Pump failure, ranging from ventricular dysfunction to acute cardiogenic shock, is now the leading cause of cardiac death. Efforts at temporary mechanical or pharmacologic support of the heart have been largely unsuccessful so that attention is now directed toward prevention of ventricular failure and limitation of myocardial infarct size or even outright prevention of infarction itself. In particular, attention has been refocused on earlier reperfusion efforts with streptokinase.

The effect of thrombolysis in acute myocardial infarction on enzymatic infarct size, left ventricular function and early mortality was studied in subsets of patients in a randomized trial (Netherlands Interuniversity Cardiology Institute). Early thrombolytic therapy with intracoronary streptokinase (152 patients) or with intracoronary streptokinase preceded by intravenous streptokinase (117 patients) was compared with conventional treatment (264 patients). All 533 patients were admitted to the coronary care unit within 4 hours after onset of symptoms indicative of acute myocardial infarction. Of the patients eligible for this detailed analysis, 245 were allocated to thrombolytic therapy and 243 to conventional treatment. Early angiography was performed in 212 of the 245 patients allocated to thrombolytic therapy. Patency of the infarct-related artery was achieved in 181 patients (85%). Enzymatic infarct size, measured from cumulative alpha-hydroxybutyrate dehydrogenase release, was smaller in patients allocated to thrombolytic therapy (median 760 versus 1,179 U/liter in control subjects, p = 0.0001). Left ventricular ejection fraction measured by radionuclide angiography before discharge was higher after thrombolytic therapy (median 50% versus 43% in control subjects, p = 0.0001). Twelve month mortality was lower in patients allocated to thrombolytic therapy (8% versus 16% in the control group, p < 0.01). In multivariate regression analysis infarct size limitation, improvement of left ventricular ejection fraction and 3 month mortality were predicted by IST, time from onset of symptoms to admission and Killip class at admission. Thrombolysis was most useful in patients admitted within 2 hours after onset of symptoms and in patients with a SST segment of 1.2 mV or more. On the other hand, no beneficial effects of streptokinase on enzymatic infarct size, left ventricular function or mortality were observed in the subset of patients with SST less than 1.2 mV, admitted 2 to 4 hours after onset of symptoms. (J Am Coll Cardiol 1987;9:1375–84)
Figure 1. Curvilinear relation between the rest left ventricular (LV) ejection fraction at discharge and 1 year mortality after myocardial infarction. This relation has been found by many authors (69–71). If one could move the immediate postinfarct ejection fraction from, for example, 30 to 45% or from 45 to 60%, the gains in 1 year survival (85 to 95%) appear to be impressive.

Role of Coronary Thrombosis in Myocardial Infarction

The causal role of thrombosis in acute myocardial infarction has long been a matter for debate (6). Although since Herrick’s days it had been assumed that thrombosis was always the cause of an infarction, careful postmortem studies in the 1960s cast doubt on this theory because many patients showed infarction without complete coronary obstruction. Some researchers postulated, therefore, that thrombosis was the sequel of infarction. Such theories, based on postmortem examinations, were corrected through the detailed anatomic studies of Fulton et al. (7), which were corroborated by DeWood et al. (8), whose coronary arteriographic studies in the first few hours after myocardial infarction demonstrated that thrombosis was present in nearly all cases. The latter authors studied 517 patients within 4 hours after onset of symptoms and found a complete obstruction in 86% of cases. These data were confirmed in the recent large trial carried out by the Netherlands Interuniversity Cardiological Institute (9), which indicated complete obstruction in 84% of 264 patients who were randomized to early angiography and intracoronary thrombolysis (Table 1). Similar data were reported by others (10–14).

Recently, Falk (15) identified a ruptured atheromatous plaque as the cause of 40 of 51 recent coronary artery thrombi. This finding points to the significance of a ruptured atherosclerotic plaque in the genesis of sudden coronary artery obstruction, either by hemorrhage into an expanding plaque or by serving as a nidus for intraluminal platelet aggregation. Davies and Thomas (6) found that the same mechanism was operative whether the clinical outcome was unstable angina, myocardial infarction or sudden death.

Relevance to coronary thrombolysis. These observations bring four fundamental concepts into focus: 1) angiography can be carried out in acute myocardial infarction without major risks; 2) thrombosis is present in the majority of patients studied within the first few hours after symptoms; 3) the prevalence of complete obstruction declines as the time after the onset of symptoms lengthens; and 4) residual obstruction in and around the plaque remains a major problem even after successful lysis. Indeed, total obstruction was found in only 60% of cases when the interval after the onset of symptoms exceeded 6 hours, corresponding to the pathologic observations that, on average, complete obstruction was present in only half of the cases studied 6 to 24 hours after the onset of symptoms or death. It is therefore likely that limitation of infarct size by a strategy aimed at relief of obstruction will be successful only in patients who present themselves for therapy within hours after onset of

Table 1. In-Hospital Clinical Course (data from Netherlands study [9])

<table>
<thead>
<tr>
<th>Event</th>
<th>Control Group</th>
<th>Thrombolysis Group</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital mortality (14 days)</td>
<td>26</td>
<td>14</td>
<td>0.05</td>
</tr>
<tr>
<td>Recurrent infarction (14 days)</td>
<td>9</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>55</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Heart failure in coronary care unit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>55</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>12</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Shock</td>
<td>24</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Dopamine/dobutamine treatment</td>
<td>42</td>
<td>26</td>
<td>0.03</td>
</tr>
<tr>
<td>Respiratory support</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Intraaortic balloon pump</td>
<td>10</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Heart failure in convalescence</td>
<td>53</td>
<td>37</td>
<td>0.05</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>61</td>
<td>38</td>
<td>0.01</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>46</td>
<td>19</td>
<td>0.0004</td>
</tr>
<tr>
<td>Bleeding</td>
<td>7</td>
<td>53</td>
<td>0.0001</td>
</tr>
<tr>
<td>Coronary angioplasty</td>
<td>9</td>
<td>59†</td>
<td></td>
</tr>
<tr>
<td>Bypass surgery</td>
<td>16</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

* Only values <0.05 are reported. † Coronary angioplasty was performed more frequently in the thrombolysis group, when the 46 procedures immediately after thrombolysis are included. No significant differences were observed except for pericarditis and bleeding.
symptoms in an early stage of acute myocardial infarction, and that many patients may require balloon dilation even after successful lysis. Indeed, the experimental evidence of Sobel et al. (14) demonstrates that only reperfusion within 4 hours will limit the ultimate infarct size and achieve return toward normal cardiac function and metabolism. Recent overwhelming clinical evidence (9–28) confirms the efficacy of early reperfusion, because the greatest reduction in mortality and greatest limitation of infarct size were achieved in patients in whom lysis took place within 2 hours and who had coronary angiography as part of the procedure (9–11).

Which Proof is Available: Intravenous and Intracoronary Studies in Humans

Early reperfusion studies. The feasibility of rapid dissolution of intracoronary thrombi by systemic or selective infusion of thrombolytic substances was convincingly demonstrated in experimental series and in clinical pilot studies almost 30 years ago (16–21). This led to widespread trials of intravenous administration of streptokinase, given in varying doses and at varying time intervals, mostly with disappointing or nonsignificant results. This apparent lack of efficacy can now be explained in part by study inadequacies—too few patients, poor patient selection, inappropriate evaluation techniques and old-fashioned statistical design—but mainly by (too) late administration of streptokinase. In particular, no attempts were made to prove patency of the infarct-related artery by angiography or to measure infarct size. The older experience should therefore be eliminated from current considerations, although Yusuf et al. (22) concluded from a pooled analysis of some 6,000 patients in 24 randomized trials with intravenous streptokinase that a reduction in the odds of death by 22 ± 5% can be deduced, despite the nonsignificant results achieved in most individual studies.

Systematic efforts at restoration of anterograde flow after intracoronary administration were not introduced into clinical practice until 1979 by Rentrop and coworkers (21,25) in Germany. Since then, we have witnessed a dramatic increase in the number of patients with acute ischemic cardiac disorders who have been treated by intracoronary streptokinase infusion (26–28). The advantages of early intravenous administration combined with intracoronary lysis and aggressive follow-up treatment of residual coronary artery obstruction with coronary angioplasty or bypass surgery to optimize coronary blood flow have recently been adequately investigated. The striking benefits are entirely consistent with experimental evidence (14,29).

Factors influencing outcome of thrombolytic therapy. In our editorial in 1982 (30), in which the published data up to that year were reviewed, Rentrop and I voiced various notes of caution against excessive early enthusiasm. We pointed to the main factors that could positively or negatively influence the ultimate outcome. These included the need to know the time interval between the onset of symptoms and reperfusion, the extent of restoration of myocardial function in the region perfused by the infarct-related artery, the functional availability of collateral flow, the best route and optimal dose of the thrombolytic agents, the best agent and its side effects and the degree to which the usual sequelae of myocardial infarction, such as subsequent angina, reinfarction and death, could be reduced in the treatment group when compared with a control group randomly assigned to conventional treatment. These arguments were recently repeated by Yusuf et al. (22), although their conclusion that giant trials with thousands of patients are needed to solve these questions is debatable. In fact, the recent GISSI study (23) (Table 2) has clinched the argument by showing the greatest reduction in early mortality in the 52% of the 11,483 randomized patients who reached the hospital in time to receive their 1.5 million units of streptokinase.

Table 2. Mortality by Hours From Onset of Symptoms (data from GISSI trial [23])

<table>
<thead>
<tr>
<th>Hours</th>
<th>SK (deaths/n)</th>
<th>C (deaths/n)</th>
<th>p Value</th>
<th>Risk Ratio 95% (CI)</th>
<th>Total Mortality (%) (deaths/n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>9.2</td>
<td>12.0</td>
<td>0.0005</td>
<td>0.74</td>
<td>6.74 (0.63 to 0.87) (647/6,094)</td>
</tr>
<tr>
<td>&gt;3 to 6</td>
<td>11.7</td>
<td>14.1</td>
<td>0.03</td>
<td>0.80</td>
<td>12.9</td>
</tr>
<tr>
<td>&gt;6 to 9</td>
<td>12.6</td>
<td>14.1</td>
<td>NS</td>
<td>0.87</td>
<td>13.3</td>
</tr>
<tr>
<td>&gt;9 to 12</td>
<td>15.8</td>
<td>13.6</td>
<td>NS</td>
<td>1.19</td>
<td>14.6</td>
</tr>
<tr>
<td>&lt;1</td>
<td>8.2</td>
<td>15.4</td>
<td>0.0001</td>
<td>0.49</td>
<td>11.8</td>
</tr>
</tbody>
</table>

The data show clearly that the patients treated early (<3 hours) show the best outcome. C = controls; CI = confidence interval; n = no. of patients; SK = streptokinase.
within 3 hours after the onset of symptoms even though the drug was given intravenously. Much less benefit was demonstrated in those arriving later. A similar message came from the Jerusalem ambulance study (24) in which myocardial salvage was demonstrated in those treated with intravenous streptokinase within 1.5 hours after onset of symptoms.

As our concepts regarding the time course of ischemia evolve, particularly our views of the role of the available collateral supply and the load existing on the heart at the time of onset of coronary obstruction, we should be able to direct further therapy or interventions toward specific additional derangements. The infusion of beta-receptor blockers when excessive tachycardia or elevated blood pressure exists, calcium entry blockers when ischemia and spasm are still predominating (31) or "scavengers" of unwanted metabolites, such as oxygen radicals released during the reperfusion phase, all may be required in addition to lysis of the obstruction. In fact, they may play a major role in treatment because reperfusion, particularly when carried out late, can induce myocardial damage that may be as great as the ischemia-related necrosis.

**More recent studies in thrombolysis.** Returning to the question posed in our editorial (30): what have we learned from the smaller series and incidental observations in the years since 1980? Most importantly, early recanalization, whether by guide wire alone (21) or by clot lysis with streptokinase (9–14,16–28,32,33), urokinase or recombinant tissue plasminogen activator (rt-PA) (34–37) has been shown to limit infarct size (29,32,33), preserve cardiac function (38–46) and reduce early as well as late mortality (9,47–50). Although Schaper (29) and others (38–41) have confirmed in many animal models that, after 6 hours of complete ischemia, the amount of salvageable myocardium is insignificant, no animal model can completely mimic the human situation (29,39–41) (Fig. 2). A case can therefore be made to institute therapy after the sixth hour if ischemic signs are still present. Nevertheless, most data support the thesis that reperfusion must be established soon after occlusion, because no major beneficial effects can be expected beyond 3 to 4 hours after the onset of ischemia. Van der Giessen et al. (41) in our laboratory demonstrated in the pig that, after thrombosis, myocardial infarction could be averted only when a thrombomodulin antagonist had been given before the induction of thrombosis. In the same model, coincident therapy with nifedipine favorably altered capillary perfusion (beta-receptor blockade and oxygen scavengers are other options), although it did not change the extent of necrosis.

Thus, it remains possible that the time window for salvage can be widened to beyond 3 and perhaps up to 12 hours with additional pharmacologic agents. Although data from the pooled analysis by Yusuf et al. (22) suggest that some statistical benefit cannot be excluded when treatment is started late, the numbers are not convincing and recent data from the GISSI trial (23) indicate that lytic therapy increases mortality when treatment is begun later than 9 hours after the onset of symptoms (Table 2). Several authors (42–44) found that, whereas the extent of salvage is much less when therapy is started later than 4 hours after the onset of symptoms, late recanalization may still result in some improvement, particularly in patients who have collateral flow demonstrable by acute angiography. It is likely that in these patients, the evolution of "stuttering myocardial necrosis" is slowed when collateral flow is enhanced early on.

**Intravenous plus intracoronary thrombolysis.** The Netherlands data (9) have also shown that the best improvement in cardiac function, smallest infarct size and lowest mortality occurred in the subset of 117 patients in whom intracoronary lysis was preceded by early intravenous administration of streptokinase. In these patients, lysis was achieved a median of 3 hours after the onset of symptoms whereas the intravenous bolus of 0.5 million units of streptokinase reached the majority within 2 hours. Angiography before the start of subsequent intracoronary streptokinase treatment showed a patent coronary artery in less than half of these patients, however. Thus, improved outcome was seen in cases with persistent obstruction of the main infarct-related vessel. This finding supports the view that lytic therapy may work not only through relief of obstruction of the main infarct-related vessel, but also through improved rheology and reduced viscosity benefiting the collateral bed. This hypothesis is supported by the finding that cardiac enzyme washout was highest in those patients who were treated earliest but also occurred in those in whose infarct-related vessel remained closed. Another lesson we have learned is that although the

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**Figure 2.** The interval between interruption of coronary flow and the extent of limitation of infarct size (modified from the data by Schaper [29]). Myocardial infarct size depends on the species studied. Note that humans have a declining yield when more than 2 years since 1980? Most importantly, early recanalization, whether by guide wire alone (21) or by clot lysis with streptokinase (9–14,16–28,32,33), urokinase or recombinant tissue plasminogen activator (rt-PA) (34–37) has been shown to limit infarct size (29,32,33), preserve cardiac function (38–46) and reduce early as well as late mortality (9,47–50). Although Schaper (29) and others (38–41) have confirmed in many animal models that, after 6 hours of complete ischemia, the amount of salvageable myocardium is insignificant, no animal model can completely mimic the human situation (29,39–41) (Fig. 2). A case can therefore be made to institute therapy after the sixth hour if ischemic signs are still present. Nevertheless, most data support the thesis that reperfusion must be established soon after occlusion, because no major beneficial effects can be expected beyond 3 to 4 hours after the onset of ischemia. Van der Giessen et al. (41) in our laboratory demonstrated in the pig that, after thrombosis, myocardial infarction could be averted only when a thrombomodulin antagonist had been given before the induction of thrombosis. In the same model, coincident therapy with nifedipine favorably altered capillary perfusion (beta-receptor blockade and oxygen scavengers are other options), although it did not change the extent of necrosis.

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intravenous plus intracoronary streptokinase group from the Netherlands trial (9) and the GISSI data (23) confirm the thesis recently proposed by Verstraete (45), that intravenous administration of a lytic agent is "the only way," the initial successful reperfusion will not be sufficient when signs of ischemia persist or return. This will occur in many, if not half, of the cases because of the underlying athromatous lesion (3,7,12,15,46). Thus, the "only way" has to be modified by preparation to maintain or establish complete recanalization in those demonstrating initial success.

The Ultimate Aim: Reduce Mortality to a Few Percent

Achieving early and complete revascularization. Evidence for reduced mortality is available in the Netherlands Interuniversity Cardiology Institute Trial (9), in which 264 of the 533 patients were allocated to conventional treatment in the coronary care unit and 269 to attempted reperfusion. Of these 269 patients, 152 were assigned to streptokinase by the intracoronary route only, and 117 received 500,000 units of streptokinase intravenously before intracoronary administration. It was shown on an intention to treat principle that mortality at 14 days was 5% (14 of 269) in the group assigned to thrombolysis versus 9% (25 of 264) in the group assigned to conventional therapy, whereas at a median of 8 months, it was 9% versus 16%, a highly significant reduction in mortality (p < 0.01) (Table 1). However, the mortality in the group receiving intravenous with intracoronary streptokinase was even lower than that in the overall group, and the lowest mortality (one death in 20

Figure 3. Results of acute angiography in subsets of patients; acute catheterization was offered to patients allocated to thrombolytic therapy only. Final patency rate was lower in patients admitted 2 to 4 hours after onset of symptoms compared with patients admitted within 2 hours after onset of symptoms. IC = intracoronary; IV = intravenous; ST = sum of ST segment elevation on the ECG at admission (mV); HBDH = alpha-hydroxybutyrate dehydrogenase; Strepto = streptokinase. (Reproduced by permission of the American Heart Association, Inc. from Vermeer F, et al. [46].)

months) was achieved in the subgroup of 36 cases in which coronary lysis was combined with angioplasty (51). Including nonrandomized patients as well, we find just one death in 98 cases in 1 year. This observation strongly underpins the hypothesis that early but complete revascularization is essential by whatever means it is achieved. Furthermore, the best overall results, as assessed by preserved left ventricular function, infarct size limitation and reduction in shock, cardiac failure, ventricular fibrillation and pericarditis, were found in the group assigned to thrombolysis within 2 hours after the onset of symptoms (46) (Fig. 3).

In addition, enzyme release (alpha-hydroxybutyrate dehydrogenase) was 30% lower in the treated group, indicating a smaller size of the ultimate infarct. This was also reflected in a marked improvement in left ventricular ejection fraction, which was significantly higher, by 7% overall, in the treated compared with the control group (53% versus 46%). In the latter group, furthermore, end-diastolic and end-systolic volumes were normal. Again, the best results were seen in patients with anterior wall infarction treated within 2 hours (Fig. 3 to 6).

Role in unstable angina. Of interest are other data collected in the same time span at our center (52) in patients with unstable angina, a condition that may be considered a precursor of acute myocardial infarction. In 60 of 217 patients who had been refractory to intense, often triple, pharmacologic treatment and who were aggressively treated early with coronary angioplasty, the 1 year mortality rate was low (1%), without occurrence of subsequent infarction. This again indicates the desirability of clearing up the obstruction when postinfarction symptoms of ischemia persist after vasodilation or thrombolysis. Similar data have been found
These and other trials currently in progress promise that the results obtained with intracoronary streptokinase. The earlier thesis by Verstraete (45) that the intravenous route of early drug administration is the only realistic one is again to be amended because, even with this new agent, a significant subset of patients will require further therapy of "critical narrowing," particularly in the light of recent evidence (60) indicating that the short duration of rt-PA activity may lead to higher reclosure rates after initial success. This, in turn, strengthens our previous arguments (9,30,51) that, if relief of ischemic symptoms and signs is not complete within 2 to 4 hours after administration of intravenous rt-PA, or of any other agent, intracoronary manipulations remain mandatory because myocardium is jeopardized from the first few minutes of ischemia (14,29,38,39,50). The short duration of action of rt-PA is an advantage, not only because of the limited suppression of systemic fibrinolysis, but also because of the increased opportunity this provides for surgical intervention when obstruction persists on the basis of the underlying residual atheromatous lesion and coronary angioplasty does not offer a solution. Coincident therapy with prostacyclin stimulatory agents or thromboxane blockers (41) may well improve this strategy.

**Recommendations Under Optimal Conditions**

Because the United States (13,27), Italian (23) and Netherlands (9,46) trial results are all based on the "intention to treat principle" and on a random assignment procedure, early reperfusion of the obstructed coronary artery in acute myocardial infarction can now be recommended in health care systems in which certain essential conditions can be met. These conclusions can be derived even from nonrandomized data (47–50). The conditions are rapid referral and transport in (peri)urban populations with rapid access to a catheterization laboratory that has staff trained in these procedures. In Western Germany this is now the case for 66% of the eligible population (47) and in the Netherlands at least 75% have access to such facilities provided adequate referral arrangements have been made. Even in the United States, analysis of subsets in the Western Washington trial, the only other large scale, randomized trial (27), has indicated that similar reductions in mortality rates could be achieved in patients admitted within 4 hours. Added to these are nonrandomized studies such as those carried out in Germany (Aachen, 461 patients [47]; Mainz and Heidelberg, a total ± 700 patients [48]; Hamburg and Berlin, >1,000 patients [49]) and in France (50) (± 1,000 patients with access for 55% of the eligible population); these studies all indicate that in patients in whom early reperfusion was achieved, a marked reduction in mortality with improvement in ventricular function could be demonstrated, particularly when reperfusion was associated with early efforts at "permanent" recanalization.

**Figure 5.** Median values and quartiles of left ventricular ejection fraction at 10 to 40 days measured by radionuclide angiography in four subsets of patients in both treatment groups. Improvement of ejection fraction is most prominent in patients admitted within 2 hours after onset of symptoms. Hatched bars, Lysis; open bars, controls. Abbreviations as in Figure 4. (Reproduced by permission of the American Heart Association, Inc. from Vermeen F, et al. [46].)
The Total Experience Indicates and Warrants the Following New Positions for the Medical Profession

1. Thrombus formation is present in $\pm 85\%$ of all patients who present within the first 4 hours after the onset of acute myocardial infarction. It is the cause of infarction.

2. Although the thrombus may lyse spontaneously, this usually occurs after the fourth hour, by which time the interruption of blood supply has typically led to permanent damage of myocardial tissue, so that we cannot afford to wait and see.

3. Coronary angiography and intracoronary manipulations can be carried out in centers with properly trained personnel without undue complications in those patients in whom ischemia returns or persists after previously initiated intravenous lytic therapy.

4. Intracoronary streptokinase, preferably preceded by intravenous streptokinase, is currently the most effective method to lyse a thrombus provided it is administered early after the onset of symptoms. It has halved the 1 year mortality rate from 15.9 to 8.5% in the recent Netherlands trial (Fig. 6).

5. Intravenous streptokinase, when given within 0 to 3 hours of onset of symptoms, can achieve similar results (GISSI trial).

6. Intracoronary administration must therefore be considered a sequel to intravenous therapy when recanalization by the intravenous route, on average achieved in only 50 to 55% of cases, has not alleviated ischemia. Although rheologic factors (opening of collateral vessels, decreased viscosity) may be beneficial, even when the main obstruction has not yet been resolved, they are of secondary importance.

7. The reported data for recombinant tissue plasminogen activator (rt-PA) thus far indicate it to be superior to intravenous streptokinase. Although recocclusion rates with rt-PA are higher than with streptokinase (55), early coronary angioplasty has been advocated and proved successful (57). It may well be the combination of the future, when rt-PA becomes generally available as current trials are completed.

8. It has been shown that when residual stenosis is detected by clinical signs (such as recurrence of pain, ST segment elevation or increases in creatine kinase release) early coronary angioplasty or surgical bypass grafting can achieve optimal recanalization, thus reducing 1 year mortality to a few percent ultimately.

9. Early reperfusion will lead to smaller infarct size (58,59) and maintained left ventricular function (60), thus explaining the much improved prognosis and survival rates (9).

10. Early coronary angioplasty and bypass surgery without prior pharmacologic lysis have shown similar benefits in selected centers, but they are costly and applicable only to patients who can reach a catheterization laboratory within 2 hours and who have not had prior therapy.

11. It will be more a matter of rearranging existing facilities (rapid detection, referral, admission) than of finding the optimal reperfusion strategy that will ultimately decide whether the full benefits of this new therapeutic approach can be enjoyed by a majority of patients with acute infarction.

**Immediate Future**

Therapeutic complications. Although these conclusions indicate that, to reduce unnecessary death, early reperfusion must be recommended in all patients with suspected acute coronary artery obstruction in whom no contraindications exist, many practical restrictions remain (30,61,63). The need for cardiac catheterization in perhaps >50% of cases to verify the quality and the extent of recanalization, particularly in patients with persistent signs of ischemia, can be met only in appropriately equipped and strategically located centers (47,63) whose number will have to be increased. Furthermore, the inevitable delays in recognizing symptoms, the need to call the appropriate authority or the physician, the delay in transport and the limited availability of catheterization laboratories or operating rooms on permanent standby will initially influence the utility of such an approach. Therefore, if a simple intravenous thrombolytic agent were widely available (such as human tissue rt-PA, which is currently a leading candidate) or an improved streptokinase derivative, if it were to be proved as effective (BRL.26922), together with aggressive anti-ischemic therapy with cardioprotective agents (such as the combination of an effective beta-receptor blocker with a calcium...
antagonist [on theoretical grounds, the combination of atenolol with nifedipine which is the leading contender] [31,67]) or with an afterload-reducing agent (such as captopril), then an ambulance-based early treatment system (68) will gain further in attractiveness. If rt-PA, which is a natural activator of the fibrinolytic system and is now produced by a recombinant DNA technique, were to become available on a large scale and if the current initial trials that yield up to 70% reperfusion within 1 to 4 hours after intravenous administration of rt-PA were to show the same improvement in left ventricular function and reduction in death rates, as the best streptokinase trials now do, it would certainly constitute a major breakthrough and revolutionize the treatment of acute myocardial infarction.

A European trial is now under way to judge its efficacy on three groups of patients with acute myocardial infarction: 1) patients receiving conventional treatment with intravenous rt-PA; 2) patients receiving intravenous rt-PA followed by coronary angiography and, when needed, coronary angioplasty; and 3) patients receiving conventional coronary care unit treatment with placebo. End points are ventricular fibrillation and mortality.

Future treatment strategies. If results are positive, a futuristic picture can be conceived of widespread administration of plasminogen activator combined with cardioprotective agents in the first few hours after the onset of acute myocardial infarction by the general practitioner or ambulance service. On admission to the coronary care unit within 6 hours (time having been gained by early intravenous administration of the lytic agent), those patients with residual or returning ischemic signs of ischemia would be immediately catheterized with the aim of permanent recanalization by angioplasty or bypass surgery. The other, "cooled off" patients would not need urgent intervention, although on angiography many would be found to have severe obstruction which could be handled electively. Proof of the efficacy of such a strategy lies in application of this scheme to all patients suffering from acute myocardial infarction in a given health region. The possibility of conducting such a large scale approach must be available in cities the size of Newcastle, Mainz, Rotterdam or Seattle with their "modest" number of 300,000 to 600,000 citizens. Well organized transport systems and properly distributed health care centers have already proved their value in reducing sudden death in these cities and could serve as its basis.

The ultimate hope is that, indeed, myocardial infarct size can be limited or infarction avoided altogether with a resultant halving of death rate, the cost savings, solely from not incurring expensive postmyocardial infarction intervention measures such as treatment of cardiogenic shock or cardiac failure, could easily outweigh the modest increase in initial costs required by early treatment (67). If this is correct, both the quality and the duration of life after infarction could be increased at an acceptable cost.

References


68. Reperfusion in Acute Infarction Rotterdam (REPAIR). Design and protocol available on request.

