Serial Angiographic Assessment of Coronary Artery Obstruction and Collateral Flow in Acute Myocardial Infarction

Report From the Second Mount Sinai–New York University Reperfusion Trial

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In the Second Mt. Sinai–New York University Reperfusion Trial, in which change of ejection fraction was the primary end point, the following secondary end points were prospectively assessed by serial coronary angiography: patency of the infarct artery both before intervention and 10–14 days later, acute and delayed recanalization rates, presence or absence of collateral flow, and complication rates of acute interventional catheterization. We assigned 393 patients randomly to groups receiving acute cardiac catheterization and a double-blind intracoronary infusion of streptokinase (SK arm), both streptokinase and nitroglycerin (SK-NTG arm), nitroglycerin alone (NTG arm), or conventional therapy without acute catheterization (control arm). Prospective stratification was based on duration of infarct pain before randomization: group A, less than 2 hours; Group B, 2–12 hours. Baseline patency rates were comparable in patients studied within 6 hours (30%, 40 of 135) and those studied later (24%, 32 of 133). This finding refutes the hypothesis that spontaneous recanalization occurs frequently after 6 hours. The acute recanalization rates of the SK arm (60%, 40 of 67) and the SK-NTG arm (63%, 29 of 62) did not differ. During streptokinase infusion, more vessels recanalized in group A (81%, 22 of 27) than in group B (56%, 57 of 102) (p<0.01); this was due to a significant reduction of recanalization rates from 75% (48 of 64) to 45% (26 of 62) with treatment after 6 hours (p<0.01). Delayed recanalization, that is, patency at end point but not postintervention, was seen in 17% (17 of 100) of total occlusions treated with streptokinase. In group A, all total occlusions treated with streptokinase recanalized either acutely (20 of 22) or delayed (two of 22), whereas in group B, 23% (18 of 78) remained obstructed. The reocclusion rate in the SK arms was 17% (11 of 65). In the NTG arm, recanalization occurred during intervention in 4% (two of 47) and delayed in 45% (21 of 47). At end-point angiography, the patency rates of the NTG arm (62%, 41 of 66) and the control arm (58%, 36 of 62) were comparable; those of the SK arms were higher (75%, 105 of 140) (p<0.01). Total occlusion was associated with collateral flow in 33% (66 of 199) at baseline; the prevalence of collaterals did not increase with time to angiography, which indicates that they had developed before the index event. At end-point angiography, the prevalence of collaterals had increased to 90% (38 of 42) in patients with persistent total occlusion, which demonstrates a second distinct phase of collateral development. The composite end point of either death, cardiac arrest, cardiogenic shock, or life-threatening ventricular arrhythmia occurred more frequently (p<0.001) during interventional catheterization than during the corresponding observation period in the control group; however, mortality at 24 hours and at hospital discharge was not increased in the intervention arms. (Circulation 1989;80:1166–1175)
Coronary occlusion during the acute stage of myocardial infarction results from a complex interaction of factors including plaque fissure, platelet deposition, arterial spasm, and fibrin deposition. Spontaneous recanalization, which has also been documented, may result from resolution of spasm, breakdown of platelet deposits, and activation of the endogenous thrombotic system. The balance of these processes can be shifted toward recanalization by administration of thrombolytic agents but not spasmolytic agents such as nitroglycerin.

Changes of antegrade flow result in altered pressure gradients across collateral beds and variations in collateral flow. In the present study, we assessed occlusion status of the infarct artery and collateral flow to the infarct region by serial angiography in patients treated with an intracoronary infusion of streptokinase, nitroglycerin, or both agents within 12 hours of onset of infarction. We, therefore, were able to compare these angiographic parameters prospectively in patients who received a thrombolytic agent and in those who did not. Additionally, we evaluated the time dependence of infarct vessel patency and collateral flow at baseline angiography, as well as the time dependence of intracoronary streptokinase in achieving recanalization. Finally, we assessed the complications of interventional angiography in acute myocardial infarction.

The angiographic and clinical results presented in this study are secondary end points in the Second Mt. Sinai–New York University Reperfusion Trial, in which ejection fraction change was the primary end point. As reported previously, the greatest improvement in ejection fraction occurred in patients with collateralized total occlusion at preintervention angiography who were assigned to thrombolytic therapy; this benefit was potentiated by the concomitant administration of nitroglycerin. In patients with initial subtotal occlusion, thrombolytic therapy was found to be of no short-term benefit.

Methods

Trial Design

The trial design has been published. Consent patients in whom thrombolytic therapy was not contraindicated were eligible if they presented within 12 hours of the onset of myocardial ischemic pain of at least 30 minutes duration and demonstrated either new ST segment elevations or depressions of at least 0.1 mV, or presumably new pathologic Q waves in two contiguous leads of the screening electrocardiogram. Patients were prospectively stratified according to duration of pain before randomization into two groups: group A, patients having pain for less than 2 hours; group B, patients having pain for 2–12 hours. Patients were randomly assigned to one of three intervention arms or a control arm. In the intervention arms, acute cardiac catheterization was followed by a double-blind intracoronary infusion of either streptokinase (SK arm), nitroglycerin (NTG arm), or streptokinase combined with nitroglycerin (SK–NTG arm). In the control arm, acute cardiac catheterization and intracoronary drug infusions were not performed. On day 10–14, end-point coronary angiography and left ventriculography were performed in all consenting patients including those of the control arm. Thus, serial angiograms were obtained in the three intervention arms, whereas in the control arm only an end-point angiogram was performed.

The angiographic end points were: patency status of the infarct related artery before intervention and 10–14 days later, acute and delayed recanalization rates, reocclusion rates, and presence or absence of collateral flow to the infarct area before intervention and 10–14 days later. Infarct-vessel patency and collateral flow at baseline angiography, as well as recanalization rates with streptokinase, were assessed as a function of the time interval from onset of infarct pain to interventional angiography. The clinical end points were mortality, cardiac arrest, ventricular arrhythmias requiring electrical conversion, cardiogenic shock, reduction of hematocrit to less than 30%, need for blood transfusions, reduction of fibrinogen levels after interventional therapy, reinfarction rates, and the incidence of special procedures including intra-aortic balloon counterpulsation, percutaneous transluminal coronary angioplasty, and coronary artery bypass surgery.

Randomization and Interventional Catheterization

Randomization was carried out by opening a consecutively numbered sealed opaque packet that contained two vials. In the intervention patients, one vial contained a powder, either 250,000 units streptokinase or a placebo; the other vial contained a liquid, either 1.2 mg nitroglycerin or 5% dextrose in water. There was an equal probability that the powder, the liquid, or both were active. In the 25% of patients randomized to the control arm, both vials contained a blue liquid; there was a set of instructions stating “Medical Therapy—No Acute Intervention.”

In those patients randomized to interventional therapy, coronary angiography was performed after preintervention nuclear studies. The noninfarct vessel was visualized first. Contrast cineventriculography was not performed as part of the interventional angiogram. During intracoronary drug infusion, the infarct-related artery was visualized in a fixed projection every 15 minutes.

The powder and liquid were reconstituted and added to a 1-1 bottle of 5% dextrose and water and infused into the ostium of the infarct-related artery at a rate of 8 ml/min. If the powder was streptokinase, the resultant infusion rate was 2,000 IU/min; if the liquid contained nitroglycerin, the infusion rate was 0.01 mg/min. The intracoronary drug infu-
sion was performed through standard diagnostic catheters that, in patients with total obstruction of the left anterior descending or left circumflex artery, were advanced just beyond the origin of the affected vessel whenever feasible. Special catheters for subselective infusion were not used. The intracoronary drug infusion was maintained for a minimum of 75 minutes. If recanalization occurred, it was continued for at least an additional 30 minutes, to a maximum of 120 minutes.

Concomitant Therapy

Immediately after arterial access in intervention patients and baseline evaluation in control patients, a bolus of 10,000 units heparin was administered and anticoagulation was maintained with heparin followed by warfarin for 3 months. Additional details of concomitant and follow-up medical therapy have been described.6 Acute intra-aortic balloon counterpulsation was used not only in patients who showed clinical signs of cardiogenic shock, as in our first trial, but also in clinically stable patients if the preintervention gated blood-pool scan revealed an ejection fraction of less than 30% and either the cardiac index was less than 1.8 l/min/m² or the pulmonary wedge pressure was more than 25 mm Hg. Whenever possible, neither coronary angioplasty nor bypass surgery were performed before end-point data acquisition.

Data Evaluation

The core laboratory interpreted the angiograms of each intervention patient sequentially from preintervention to end-point study. Subsequently, the end-point angiograms of all patients were read without knowledge of the acute angiographic findings or whether the patient had been treated conventionally. Location and severity of coronary artery lesions were recorded according to the CASS criteria.10 The infarct-related artery was identified in the data center by clinical investigators on the basis of the composite angiographic, electrocardiographic, and nuclear data. The infarct-related artery was classified as “totally obstructed” if there was complete cessation of antegrade flow; it was called “patent” if there was any antegrade flow beyond the culprit lesion. Collateral vessels were determined to be present if any segment of the infarct-related artery filled in any other than a continuous antegrade manner.

Complications and special procedures were assessed in two categories, those occurring during or directly related to intervention and those occurring in hospital through day 14. The incidence of a composite adverse outcome, defined as either death, cardiac arrest, cardiogenic shock, or ventricular arrhythmia requiring electrical conversion, was assessed during intervention and in the control group during a corresponding 90-minute observation period after baseline data acquisition. Mortality was determined at 24 hours after randomization, at hospital discharge, and after 2 years. Fibrinogen was determined by the heat precipitation method before and immediately after interventional catheterization and, in control patients, before and after the 90-minute observation period.

Statistical Analysis

This trial was analyzed by intention to treat. The influence of time was assessed according to the prospective stratification by comparing the variables in groups A and B. In the intervention arms, time to catheterization was also considered. Continuous variables are expressed as mean±SD, except where SEM was used. Differences in the distribution of baseline variables among the four treatment arms were compared using analysis of variance for continuous variables and χ² analysis for categoric variables. Likelihood ratio, χ², and Fisher’s exact test were used to analyze all categoric variables.

Results

Patient Profile

The study population consisted of 393 patients; 97 were randomly assigned to the SK arm, 99 to the NTG arm, 96 to the SK-NTG arm, and 101 to the control arm; 78 patients were enrolled in group A and 315 were enrolled in group B. Time from onset of pain to interventional catheterization was 3.2±0.7 hours in group A and 7.1±2.4 hours in group B (Table 1). There were no significant differences in baseline characteristics between groups A and B (Table 1) or between treatment arms. The intervention arms did not differ from one another in prevalence of subtotal obstruction of the infarct artery, collateral flow to the infarct area, or in duration of intracoronary infusion (85.3±24.5 minutes). The total dose of streptokinase in the two streptokinase arms was 173,000±53,000 IU.

Baseline Angiography

Preintervention angiograms were available in 272 of 292 intervention patients; in 20 patients who were evenly distributed between intervention arms, angiographic data were not available primarily due to death or profound hemodynamic instability before completion of the baseline study. Of those patients with preintervention angiograms, 55 were in group A and 217 were in group B. In 268 of these patients, the time interval between onset of infarct pain and interventional angiography could be determined.

Initial Subtotal Obstruction

The prevalence of initial subtotal obstruction of the infarct-related artery was 27% (73/272). It was not related to duration of infarct pain before presentation by prospective stratification (group A, 31%, 17 of 55; group B, 26%, 56 of 217) or by time to angiography (Table 2); patients studied within 6 hours had a subtotal lesion in 30% (40 of 135) of the
TABLE 1. Baseline Variables

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>78</td>
<td>315</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>56.9±10.1</td>
<td>57.4±10.0</td>
<td>NS</td>
</tr>
<tr>
<td>Male (%)</td>
<td>85</td>
<td>75</td>
<td>0.068</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>32</td>
<td>43</td>
<td>0.060</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>13</td>
<td>22</td>
<td>0.083</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>70</td>
<td>64</td>
<td>NS</td>
</tr>
<tr>
<td>Family history of CAD (%)</td>
<td>43</td>
<td>43</td>
<td>NS</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>17</td>
<td>14</td>
<td>NS</td>
</tr>
<tr>
<td>Current MI location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior (%)</td>
<td>53</td>
<td>46</td>
<td>NS</td>
</tr>
<tr>
<td>Inferior (%)</td>
<td>44</td>
<td>48</td>
<td>NS</td>
</tr>
<tr>
<td>Lateral (%)</td>
<td>3</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>45.9±14.3</td>
<td>46.8±15.0</td>
<td>NS</td>
</tr>
</tbody>
</table>

Time to
- Randomization (hr) 1.7±0.4 5.1±2.3
- Catheterization (hr)* 3.2±0.7 7.1±2.4

Dose
- Streptokinase (IU)* 180.860±42.590 171.700±54.910 NS
- Nitroglycerin (mg)* 0.85±0.023 0.84±0.22 NS

Extent of CAD
- One-Vessel (%) 46 48
- Two-Vessel (%) 40 35 NS
- Three-Vessel (%) 14 17

Infarct vessel
- LAD (%) 56 47
- CIRC (%) 17 15 NS
- RCA (%) 26 37
- Left main (%) 1 1

CAD, coronary artery disease; LAD, left anterior descending coronary artery; CIRC, left circumflex coronary artery; RCA, right coronary artery; Left main, left main coronary artery. *Intervention.

cases, and those studied after 6–14 hours had a subtotal lesion in 24% (32 of 133) of the cases.

Collaterals at Baseline

Collaterals to the infarct-related artery were seen before intervention in 27% (74 of 272) of the patients; they were significantly more common in patients with complete obstruction of the infarct-related artery (33%; 66 of 199) than in those with subtotal obstruction (11%; eight of 73) (p<0.001). The prevalence of collaterals was not related to presentation time by prospective stratification considering all patients (group A, 25%, 14 of 55; group B, 28%, 60 of 217) or by 2-hour intervals considering only those patients with initial total obstruction (Table 3).

Acute Response to Intracoronary Interventions

Acute recanalization rates could be assessed in those 194 patients with total occlusion at baseline angiography in whom preintervention and postintervention angiograms were available. In patients assigned to the streptokinase arms, the acute recanalization rate was 61% (79 of 129). There was no difference between patients assigned to the SK arm

<table>
<thead>
<tr>
<th>Patients studied (n)</th>
<th>55</th>
<th>81</th>
<th>66</th>
<th>37</th>
<th>28</th>
<th>267</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient artery (%)</td>
<td>29</td>
<td>30</td>
<td>27</td>
<td>24</td>
<td>14</td>
<td>27</td>
</tr>
</tbody>
</table>

*As a function of time interval from onset of pain to angiography (time to angiography).
(60%, 40 of 67) and those assigned to the SK-NTG arm (63%, 39 of 62). However, acute recanalization rates of the two streptokinase arms depended on the time interval from onset of pain to initiation of therapy (Figure 1); they were significantly higher in group A (81%, 22 of 27) than in group B (56%, 57 of 102) \((p<0.01)\). In patients treated after more than 6 hours, the recanalization rate decreased significantly from 75% (48 of 64) to 45% (28 of 62) \((p=0.006)\) (Figure 1). The acute recanalization rate in the NTG arm of 8% (five of 65) was not related to time to angiography.

Serial Angiography

Serial preintervention, postintervention, and pre-discharge angiograms were available in 196 patients. Complete serial angiograms were not available in 96 intervention patients primarily due to death before end-point angiography or patient refusal to undergo the repeat study. The patients with incomplete angiographic data were more frequently female than were those with complete studies (32% versus 18%, \(p<0.01\)) and slightly older (59±10 versus 56±10 years, \(p=0.03\)). In all other baseline variables, particularly ejection fraction, extent of coronary artery disease, and localization of myocardial infarction, the two groups were comparable.

The infarct-related artery was initially completely occluded in 147 of the 196 patients with serial angiograms (100 patients in the streptokinase arms, 47 in the nitroglycerin arms); it was subtotally obstructed in 49 patients (33 in SK arm, 16 in NTG arm).

Acute and Delayed Recanalization

The acute recanalization rate of the streptokinase arms was 65% (65 of 100) in this subset of patients; additionally we found delayed recanalization, that is, patency at end-point angiography but total occlusion at 90 minutes in 17% (17 of 100). All 22 group A patients with initial complete obstruction experienced recanalization either during streptokinase infusion or by end point, whereas 23% (18 of 78) of group B patients never demonstrated recanalization \((p=0.002)\) (Figure 2). The combined acute and delayed recanalization rate of patients who received streptokinase within 6 hours was 96% (49 of 51); in

![Graph of acute recanalization rates with intracoronary streptokinase as function of time interval from onset of pain to beginning of therapy. (Number of patients studied)/(number of patients who experienced recanalization) is indicated within bars. (In three patients, time interval could not be determined.)](image)

![Pie charts of acute and delayed recanalization in patients treated with intracoronary streptokinase or intracoronary streptokinase plus intracoronary nitroglycerin (streptokinase arms) and in patients treated with intracoronary nitroglycerin alone (nitroglycerin arm).](image)

### Table 3. Prevalence of Collateral Flow to a Totally Occluded Infarct Artery at Baseline Angiography*

<table>
<thead>
<tr>
<th>Time to angiography (hr)</th>
<th>2–4</th>
<th>4–6</th>
<th>6–8</th>
<th>8–10</th>
<th>10–12</th>
<th>12–14</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with total Occlusion studied (n)</td>
<td>40</td>
<td>56</td>
<td>48</td>
<td>52</td>
<td>196</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Collaterals (%)</td>
<td>33</td>
<td>30</td>
<td>29</td>
<td>38</td>
<td>33</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*As a function of time interval from onset of pain to angiography (time to angiography).

### Table 4. Incidence of Persistent Complete Coronary Artery Occlusion Before Intervention, Immediately After Intervention, and at End-Point Angiography in the 97 SK and SK-NTG Patients*

<table>
<thead>
<tr>
<th>Time to therapy (hr)</th>
<th>2–4</th>
<th>4–6</th>
<th>6–8</th>
<th>8–10</th>
<th>10–12</th>
<th>12–14</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients studied (n)</td>
<td>22</td>
<td>29</td>
<td>16</td>
<td>15</td>
<td>9</td>
<td>6</td>
<td>97</td>
</tr>
<tr>
<td>Persistent occlusion (%)</td>
<td>0</td>
<td>7</td>
<td>44</td>
<td>20</td>
<td>44</td>
<td>33</td>
<td>19</td>
</tr>
</tbody>
</table>

*As a function of time interval between onset of pain and initiation of therapy.
angiography related artery and Reocclusion recanalization during angiography.

Reocclusion

Reocclusion at end-point study was seen in 17% (11 of 65) of patients who had demonstrated reperfusion during streptokinase infusion. Among patients with subtotal obstruction at baseline, end-point angiography revealed complete obstruction of the infarct-related artery in 15% (five of 33) after streptokinase and in 13% (two of 16) after nitroglycerin infusion.

Delayed Appearance and Disappearance of Collaterals

The evolution of angiographically demonstrable collaterals was assessed in those 98 patients with complete obstruction at baseline angiography who either never demonstrated recanalization (n=42) or who experienced acute recanalization that was sustained at end-point angiography (n=56). In patients with persistent coronary artery occlusion, the incidence of demonstrable collaterals increased from 33% at baseline angiography to 90% at end-point study, whereas in patients with sustained reperfusion, the incidence of collaterals decreased from 38% to 7% (Figure 3).

Patency Rates at Endpoint Angiography

End-point angiograms were analyzed in all four treatment arms (n=268). The infarct-related artery was patent in 75% (105 of 140) of patients treated with intracoronary streptokinase alone or in combination with nitroglycerin. There was no significant difference in patency rates between patients in the SK arm (79%, 55 of 70) and those in the SK-NTG arm (71%, 50 of 70). Group A patients who received thrombolytic therapy showed significantly higher end-point patency rates (93%, 27 of 29) than group B patients (70%, 78 of 111) (p<0.01). When time to therapy was considered, a significant decrease of end-point patency rates in patients treated more than 6 hours after pain onset became obvious (Table 5). In patients treated within 6 hours, the end-point patency rate was 86% (57 of 66), whereas it was 63% (42 of 67) in patients treated later (p<0.05).

The end-point patency rates of the nitroglycerin arm (58%, 36 of 62) and the control arm (62%, 41 of 66) did not differ from one another. The 60% (77 of 128), end-point patency rate of these two arms was significantly lower than the 75% (105 of 140) end-point patency rate of the streptokinase arms (p<0.001). This difference was entirely due to the higher patency rate of patients who received streptokinase within 6 hours of pain onset; the end-point patency rates of patients who received streptokinase after more than 6 hours and of patients who did not receive streptokinase were not different from one another.

Complications and Mortality

The composite adverse outcome of either death, cardiac arrest, cardiogenic shock, or ventricular arrhythmia requiring electrical conversion occurred in 30 patients during the acute intervention but in only one control patient during the corresponding observation period (p<0.001). There was no difference in these major complications among the three intervention arms.

Although three of the 292 intervention patients died in the catheterization laboratory (two in the SK arm, one in the NTG arm) and none of the 101 control patients died during the corresponding observation period, there was no significant difference in mortality among the four treatment arms within the first 24 hours after randomization or through the hospital course of treatment (Table 6). Similarly, cardiogenic shock, which occurred in 4% of patients during interventional catheterization but not in any control patient during the observation period, was evenly distributed by study end point between intervention (10%) and control patients (9%).

![Graph of incidence of collaterals to infarct-related artery before intervention and at day 10–14 angiography in 42 patients in whom infarct vessel was never recanalized and in 56 patients who experienced recanalization during intracoronary streptokinase infusion and had a patent-infarct vessel at day 10–14 angiography.](image)

**Figure 3.** Graph of incidence of collaterals to infarct-related artery before intervention and at day 10–14 angiography in 42 patients in whom infarct vessel was never recanalized and in 56 patients who experienced recanalization during intracoronary streptokinase infusion and had a patent-infarct vessel at day 10–14 angiography.

<table>
<thead>
<tr>
<th>Time to therapy (hr)</th>
<th>2–4</th>
<th>4–6</th>
<th>6–8</th>
<th>8–10</th>
<th>10–12</th>
<th>12–14</th>
<th>All</th>
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<tbody>
<tr>
<td>Patients studied (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>133</td>
</tr>
<tr>
<td>Infarct vessel patent (%)</td>
<td>93</td>
<td>82</td>
<td>55</td>
<td>80</td>
<td>55</td>
<td>57</td>
<td>74</td>
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*As a function of the time interval between onset of pain and initiation of therapy.
TABLE 6. Cumulative Mortality by Treatment Arm During Intervention

<table>
<thead>
<tr>
<th>Arm</th>
<th>During intervention</th>
<th>24 Hours</th>
<th>In hospital</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>n</td>
<td>n</td>
</tr>
<tr>
<td>SK</td>
<td>(97)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>SK-NTG</td>
<td>(96)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>NTG</td>
<td>(96)</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Control</td>
<td>(101)</td>
<td>0†</td>
<td>5</td>
</tr>
</tbody>
</table>

*Within 24 hours of randomization and by hospital discharge; (†), total number of patients per treatment arm.

A 90-minute observation period corresponding to the intervention period was considered.

During hospitalization, both anemia (p<0.01) and blood transfusion (p<0.01) were more common in intervention than in control patients (Table 7); however, there were no significant differences among the three intervention arms. Fibrinogen levels decreased from baseline to preintervention by 26% in patients assigned to the streptokinase arms (p<0.01), whereas there was no significant decrease in the NTG or conventional arm (Table 7).

Intra-aortic balloon counterpulsation was used in 10% of the patients; there were no differences among the treatment arms. In keeping with the protocol of this study, the incidence of revascularization by percutaneous transluminal coronary angioplasty or coronary artery bypass surgery before end-point studies was less than 5% (19 of 393). The reinfarction rate of 4% did not differ significantly among treatment arms.

Discussion

Trial Design

Due to the presumed time dependence of myocardial necrosis, it is common clinical practice to restrict acute angiography and interventions after the first 6 hours of pain onset to those patients who present with ongoing chest pain and electrocardiographic evidence of incomplete infarction. In the present trial, the criteria for enrollment were uniform during the first 12 hours of chest pain. Thus, the influence of the time interval from onset of infarction to interventional angiography on baseline occlusion status of the infarct-related artery, baseline collateral flow, and recanalization rates

TABLE 7. Incidence of Anemia (Hematocrit, <30%) and Blood Transfusions and Decrease of Fibrinogen in Four Treatment Arms

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>SK</th>
<th>SK-NTG</th>
<th>NTG</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia (%)</td>
<td>6</td>
<td>10</td>
<td>15</td>
<td>3</td>
</tr>
<tr>
<td>Transfusion (%)</td>
<td>10</td>
<td>20</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Change of fibrinogen (%)</td>
<td>-29</td>
<td>-20</td>
<td>-4</td>
<td>-1</td>
</tr>
</tbody>
</table>

*Incidence of anemia and blood transfusions is expressed as percentage of patients in each treatment arm; change of fibrinogen is expressed as percent decrease from preintervention value.

with intracorony streptokinase could be determined prospectively.

Performance of serial angiography before intracorony drug infusion, during intervention, immediately after intervention, and 10–14 days later in patients with acute myocardial infarction who were randomly assigned to an intracoronary infusion of streptokinase, nitroglycerin, or both drugs enabled us to compare acute as well as delayed recanalization rates in the presence and absence of thrombolytic therapy. Furthermore, we assessed the appearance and disappearance of collateral flow to the infarct area from baseline to day 10–14 in patients with permanent total coronary occlusion and in those who experienced sustained recanalization.

Finally, we designed this trial to assess complication rates of interventional catheterization in the acute stage of myocardial infarction with and without intracoronary thrombolysis. This was achieved by including a control group in which acute cardiac catheterization was not performed and an intervention group that did not receive thrombolytic therapy.

Spontaneous Recanalization

In the present trial, the prevalence of subtotal obstruction of the infarct artery did not increase with the time interval between onset of pain and baseline angiography. This result confirms, in a larger patient population, a finding of our first trial and contradicts the data of DeWood et al., who reported a significant increase in patency rates in patients studied more than 6 hours after pain onset. In contrast to our study, his results were obtained from a database gathered retrospectively and thus more likely to be subject to selection bias. Our data refute the hypothesis that there is a high incidence of spontaneous recanalization between 6 and 12 hours or, for that matter, between 3 and 14 hours after onset of infarction. Spontaneous recanalization, however, appears to occur frequently either earlier, that is, within 3 hours, or "delayed," that is, more than 14 hours after symptom onset. Early spontaneous recanalization is the most likely explanation of subtotal occlusion of the infarct artery at baseline angiography, which we observed in 27% of our patients. This hypothesis is supported by the significant ejection fraction improvement that has been found consistently in this subgroup of patients. This early spontaneous recanalization is probably due to relief of coronary spasm, endogenous lysis of a platelet thrombus, or both. Delayed spontaneous recanalization that occurred after the acute intervention and before end-point study was documented angiographically in about half of the patients treated with intracoronary nitroglycerin and systemic anticoagulants and was probably unrelated to the nitroglycerin because the end-point patency was identical in the control arm. Therefore, delayed spontaneous recanalization involves the time-consuming process of lysis of an established fibrin thrombus by the intrinsic fibrinolytic system.
Time Dependence of Streptokinase Efficacy

A relation between intracoronary streptokinase dose and acute recanalization rates has not been established. Our study is the first to confirm and define the time dependence of the efficacy of intracoronary streptokinase with prospectively obtained data. Intracoronary administration of streptokinase during the first 6 hours of myocardial infarction results in recanalization rates similar to those found with intravenous r-TPA but much higher than those rates documented with intravenous streptokinase. The efficacy of intracoronary streptokinase decreases markedly after 6 hours of infarct pain. Therefore, the observed time dependence of streptokinase on mortality results not only from progressive myocardial necrosis but also from the decreased recanalization rates of this agent with time. The efficacy of other modes of thrombolytic therapy beyond 6 hours has not been systematically assessed.

Failure of thrombolytic therapy to achieve coronary artery recanalization in a sizable proportion of patients, regardless of the agent and the route of administration, has led to the assumption that acute coronary occlusion may be due to factors other than fibrin thrombus in some patients. The finding that 17% of all patients with initial total obstruction of the infarct-related artery had persistent occlusion after a 90-minute infusion of streptokinase but a patent vessel 10–14 days later indicates that a 90-minute angiographic observation period may result in an underestimation of the recanalization rates of this agent. The combined acute and delayed recanalization rate of 96% in patients who received intracoronary streptokinase 2–6 hours after onset of infarction supports the hypothesis that observed total coronary artery obstruction in the early hours of acute myocardial infarction is almost universally due to a fibrin thrombus. The marked increase of resistance to thrombolytic therapy after 6 hours is probably due to progressive stabilization of fibrin and apposition of thrombotic material.

Evolution of Collateral Flow

Appearance and disappearance of collateral flow have been found to be related to interruption and restoration of antegrade flow in previous human studies using bypass surgery and angioplasty as models. The present study allows a further analysis of the incidence and time course of the development of collateral flow in patients with thrombotic coronary occlusion.

We observed no increase in the prevalence of angiographically apparent collateral flow with time-to-baseline angiography. Therefore, it is unlikely that these collateral channels developed in response to the current total occlusion. This conclusion is supported by the experimental observation that the first cellular mitoses occur only 24 hours after coronary obstruction. The data support the hypothesis that the collateral channels that were visible at baseline angiography had developed in response to an antecedent high-grade coronary artery obstruction and were recruited when antegrade flow ceased.

The increase in the incidence of collaterals from 33% at baseline to 90% at end-point angiography in those patients in whom the infarct artery remained obstructed indicates that growth of collateral channels occurs nearly uniformly in humans within 10 days of sustained coronary occlusion.

Complications and Mortality

We observed a significant increase of life-threatening complications during interventional catheterization as compared with the corresponding observation period in the control group. However, the lack of an increase in mortality at 24 hours or at hospital discharge in the intervention arms indicates that these complications could be managed successfully. The increase of both morbidity and mortality reported by several authors with the use of acute angioplasty may be related to the greater technical complexity of these interventions.

The observed decrease of fibrinogen levels in the streptokinase arms was significant albeit less marked than in other studies; this may be related to differences in the streptokinase dose and in the methods used to assess fibrinogen levels. The incidence of bleeding complications in the streptokinase arms of our study is in accord with other studies in which acute catheterization was combined with intracoronary streptokinase infusion or intravenous recombinant tissue-type plasminogen activator therapy. Because bleeding complications occurred with equal frequency in the NTG arm, where no decrease of fibrinogen was seen, it appears that the principal cause of bleeding in patients subjected to acute interventional catheterization is the combination of an arterial injury with prolonged systemic anticoagulation. Primary angioplasty has been advocated as an alternative to thrombolytic therapy to achieve coronary artery recanalization with a low risk of bleeding. However, the risk of thrombotic reclosure necessitates prolonged heparinization after primary angioplasty. This therapeutic modality, therefore, will probably be associated with an incidence of hemorrhagic complications comparable with that incidence found in our intervention arms. This risk is not negligible.

Appendix

The Second Mount Sinai–New York University Reperfusion Trial included the following participants:

Steering Committee

K. Peter Rentrop, MD, Chairman; Frederick Feit, MD, Secretary; Warren Sherman, MD, Arthur Fox, MD, Richard Gorlin, MD, Kenneth McKusick, MD, Arlie Cameron, MD, Stanley Goldsmith, MD, Mariano Rey, MD.
Clinical Units, Principal Investigators

Mount Sinai Medical Center, NY: K. Peter Rentrop, MD, Principal Investigator; Marc Cohen, MD, John Ambrose, MD, Heinrich Blanke, MD, Barry Cohen, MD, Mark Milner, MD, Jeffrey Cowen, MD, Rohit Arora, MD, Stephen Winters, MD, Robert Phillips, MD, Robert Reichstein, MD, Robert Levine, MD, Rao Betina, MD, Susan Hosat, MS.

Bellevue Hospital, NY: Frederick Feit, MD, Principal Investigator; Peter Stecy, MD, Mariano Rey, MD, Mark Nachamie, MD, William Cole, MD, Frank Politzer, MD, Jeffrey Kramer, MD, Mark Ehrich, MD, Gary Friedman, MD, Stephan Siegel, MD, Frank Prior, MD, Michael Attubato, MD, James Slater, MD, Aaron Gindea, MD, Sharon Napoli, RN, Susan Harty, RN, Virginia Bernardin, RN.

City Hospital at Elmhurst, NY: Warren Sherman, MD, Principal Investigator; Richard Schneider, MD, Principal Investigator (former); Robert Perdoncin, MD, William Schwartz, MD, Francis Lane, MD, Hee Lee, MD, R. Patel, MD, Naomi Hill, RN.

Data Coordinating Center: John Thornton, PhD, Principal Investigator; Ford Calhoun, PhD, Harry Smith Jr., PhD, Richard Fagerstrom, PhD, Jim Holt, MS, Lainy Berkowitz-Rudolph, RN, Jean Fisher, PhD, Mark Van Buskirk, MS, Gail McAvay, MS.

Angiography Core Laboratory, St. Luke’s Hospital, NY: Arlie Cameron, MD, Principal Investigator; Harvey Kemp, MD.

Electrocardiography Core Laboratory, New York University Hospital School of Medicine, NY: Mariano Rey, MD, Principal Investigator.

Radionuclide Ventriculography Core Laboratory, Harvard University School of Medicine, Boston, Massachusetts: Kenneth McKusick, MD, Principal Investigator; Tsunehiro Yasuda, MD.

Thallium Scintigraphy Core Laboratory, Mount Sinai and New York University Schools of Medicine, NY: Stanley Goldsmith, MD, Principal Investigator; Joseph Sanger, MD, Stephen Horowitz, MD, Mary Farrell.

Hematology Core Laboratory, Mount Sinai Medical Center, NY: Jacob Rand, MD, Principal Investigator.

Safety and Data Monitoring Committee: William B. Hood Jr., MD, Chairman; Lewis C. Becker, MD, Paul Canner, PhD, Jay H. Cohn, MD, Max Halperin, PhD, Thomas Kilipp III, MD, Victor J. Marder, MD, Elliot Rapaport, MD, Harmon Smith, PhD, Thomas L. Robertson, MD, Ex Officio Member.

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