Randomized Comparison of Rescue Angioplasty With Conservative Management of Patients With Early Failure of Thrombolysis for Acute Anterior Myocardial Infarction

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**Background** When used in the setting of acute myocardial infarction, intravenous thrombolytic agents fail to achieve early infract artery patency in 15% to 50% of patients. We tested the hypothesis that immediate balloon angioplasty applied to patients with failed early reperfusion would improve left ventricular function and clinical outcome at 30 days compared with conservative management alone.

**Methods and Results** One hundred fifty-one patients with first anterior wall infarction treated with any accepted intravenous thrombolytic regimen and angiographically demonstrated to have an occluded infract vessel within 8 hours of chest pain onset were randomized to aspirin, heparin, and coronary vasodilators (conservative therapy) or to this therapy and balloon angioplasty supplemented by further thrombolytic therapy as needed. Left ventricular function was assessed using multiple-gated equilibrium radionuclide technique to determine ejection fraction, and adverse clinical outcome was assessed evaluating death, ventricular tachycardia, and class III or IV heart failure at 30 days. Seventy-three patients were randomized to conservative therapy and 78 to angioplasty. The two groups were well balanced for patient age (59±11 years), sex (82% were male), and time to randomization (4.5±1.9 hours). Angioplasty was technically successful in 72 of 78 randomized patients (92%). Two patients randomized to conservative therapy crossed over to angioplasty within 72 hours. Resting 30-day ejection fraction was 40±11% in the angioplasty group and 39±12% in the conservative group (P=.49), but ejection fraction with exercise was 43±15% and 38±13% for the angioplasty and conservatively treated groups, respectively (P=.04). Adverse clinical outcomes included death in 5% and 10% (P=.18), severe heart failure in 1% and 7% (P=.11), and either death or severe heart failure in 6% and 17% (P=.05) of the angioplasty and conservatively managed groups, respectively.

**Conclusions** When applied to patients with first anterior infarction, rescue angioplasty appears to be useful in the prevention of death or severe heart failure, with improvement in exercise, but not resting, ejection fraction. This strategy deserves further study and highlights the potential advantage of early mechanical restoration of infract vessel patency when thrombolytic therapy has failed. (*Circulation*, 1994;90:2280-2284.)

**Key Words** angioplasty • thrombolysis • infarction

 Intravenous thrombolytic therapy given to patients with acute myocardial infarction demonstrably reduces mortality,1,2 probably by improving systolic and diastolic ventricular function and reducing susceptibility to life-threatening ventricular arrhythmias, although these mechanisms appear to be uniquely dependent on the time from infarct onset to treatment and are not all operative in every patient.3-6

With this form of therapy, early (90-minute) infarct artery patency is established in only 50% to 85% of patients,7,8 and 90-minute TIMI 3 flow has been shown to be a marker of subsequent survival.9,10 Early coronary angioplasty may successfully open 75% to 85% of occluded arteries in this setting,11 and in part because it seems intuitive to many physicians that the infract artery should be opened promptly, angioplasty is frequently applied in this setting despite the absence of clinical trials justifying its use.11,12

It is well recognized that 30% to 60% of infract arteries that are closed 90 minutes after thrombolytic therapy will open within the time window when clinical benefit may still accrue.13,14 Furthermore, rescue angioplasty may be costly and, when it fails, is associated with a high mortality;11 therefore, its practice remains highly controversial.11,12

Our aim was to assess the clinical benefit of rescue angioplasty in a select relatively homogeneous and high-risk (no prior myocardial infarction, chest pain of less than 8 hours, anterior location) patient population in a randomized study of 151 patients from 20 centers.

**Methods**

**Patients**

Between January 1990 and March 1993, all patients meeting enrollment criteria at 20 sites were sought for randomization.
To assess possible bias in patient recruitment, a registry of eligible but nonrandomized patients with cursory demographic and outcome data was kept.

Patients were eligible for randomization if they met all the following inclusion criteria: (1) anterior myocardial infarction with ST-segment elevation $\geq 2$ mV in at least two of six precordial leads with cardiac catheterization within 6 hours of chest pain onset; with severe ongoing chest pain, the time window could be extended to within 8 hours at the discretion of the investigator; (2) treatment with any acceptable intravenous thrombolytic regimen (including but not limited to streptokinase [1.5 million U], tissue-type plasminogen activator [TPA; 100 to 125 mg], and urokinase [3 million U]); (3) age 21 to 79 years; (4) TIMI flow grade 0-1 in the left anterior descending coronary artery (LAD) after intracoronary nitrate administration and at least 90 minutes after initiation of thrombolytic therapy; and (5) ability to give informed consent.

Patients were excluded from study entry for any of the following reasons: (1) cardiogenic shock (systolic blood pressure $<90$ mm Hg after fluid resuscitation and treatment of bradycardia $<60$ beats per minute); (2) prior myocardial infarction; and (3) left main stenosis $\geq 50\%$ in diameter. Approval of the protocol by local institutional review boards was obtained before patient randomization.

**Randomization and Treatment Assignments**

Patients were randomized using a closed-envelope system and a permuted block design, stratifying for investigational site and time from chest pain onset to randomization ($\geq 4$ or $<4$ hours). Before catheterization, all patients received aspirin (325 mg chewed) and adequate sedation. Catheterization and angioplasty were performed using standard technique.\(^{15}\) Performance of angioplasty was limited to investigators with demonstrated expertise in this setting ($\geq 50$ procedures with $\geq 80\%$ success). It was recommended that noninfarct artery stenoses not be dilated. For patients randomized to angioplasty who had received fibrin-specific thrombolytic agents, additional streptokinase (500 000 U) or urokinase (1 million U) was given as part of the standard treatment consequence to the potential adverse interaction between fibrin-specific agents and angioplasty noted in several prior nonrandomized studies\(^ {11}\) (and since refuted by randomized studies\(^ {16}\)). Use of intra-aortic balloon counterpulsation was left to the discretion of the operator. After initial randomized treatment, all patients received aspirin (80 to 325 mg/d), intravenous nitrates for at least 24 hours, and intravenous or high-dose ($>10 000$ U BID) subcutaneous heparin for at least 3 days, as tolerated. Treatment of heart failure was specified to include digitalis, diuretics, and an angiotensin-converting enzyme inhibitor as possible. In patients randomized to conservative management, angioplasty or bypass surgery was proscribed for 72 hours. Data were collected on standardized forms by trained research personnel and, with the procedural cineangiograms, were mailed to the Data Analysis Laboratory for review and compilation.

Additional protocol-mandated studies included 24-hour Holter monitor for ventricular arrhythmias at 5 to 7 days, left ventricular ejection fraction by multiple-gated radionuclide ventriculography at 25 to 35 days, evaluation of severity of heart failure at 25 to 35 days and 1 year by a noninterventional cardiologist with expertise in heart failure, and assessment of vital status at 30 days and 1 year.

**Statistical Analysis**

Normally distributed data are presented as mean±1 SD. Nonnormally distributed data are presented as median and interquartile range. Comparisons between treatment groups were performed using Student's $t$, Mann-Whitney, and Pearson $\chi^2$ tests, where appropriate. All tests are two-sided.

The prespecified primary end point was 25- to 35-day ejection fraction, with a value of 20% imputed for nonsurvivors. Sensitivity analyses were also performed using no imputation and imputation of 0% for nonsurvivors. Prespecified secondary end points were a composite of death, severe (New York Heart Association functional class III or IV) heart failure, and ventricular tachycardia (sustained or nonsustained occurring at least 48 hours after infarction onset), and each of the individual clinical end points, assessed at 30 days. Sample size was determined by expected primary and secondary end points. One hundred thirty-eight patients would be required to detect a 4±12% difference in ejection fraction with two-sided $P=.05$ and $\beta=.80$.

A three-member Data and Safety Committee was charged with assessing the ethics of continuing the study after data from the first 100 patients were reviewed. The investigators remained blinded to study outcome at all times.

**Results**

Baseline clinical and angiographic data for randomized patients are enumerated in Table 1. Randomized groups were well balanced (Table 1) for all parameters evaluated. The registry group ($n=134$) had similar characteristics except that time from infarction onset was considerably less (3.0±1.9 versus 4.5±1.9 hours, $P=.001$).

Procedural and 30-day ventriculographic and clinical outcomes are shown in Table 2. In the angioplasty group, that procedure was successfully performed (final TIMI flow grade $\geq 2$ and percent stenosis $\leq 50\%$) in 0 of 72 attempts (92%). Infarct artery patency at prehospital discharge in centers that routinely performed catheterization at that time was 35 of 38 (92%) for the angioplasty group and 10 of 24 (42%) for the conservatively managed group ($P=.001$). Thirty-day clinical outcomes were available in all patients, and ventriculographic outcomes were available in 130 of 140 (93%) eligible patients. There was no difference in resting ejection fraction or the incidence of ventricular tachycardia, but angioplasty appeared to reduce death or severe heart failure ($P=.05$) as well as improve exercise ejection fraction ($P=.04$) and possibly reduce severe heart failure alone ($P=.11$). Causes of death in the

### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Angioplasty</th>
<th>Conservative</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>78</td>
<td>73</td>
</tr>
<tr>
<td>Age, y</td>
<td>59±11</td>
<td>59±11</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>79</td>
<td>85</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>44</td>
<td>56</td>
</tr>
<tr>
<td>Time from MI, h</td>
<td>4.5±1.9</td>
<td>4.5±1.9</td>
</tr>
<tr>
<td>Systolic BP, mm Hg</td>
<td>126±23</td>
<td>135±26</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>84±15</td>
<td>83±17</td>
</tr>
<tr>
<td>Killip class $\geq 2$, %</td>
<td>21</td>
<td>26</td>
</tr>
<tr>
<td>Multivessel disease, %</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>Ongoing angina at the time of catheterization, %</td>
<td>81</td>
<td>67</td>
</tr>
<tr>
<td>Proximal occlusion site, %</td>
<td>46</td>
<td>51</td>
</tr>
<tr>
<td>TIMI 1 flow, %</td>
<td>36</td>
<td>46</td>
</tr>
<tr>
<td>Angiographic collaterals, %</td>
<td>32</td>
<td>37</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; BP, blood pressure; and bpm, beats per minute.
Prior studies had found postinfarction survival to be correlated with resting or exercise ejection fraction, left ventricular end-systolic volume, ventricular arrhythmias, and heart failure. Logistical concerns dictated that the primary end point for this study be ejection fraction, in that it was readily obtainable and that with a modest number of patients the potential for a meaningful difference in outcome could be assessed (a 4% difference in ejection fraction in a group of patients with anterior infarction might "translate" into a 4% to 7% absolute percentage difference in mortality). At the same time, however, it was recognized that a disparity between ejection fraction and survival had been noted in several prior studies, and therefore clinical end points were prespecified as secondary end points.

Indeed, no benefit from angioplasty was found on resting ejection fraction measured at 30 days, even in patients treated relatively early, or in freedom from ventricular tachycardia. However, patients randomized to angioplasty did appear to have a reduction in the combination of death and severe heart failure and in ejection fraction with exercise at 30 days. These apparent benefits were noted despite the fact that there appeared to be a strong investigator bias not to randomize patients presenting particularly early in the course of their infarction.

Reperfusion within the first 1 to 2 hours of myocardial infarction appears necessary to routinely obtain a sizable benefit in systolic ventricular function assessed by ejection fraction. Given the inherent time delay with the current strategy of rescue angioplasty—90 to 120 minutes to make the difficult diagnosis of failed reperfusion and another 30 to 60 minutes to rush the patient to the catheterization laboratory, perform diagnostic angiography, and then perform rescue angioplasty—it probably is not surprising that benefit measured by resting ejection fraction could not be demonstrated. However, reperfusion therapy by thrombolytic therapy has been shown to improve survival when administered up to 12 hours after infarct onset, and it has been suggested that this benefit occurs via changes in ventricular diastolic function and healing, and possibly via a decrease in susceptibility to serious arrhythmias. Nearly immediate improvement in diastolic function with very delayed reperfusion has been demonstrated in animal models of infarction, and reduction in ventricular tachycardias by streptokinase therapy was observed in GISSI I. Assuming this paradigm to be correct, then any benefit from rescue angioplasty would need to result from angioplasty affecting a higher incidence of, or earlier, reperfusion than might be expected by delayed lytic-mediated reperfusion and not be offset by any adverse effect of the angioplasty procedure itself. Data from this study and its much smaller predecessor, taken together, strongly suggest that rescue angioplasty may exert a benefit for selected patients and that the responsible mechanism(s) likely involve improved diastolic function and/or systolic function under stress.

Such conclusions must be tempered by an understanding of the source from which they are drawn. First, the entire “universe” of patients randomized to assess potential benefit of rescue angioplasty numbers less than 200, and like primary angioplasty, the benefit, although substantial in relative terms, has been demon-
stratified only in a small population compared with intravenous thrombolytic therapy. Second, the angioplasty success rate of 92% in this study is considerably higher than that previously reported in most series11 and may not be representative of that achieved in the community. Third, only patients with anterior wall infarcts were included in this study. This is known to be a high-risk subset with large infarcts, as witnessed by an average ejection fraction 10 to 15 points lower than that noted in most reperfusion studies assessing ventricular function.30,31 and therefore they have much to gain.22 Any benefit seen, were it to be reproducible, should not necessarily be generalized to all patients with myocardial infarction treated by all interventional cardiologists. Conversely, a modest but clinically meaningful benefit of rescue angioplasty on systolic ventricular function could have been obscured by differences in technique at the 20 centers or by the apparent bias within this study not to randomize patients seen in the first few hours of their infarction.

The results provide support for (1) immediate catheterization and angioplasty of patients with large infarcts who have received thrombolytic treatment and are suspected not to have had early reperfusion within 6 to 8 hours of symptom onset, and (2) development of noninvasive techniques to accurately and rapidly detect reperfusion so as to better identify patients likely to benefit from this strategy.

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