have been small.

There is another financial side to this. Cardiologists do not get paid to give thrombolytic therapy, but they are paid well to perform a primary angioplasty. How well a procedure helps pay the bills

could have an effect on how it is embraced.

A final point is the comparative standard of thrombolytic therapy. All the trials to date have used conventional dosages of t-PA or streptokinase, not accelerated t-PA, which is clearly superior.

IN DEFENSE OF ANGIOPLASTY

DR. TOPOL: Although I had viewed primary angioplasty somewhat negatively in light of these points, I changed my mind when we realized how critical it is to establish complete blood flow (grade 3 by the criteria of the TIMI trial). In the GUSTO trial, 2400 patients underwent angiography, 1200 of them at 90 minutes.[11] Patients who had TIMI grade 3 flow at 90 minutes had a mortality rate of only 4.3%, patients who had TIMI grade 2 flow had 7.9% mortality, and patients with TIMI grade 1 flow had 9.2% mortality. Grades 2 and 3 used to be lumped together, and statements that thrombolysis produces 85% patency included TIMI grades 2 and 3 together.[12]

One can actually predict the mortality rate with different strategies by how well these strategies open the blocked coronary artery. In GUSTO, the predicted mortality rate with accelerated t-PA was 6.27%, and the actual mortality rate was 6.31%. Similarly, the predicted mortality rate with t-PA plus streptokinase was 6.97%; the actual rate was 6.96%. The predicted rate with streptokinase and intravenous heparin was 7.25%; the actual rate was 7.36%. With subcutaneous heparin the predicted rate was 7.28; the actual rate was 7.44%. The *r* value was .93.[1]

Approximately 85% to 90% of patients who undergo angioplasty achieve TIMI grade 3 flow; with the best thrombolytic strategy today (as documented in GUSTO), only 54% do so.[11] Assuming the same model applies as with thrombolysis, the predicted mortality rate with angioplasty would be approximately 4.5%. The mortality rate in the collective meta-analysis was 2.6%, but I suspect the real rate may be approximately 5% when large enough populations are prospectively studied.

GUSTO-2

This unsettled issue needs further study. The ongoing 12 000-patient GUSTO-2 trial employs a 2 × 2 factorial design and a core angiographic laboratory and should provide some definitive answers. We intend to randomize 1200 patients with myocardial infarction and ST-segment elevation to treatment with either primary angioplasty or accelerated t-PA

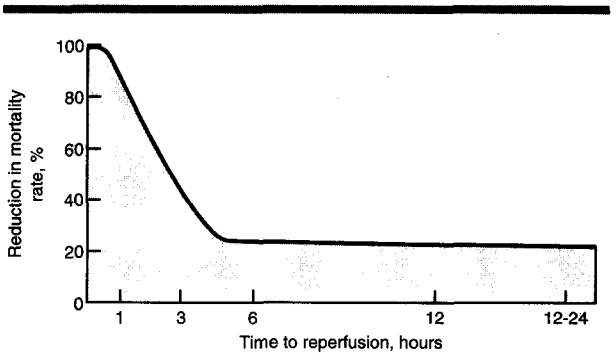

FIGURE. Hypothetical relation between the reduction in the mortality rate and the time to reperfusion after a myocardial infarction. The extent of salvage may also be a function of the time to reperfusion. The reduction in the mortality rate within the first 1 to 2 hours is primarily due to myocardial salvage. Later, reperfusion results in lesser salvage, although the mortality rate is still reduced. Adapted from Gersh and Anderson, reference 2.

therapy and to 3 days of treatment with either recombinant hirudin or heparin.

The TIMI-5 trial[13] demonstrated the advantage of hirudin over heparin for increasing TIMI grade 3 patency at 90 minutes. Approximately 60% of patients achieved TIMI grade 3, compared with 54% in GUSTO.

DR. GERSH: Angioplasty can produce an intramural hematoma or dissection. Does hirudin make that worse, or does it reduce the thrombus on top of the plaque? Angioplasty after thrombolysis can cause an intramural dissection that travels down the length of the artery.

DR. TOPOL: The importance of the operator's skill in performing the angioplasty cannot be understated. The sites participating in GUSTO-2 are experienced and have a high volume. Interestingly, although we think of angioplasty as a US strategy, many sites in Europe, the United Kingdom, Australia, and Canada are participating.

DR. GERSH: I also want to see this important trial done, for all the reasons you mentioned. Nevertheless, I remain convinced that primary angioplasty will never be the *routine* therapy of choice in this country. We cannot afford it. Should it be the routine treatment of choice in major hospitals and tertiary care centers? Perhaps.

Here are my caveats. The earlier and more completely one opens the artery, the more myocardium one will salvage (*Figure*). The window of opportu-

nity is fairly small, and after 3 or 4 hours, it does not matter whether you get TIMI grade 3 flow. That is why the amount of salvage was identical in our trial when angioplasty or t-PA (not accelerated t-PA) was started 220 minutes or more after the onset of symptoms.[6] The crux is to shorten the time to the administration of a lytic agent.

DR. TOPOL: I agree. In GUSTO, after 180 minutes, the patency profile had absolutely no correlation with survival. But one cannot ignore the data for primary angioplasty: a collective mortality rate of 2.6%, for all age trials.

DR. GERSH: I concede that point. As I look at the primary angioplasty data, I have to admit that despite all the caveats, the mortality rate is low. I also have to accept that recent data from the Dutch trial does suggest that reperfusion by primary angioplasty may be superior to reperfusion with intravenous streptokinase, providing the time differences between the two treatments are small. In that study, primary angioplasty did result in smaller enzymatically determined infarct size and better preserved myocardial function compared with patients treated with intravenous streptokinase.[7]

DR. TOPOL: Primary angioplasty also provides a quick view of the coronary anatomy. This identifies patients at very high risk. In the PAMI trial and other trials,[9] approximately 10% of patients never had angioplasty—some were sent directly for emergency bypass surgery. On the other hand, some patients have relatively normal coronary arteries and can be spared the risk of a thrombolytic agent.

DR. GERSH: That is a valid point. I would caution though that some physicians may perform angioplasty too aggressively and try to dilate all the lesions. There is no justification for that; in fact, it is contraindicated. The abiding principle is to dilate only the "culprit" artery. I would also hope that physicians would keep in mind the time factor and realize that after 3 hours, they should just do what is cheaper and easier.

AUDIENCE: Should paramedics begin thrombolytic therapy before the patient even enters the hospital?

DR. GERSH: Yes. In the MITI registry there was no advantage to doing this, but their door-to-needle time in the emergency room was extremely fast. Hospitals should examine their waiting time: every month one comes across a patient who has sat around for an hour or two.

DR. TOPOL: In one trial of 6000 patients, prehospital therapy reduced the time from the onset of symptoms to the start of therapy by 65 minutes and reduced mortality by 13%. Regression analysis of GUSTO data showed similar results: starting treatment 1 hour earlier reduced the mortality rate by approximately 14%.

DR. GERSH: Patients who live close to the hospital may not need it. But in a trial in a remote area of Scotland, where it took an average of 2 hours to reach the hospital, domiciliary therapy halved the mortality rate.[14] Even before thrombolytic agents were available, in a series in Belfast, Northern Ireland by Partridge and colleagues in the 1970s, prehospital treatment with beta blockers and atropine produced dramatic results. The bottom line is whatever you do, time is of the essence. It may well be that primary angioplasty is superior to thrombolytic therapy in achieving TIMI grade 3 flow, and in ideal circumstances in which there is no time difference between the two forms of treatment, the results of primary angioplasty may be expected to be better. Nonetheless, in most cases, the delays before receiving primary angioplasty are relatively unavoidable, which will tilt the balance in favor of thrombolytic therapy, particularly if this can be given expeditiously and if newer drugs result in higher and more rapid rates of reperfusion with TIMI grade 3 flow. One should never forget that the therapeutic window for salvage is narrow, and during this time frame, delays in initiating treatment translate directly into loss of muscle.

REFERENCES

1. **The GUSTO Investigators.** An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993; **329:**673–682.
2. **Weaver WD, Cerqueira M, Hallstrom AP, et al.** Prehospital-initiated vs hospital-initiated thrombolytic therapy. The Myocardial Infarction Triage and Interventional Pre-Hospital Trial. JAMA 1993; **270:**1211–1216.
3. **ISIS-3 (Third International Study of Infarct Survival) Collaborative Group.** ISIS-3: a randomised comparison of streptokinase vs tissue plasminogen activator vs anistreplase and of aspirin plus heparin vs aspirin alone among 41,299 cases of suspected acute myocardial infarction. Lancet 1993; **339:**753–770.
4. ***Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico.*** GISSI-2: a factorial randomised trial of alteplase versus streptokinase and heparin versus no heparin among 12,490 patients with acute myocardial infarction. Lancet 1990; **336:**65–71.
5. **Gersh BJ, Anderson JL.** Thrombolysis and myocardial salvage. Results of clinical trials and the animal paradigm—paradoxic or predictable? Circulation 1993; **88:**296–306.

6. **Gibbons RJ, Holmes DR, Reeder S, Bailey KR, Hopfenspirger MR, Gersh BJ.** Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. The Mayo Coronary Care Unit and Catheterization Laboratory Groups. N Engl J Med 1993; **328:**685–691.
7. **Zijlstra F, De Boer MJ, Hoointje JCA, Reiffers S, Reiber JH, Suryapranata H.** A comparison of immediate coronary angioplasty with intravenous streptokinase and acute myocardial infarction. N Engl J Med 1993; **328:**680–684.
8. **Ribeiro EE, Silva LA, Carneiro R, et al.** A randomized trial of direct PTCA versus intravenous streptokinase in acute myocardial infarction [abstract]. JACC 1991; **17:**152A.
9. **Grines CL, Browne KF, Marco J, et al.** A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. N Engl J Med 1993; **328:**673–679.
10. **Cheseboro JH, Knatterud G, Roberts R, et al.** Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Circulation 1987; **76:**142–154.
11. **The GUSTO Angiographic Investigators.** The effects of tissue plasminogen activator, streptokinase, or both, on coronary-artery patency, ventricular function, and survival, after acute myocardial infarction [published erratum appears in N Engl J Med 1994; **330:**516]. N Engl J Med 1993; **329:**1615–1622.
12. **Karagounis L, Sorensen SG, Menlove RL, Moreno F, Anderson JL.** Does thrombolysis in myocardial infarction (TIMI) perfusion grade 2 represent a mostly patent or a mostly occluded artery? Enzymatic and electrocardiographic evidence from the Team 2 study. Second Multicenter Thrombolysis Trial of Eminase in Acute Myocardial Infarction. JACC 1992; **19:**1–10.
13. **Cannon CP, McCabe CH, Henry TD, et al.** A pilot trial of recombinant desulfatohirudin compared with heparin in conjunction with tissue-type plasminogen activator and aspirin for acute myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 5 trial. JACC 1994; **23:**993–1003.
14. **Rawles J, on behalf of the GREAT Group.** Halving of mortality at 1 year by domiciliary thrombolysis in the Grampion Region Early Anistreplase Trial. JACC 1994; **23:**1–5.