Recent randomized trials in acute myocardial infarction suggest that infarct size reduction need not be achieved for intravenous streptokinase to improve patient survival. If this is the case, attempts to achieve late revascularization may be justified. To assess the results of late primary coronary angioplasty performed in the setting of acute myocardial infarction, the clinical and angiographic data as well as hospital outcome of 139 consecutive patients treated with coronary angioplasty without prior thrombolytic therapy 6 to 48 h after the onset of chest pain (late group) were compared with those of 117 patients treated with primary angioplasty <6 h after the onset of chest pain (early group); time to angioplasty was assessed as a covariate of survival.

In the 139 patients treated ≥6 h after the onset of chest pain, the mean age (± SD) was 57 ± 12 years and the median time to angioplasty was 15 h; 61% had multivessel disease, 14% were in cardiogenic shock and the mean left ventricular ejection fraction was 44 ± 12%. Angioplasty was successful (final diameter stenosis <70% and Thrombolysis in Myocardial Infarction [TIMI] flow grade ≥2) in 78% of patients. Successful angioplasty was associated with a 5.5% in-hospital mortality rate, whereas unsuccessful angioplasty was associated with a 43% hospital mortality rate (p < 0.001).

Multivariate testing in all patients identified four independent predictors of in-hospital death: cardiogenic shock (p < 0.001), unsuccessful angioplasty (p = 0.001), ejection fraction ≤30% (p = 0.002) and patient age (p = 0.004). Time to angioplasty was not a predictor of outcome (p = 0.56). Unsuccessful angioplasty, however, was associated with a particularly high mortality rate in patients with anterior infarction or ejection fraction ≤30%. Thus, late emergency angioplasty may be justified when the likelihood of angioplasty success is very high. Randomized trials are needed to assess the utility of late coronary reperfusion in the setting of acute myocardial infarction.

Although time-dependent myocardial salvage is generally thought to be the mechanism by which reperfusion therapy improves survival in patients with acute myocardial infarction (1), recent randomized trials (2,3) have shown a survival benefit without a demonstrated or expected reduction in infarct size or improvement in left ventricular function. This has led to the concept that myocardial reperfusion, even if established relatively late in the course of acute myocardial infarction, may be of benefit, perhaps by decreasing malignant arrhythmias (4), by improving infarct healing (5) or by other means. If this is the case, then attempts to reestablish arterial patency in selected patients who present to the hospital relatively late in the course of infarction may be justified.

To assess the results of late primary coronary angioplasty, we reviewed the clinical and angiographic data and hospital outcome of 139 consecutive patients treated with primary coronary angioplasty 6 to 48 h after the onset of chest pain (late group) and compared their outcome with that of 117 consecutive patients treated with primary angioplasty within 6 h of symptom onset (early group).

Methods

Study patients. The late study group comprised 139 patients with acute myocardial infarction treated by angio-
plasty without prior thrombolytic therapy 6 to 48 h after the onset of symptoms at the University of Michigan from 1983 until the end of December 1987. Thirteen other patients were excluded because their procedural cineangiogram was unavailable for review (n = 9) or the pre- or postdilation cineangiogram was of insufficient quality to allow for quantitative analysis (usually because the angiographic guide wire was placed across the stenosis that had been dilated) (n = 4). Twenty-six of the patients had participated in a previously reported randomized trial (6) assessing interventions in acute myocardial infarction. The results in the study group were compared with those from all 117 patients treated with primary coronary angioplasty (no prior thrombolytic therapy) within 5.9 h of the onset of chest pain who otherwise met the same criteria.

During this time period, several randomized trials (7,8) assessing the efficacy of thrombolytic therapy in the setting of acute myocardial infarction were underway. The exclusion from these trials of patients older than 75 years and with cardiogenic shock may have increased the mix of such patients referred for primary angioplasty. Coronary angioplasty was performed after patients gave informed consent and under guidelines approved by the Committee to Review Clinical Research and Investigation at the University of Michigan Medical Center.

**Indications for angioplasty.** All patients underwent coronary angioplasty on the basis of clinical evidence of ongoing ischemia (persistent precordial, arm or neck discomfort or electrocardiographic ST or T wave changes) or hemodynamic compromise. Patients were usually not considered to be eligible for angioplasty if they had ≥60% diameter stenosis of the left main coronary artery, ≥70% stenosis of both the proximal left anterior descending and left circumflex coronary arteries or distal occlusions in tortuous vessels that were not believed to be technically suitable for the procedure. Patients were not necessarily excluded because of advanced age or poor left ventricular function and, in fact, the concurrent presence of clinically evident severe left ventricular dysfunction in patients >6 h after the onset of chest pain often prompted referral for cardiac catheterization and angioplasty.

**Angioplasty technique.** The technique of coronary angioplasty utilized has been previously described (6). Briefly, all patients received sublingual nitroglycerin (400 μg) to exclude coronary spasm and intravenous morphine for chest pain, and all had cardiac catheterization performed after the placement of vascular sheaths and administration of 3,000 to 5,000 U of heparin. After it was determined that a patient's coronary anatomy was suitable for angioplasty, an additional 5,000 to 7,000 U of intravenous heparin was given and angioplasty was performed. After adequate reduction of the stenosis had been accomplished, patients were treated with intravenous heparin (for 3 to 10 days), aspirin (80 to 600 mg daily) and an oral calcium channel blocker and nitrate (as tolerated). All patients were initially monitored in the intensive care unit. Hemodynamic monitoring was performed, and adjunctive treatment was administered as clinically indicated.

**Clinical variables.** Clinical data had been prospectively entered onto case report forms at the time of the catheterization. Case report forms and patient charts were reviewed by an independent observer, unaware of angiographic and in-hospital outcome, to assure completeness and accuracy of the data. Ten clinical variables were analyzed for all patients: 1) age; 2) gender; 3) diabetes mellitus; 4) prior myocardial infarction; 5) infarct site (anterior or inferior/posterior); 6) time from onset of chest pain to coronary angioplasty; 7) systolic blood pressure on arrival in the cardiac catheterization laboratory; 8) presence of cardiogenic shock (defined as systolic blood pressure after volume replacement ≤80 mm Hg without, or ≤89 mm Hg with, the use of an intravenous inotropes agent or balloon counterpulsation support); 9) postangioplasty recurrent ischemia (defined as the need for repeat angioplasty or bypass surgery, a secondary increase in creatine kinase isoenzymes or silent total occlusion of the site dilated found on predischarge angiography); and 10) in-hospital death. Additional data were retrieved and analyzed retrospectively for patients who had died after angioplasty; these included time from angioplasty until death, peak creatine kinase level, cause of death and necropsy results.

**Angiographic variables.** The following angiographic variables were entered prospectively at the time of catheterization by observers unaware of clinical outcome: pre- and postangioplasty percent diameter stenosis measured with use of a computer-assisted quantitative angiographic system (9), and pre- and postangioplasty Thrombolysis in Myocardial Infarction (TIMI) coronary flow grade (10).

**Statistical analysis.** Data were entered into the University of Michigan PTCA for Acute Infarction Database, a relational data base that uses SYSTAT software (11).

Data are presented as mean values ± SD except where noted. Unpaired Student's t tests and chi-square analyses were used to compare continuous and categorical single variables with outcome. Two-tailed p ≤ 0.05 was considered significant, although values of 0.05 < p < 0.10 are included for completeness (12). Multivariate logistic regression analyses with alpha to enter and remove variables = 0.15 (13) were used to test hypotheses regarding the independent effect of variables on the in-hospital mortality rate. To test the independent effect of angioplasty success on the mortality rate after the contribution of other important predictors of outcome, a final multivariate analysis was performed, first forcing the previously significant variables into the equation (14,15), and then entering angioplasty outcome into the model.
Results

Patient characteristics. The characteristics of the 256 patients and the coronary stenosis dilated in both the time 0 to 5.9 h (early) (n = 139) and 6 to 48 h (late) (n = 117) angioplasty groups are enumerated in Table 1. Because of the selection pressures noted in the previous section, the groups differed slightly in patient composition. In general, patients with late angioplasty had more extensive disease and more severe left ventricular dysfunction.

Initial angioplasty results and in-hospital events for early and late angioplasty groups (Table 2). There were no differences between the groups in terms of procedural success, improvement in ejection fraction, recurrent ischemia after apparently successful angioplasty or incidence of in-hospital death. When late angioplasty was successful, the mortality rate was 5.5%, but when it was unsuccessful, it was 43.3% (p < 0.001).

Correlates of in-hospital mortality for all patients treated (Table 3). Of the variables tested, seven were significant univariate predictors of increased in-hospital mortality rate: cardiogenic shock (p < 0.001), unsuccessful angioplasty (p < 0.001), low left ventricular ejection fraction (p < 0.001), patient age (p < 0.001), total occlusion before angioplasty (p = 0.003), prior myocardial infarction (p = 0.03) and triple vessel coronary artery disease (p = 0.055). In multivariate testing, there were four independent predictors of the in-hospital mortality rate: cardiogenic shock, unsuccessful angioplasty, low ejection fraction and patient age.

Effect of time to angioplasty on influence of successful angioplasty on mortality rate. Time to angioplasty was weakly correlated with the incidence of in-hospital death in univariate testing (coefficient = 0.003, constant = 0.099, p = 0.08). Time was then entered into a multivariate analysis utilizing both the early- and late-treated patients with the following independent variables: cardiogenic shock, ejection fraction, angioplasty success, patient age and time from the onset of chest pain to angioplasty, and with mortality as the end point (Table 3). Cardiogenic shock, angioplasty success, low ejection fraction and patient age were independent predictors of outcome, whereas time from the onset of chest pain (p = 0.56) was not a predictor of outcome.

Causes and timing of in-hospital death after late angioplasty. Because of the high mortality (13 of 30 = 43%) of patients with unsuccessful late angioplasty, these 13 patients were characterized separately and compared with the 30 who survived a failed angioplasty procedure. Of the 13 patients who died, 9 (69%) were men, their mean age was 62 ± 10 years, 10 (77%) had anterior infarction and the mean time to angioplasty was 20 ± 17 h. Death occurred 42 ± 52 h (median 6 h) after angioplasty, with four deaths occurring in the catheterization laboratory. Eleven of the 13 deaths (84.5%) were attributed to cardiogenic shock. The mean peak creatine kinase concentration was 1,281 ± 432 U/liter, but the actual peak may have been missed as a result of late hospitalization in some patients. Transient reperfusion had been achieved in eight patients (61.5%). The statistical power for detecting significant differences between those dying and surviving was low because of the small number of patients involved, but those dying had a lower ejection fraction (30 ± 8% versus 43 ± 16%, p = 0.015) and more frequently had anterior infarction (77% versus 41%, p = 0.05). In addition, these patients tended to be older (62 ± 10 versus 55 ± 12 years), to have had lower blood pressure at...
angiplasty, and would seem to confirm that the primary angioplasty result, not the age of the occlusive or partially occlusive thrombus, is the primary determinant of the risk of later in-hospital recurrent ischemia (22). These results are in agreement with those reported by Yeager et al. (23) in the only other reported sizable series of this kind, except that in our analysis, left ventricular ejection fraction did not increase from baseline to prehospital discharge in either the early or the late angioplasty group.

**Effect of angioplasty on patient survival.** Successful late angioplasty conferred a relative survival advantage to patients even after consideration of other important predictors of outcome. This was not a randomized trial of late angioplasty versus conventional therapy, however, and one cannot exclude the possibility that failed angioplasty increased the likelihood of in-hospital death, especially given the high mortality rates in patients with failed angioplasty relative to historical control patients presenting late, who were treated without reperfusion (mortality rate with successful late angioplasty = 5.5%, with unsuccessful angioplasty = 43.3%, overall = 13.7% versus 13.9%) in 961 patients presenting 6 to 12 h after symptom onset in the Gruppo Italiano per lo Studio della Streptochinasi nell’Infarto Miocardico (GISSI) trial (16). A truly appropriate “control” group is, unfortunately, not available, and patients in the GISSI trial probably had a lower overall risk than did the patients treated late in this study (2% cardiogenic shock in all GISSI patients versus 14% in this study, 15% incidence of prior myocardial infarction in GISSI versus 25% in this study).

**Potential risk of late reperfusion.** Experimental studies would suggest that delayed reperfusion might well be a “double-edged sword” (24), increasing the risk of hemorrhagic infarction, with its potential consequent deleterious mechanical and functional effects (25,27). Of note, two of the five patients who underwent necropsy in this series had a hemorrhagic tear of the free wall of the left ventricle. Nonetheless, the mortality rates in this series for patients with successful angioplasty are less than one would expect from conventionally treated patients.

**Limitations.** The primary limitations of this study are the lack of a medically treated control group and the relatively small numbers of patients studied. Therefore, one cannot necessarily conclude that successful angioplasty improved

### Table 3. Correlates and Effect of Time to Coronary Angioplasty on In-Hospital Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>T</th>
<th>Multivariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiogenic shock</td>
<td>0.292</td>
<td>0.052</td>
<td>5.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Successful PTCA</td>
<td>-0.146</td>
<td>0.042</td>
<td>-3.53</td>
<td>0.001</td>
</tr>
<tr>
<td>LVEF</td>
<td>-0.005</td>
<td>0.002</td>
<td>-3.70</td>
<td>0.007</td>
</tr>
<tr>
<td>Patient age</td>
<td>0.004</td>
<td>0.001</td>
<td>2.91</td>
<td>0.004</td>
</tr>
<tr>
<td>Time to PTCA</td>
<td>0.001</td>
<td>0.002</td>
<td>0.58</td>
<td>0.562</td>
</tr>
<tr>
<td>Constant</td>
<td>0.163</td>
<td>0.130</td>
<td>1.26</td>
<td>0.210</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
patient survival because failed angioplasty may have diminished survival and factors other than those assessed in multivariable testing also may have influenced outcome.

**Implications.** In conjunction with other similarly provocative study results (2,3), these results suggest the need for a randomized trial investigating a possible survival benefit of delayed reperfusion in certain patients with acute myocardial infarction. However, the high mortality rate with failed coronary angioplasty or perhaps other forms of reperfusion therapy. However, given the mortality rates in patients with failed angioplasty, a high likelihood of success should be expected before this intervention is performed.

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