Reperfusion therapy using either intravenous thrombolytic agents or primary percutaneous transluminal coronary angioplasty (PTCA) is established therapy for acute myocardial infarction (AMI) (1–5). In experimental (6–8) and clinical studies (1–5), time to successful reperfusion is a critical determinant of outcome. Experimental models have demonstrated that other factors playing critical roles in ultimate infarct size include extent of myocardium at risk, myocardial metabolic demand and collateral blood flow to the infarct-related region (6–8).

Technetium-99m sestamibi (Tc-99m) has been used effectively in the past to measure residual and collateral blood flow, myocardium at risk and infarct size in clinical AMI (9–12). The minimal redistribution of this agent, despite restoration of hyperemic blood flow after coronary artery reperfusion, allows for measurement of these indexes without interrupting reperfusion therapy (13,14).

Previous work using Tc-99m in clinical AMI has shown a poor linear correlation between time to reperfusion therapy and final infarct size (15). Although reperfusion therapy received within 2 h is associated with the greatest benefit (5), many patients receiving late therapy also have significant degrees of myocardial salvage. In a recent meta-analysis of 22 placebo-controlled trials of thrombolytic therapy for AMI, a nonlinear relation was demonstrated between time to reperfusion and mortality (16). In that study, the beneficial effect of thrombolytic therapy was substantially higher in patients treated within 2 h of symptom onset. In patients presenting after 2 h, the effect of time to therapy on mortality was less.

To identify variables that are associated with myocardial salvage in patients with AMI, we measured time to reperfusion therapy, myocardial salvage, residual blood flow to myocardium at risk, hemodynamic data and clinical variables in 55 patients presenting with acute anterior MI who received successful reperfusion therapy. We hypothesized that time to reperfusion therapy would be the major determinant of myocardial salvage for those patients receiving such therapy within 2 h. For patients receiving reperfusion therapy after 2 h, we hypothesized that the degree of residual blood flow to the myocardium at risk, either through collateral vessels or residual anterograde flow in the infarct-related artery (IRA), would be the most important determinant of myocardial salvage.

**Time to Therapy and Salvage in Myocardial Infarction**

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**Objectives.** This study sought to examine the influence of time to reperfusion on myocardial salvage.

**Background.** Major trials of reperfusion therapy for myocardial infarction (MI) have demonstrated improved outcome for patients achieving earlier reperfusion. However, some patients experience significant benefit despite delayed reperfusion.

**Methods.** Fifty-five patients with a first anterior MI underwent successful reperfusion therapy (angioplasty or thrombolysis). Technetium-99m (Tc-99m) sestamibi was injected before reperfusion therapy and again at hospital discharge to determine the myocardial salvage index for each patient. Residual flow to the infarct territory was assessed by the nadir of the Tc-99m sestamibi count–profile curve.

**Results.** The salvage index showed wide variability (range −0.04 to 1.0), and extreme values were seen in 34.5% of the group (<0.10 in 9%, >0.90 in 25%). A high salvage index was associated with reperfusion therapy before 2 h (p = 0.02) or good residual blood flow (p < 0.01). For the 10 patients who received reperfusion therapy within 2 h, residual blood flow was not correlated with salvage (p = 0.12). For the 45 patients treated after 2 h, residual blood flow correlated significantly with salvage (r = 0.57, p < 0.0001). There was a significant interaction (p < 0.05) between residual blood flow and time to therapy, indicating that the effect of each variable on salvage depended on the value of the other. Multiple historic and hemodynamic variables were examined, but none demonstrated any association with residual flow or myocardial salvage.

**Conclusions.** In patients with acute MI, successful reperfusion therapy within 2 h is associated with the greatest degree of myocardial salvage. For patients treated after 2 h, residual blood flow to the infarct-related territory appears to be the most important determinant of myocardial salvage.

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Abbreviations and Acronyms
AMI = acute myocardial infarction
ANOVA = analysis of variance
ECG = electrocardiogram, electrocardiographic
GUSTO = Global Use of Strategies to Open Occluded Arteries
IRA = infarct-related artery
LV = left ventricular
LVEF = ejection fraction
PTCA = percutaneous transluminal coronary angioplasty
Tc-99m = technetium-99m
TIMI = Thrombolysis in Myocardial Infarction

Methods

Study group. The study group included a consecutive series of patients enrolled in a prospective study of Tc-99m in AMI who met the following inclusion criteria: 1) chest pain lasting \( \geq 30 \) min; 2) electrocardiographic (ECG) ST segment elevation of \( \geq 0.1 \) mV in at least two consecutive anterior precordial leads (leads V_1 to V_4); and 3) successful reperfusion therapy of patients enrolled in a prospective study of Tc-99m in AMI who met the following inclusion criteria: 1) chest pain lasting 11 years, range 38 to 80). Forty of these patients were included in a previous study of infarct size (15).

Clinical care. The use of aspirin, heparin, nitroglycerin and beta-blockers was in accordance with standard clinical practice and was determined by the attending cardiologist or clinical trial protocol.

Radionuclide studies. Each patient received 20 to 30 mCi of Tc-99m intravenously before reperfusion therapy and again before hospital discharge. Thirty images were obtained for 40 s each, every 6° over an arc of 180° from the 45° left posterior oblique to the 45° right anterior oblique. Images were reconstructed using standard back-projection algorithms and a Ramp-Hanning filter. Short-axis slices of the left ventricle were obtained every 6 mm and normalized to the peak counts in the heart. Circumferential count profiles were assessed using the nadir of the five short-axis Tc-99m sestamibi circumferential count–profile curves from the acute images. The nadir represents residual blood flow to the infarct zone. The technique does not distinguish between residual flow from the IRA or collateral blood flow. The basic assumption of this technique is that the depth of the profile curve is inversely proportional to residual blood flow in the infarct territory. The nadir of the count–profile curve has been previously validated and shown to correlate significantly with angiographic estimates of collateral flow in experimental (23) and clinical infarcts (15).

In patients with anterior MI undergoing acute angiography before direct PTCA, we have shown that about one-half have Rentrop grade 2 or 3 collateral vessels (15). In the present study, where most patients did not undergo acute angiography, we defined “good” collateral vessels as a nadir greater than the median, and “poor” collateral vessels as a nadir less than or equal to the median.

Historical and hemodynamic variables. The following were tested for an association with myocardial salvage: age, gender, previous angina, history of hypertension (n = 19), diabetes mellitus (n = 6), chronic beta-blocker therapy (n = 6), smoking status, presenting heart rate, presenting systolic blood pressure and presenting rate–pressure product. Angina was analyzed with respect to its presence and duration. Left ventricular ejection fraction (LVEF) was measured at hospital discharge with equilibrium radionuclide angiography using standard techniques (24).

Statistics. Data were expressed as the mean value \( \pm \) SD or the median value with percentiles when the groups were skewed. Simple linear regression analysis was done to compare residual blood flow (nadir) with the salvage index. The latter
two variables were compared with respect to time to therapy using Spearman and linear correlation. Two-way analysis of variance (ANOVA) was used to test for an interaction effect between residual blood flow and time with respect to salvage index. Linear regression analysis, one-factor ANOVA, an unpaired t test and a chi-square test were used, as appropriate, to test the association of various clinical variables with residual blood flow and salvage index.

Results

Time to reperfusion therapy. For all 55 patients, time to reperfusion therapy was 320 ± 285 min (range 88 to 1290). For patients receiving thrombolytic therapy, time from onset of chest pain to initiation of thrombolytic infusion was 188 ± 91 min (range 88 to 395). Seven patients had thrombolytic therapy initiated within 2 h. Thirty-two patients received primary PTCA. In these patients, the time from the onset of chest pain to first balloon inflation was 415 ± 337 min (range 89 to 1290). Three patients had PTCA within 2 h.

Myocardial salvage. The early perfusion defect size, or myocardium at risk, was 47 ± 14% of the LV (range 10% to 73%). Tomographic quantitation of discharge infarct size measured 22 ± 20% of the LV (range 0% to 55%). The salvage index showed wide variability with a skewed distribution (Fig. 1). The median value for the salvage index was 0.60, with 25th and 75th percentiles of 0.26 and 0.93, respectively (range −0.04 to 1.0). Five patients (9.1%) had a salvage index <0.10, suggesting minimal treatment benefit. Fourteen patients (25.5%) had a salvage index >0.90, suggesting nearly complete myocardial salvage with minimal infarction (Table 1).

Extreme values of salvage index (Table 1). When the five patients with a low salvage index (<0.10) were compared with the 14 patients with a high salvage index (>0.90), there was a highly significant difference in final infarct size and LVEF at discharge between the two groups. Treatment modality and time to treatment did not differ between the two groups. Of the five patients with a low salvage index, none received reperfusion therapy within 2 h. Of the 14 patients with a high salvage index, five received reperfusion therapy within 2 h (p = 0.17 compared with low salvage index group). None of the five patients with a low salvage index had good residual blood flow. In contrast, 11 of 14 patients in the high salvage index group had good residual blood flow (p = 0.005 vs. low salvage index group). Three patients with a high salvage index and poor residual blood flow were treated at 95 min, 128 min and 298 min. Thus, 12 of the 14 patients with a high salvage index had either reperfusion therapy within 2 h or good residual blood flow. None of the five patients with a low salvage index had early therapy or good residual blood flow (p = 0.005 vs. low salvage index group).

Residual blood flow. For all 55 patients, the nadir was 0.22 ± 0.13, with a median value of 0.19. Twenty-six patients had a nadir of >0.19 and were classified as having good residual blood flow; 29 patients had a nadir of ≤0.19 and were classified as having poor residual blood flow. For all patients, residual blood flow correlated weakly but significantly with the salvage index (r = 0.57, p = 0.0001). For the 10 patients who received reperfusion therapy within 2 h, residual blood flow did not correlate with the salvage index (rho 0.51, p = 0.12) (Fig. 2A). However, collateral blood flow did correlate with the salvage index for the 45 patients treated after 2 h (r = 0.57, p = 0.0001) (Fig. 2B). There was a significant difference between the two time groups with respect to the relation between collateral blood flow and salvage index, using analysis of covariance (p = 0.035).

Multivariable analysis. Using two-way ANOVA, both time to therapy (<2 h vs. >2 h) (F = 8.4, p < 0.006) and residual blood flow (good vs. poor) (F = 10.3, p < 0.002) were independently associated with the salvage index. A significant interaction (F = 4.1, p < 0.05) was found between residual blood flow and time to therapy, indicating that the effect of time to therapy (<2 h vs. >2 h) and residual blood flow (good vs. poor) on salvage depended on the value of the other (Fig. 3). Patients with either good residual blood flow or time to therapy <2 h, or both, had a high salvage index. The 24 patients with poor residual blood flow and treatment after 2 h had the lowest salvage index values (0.32 ± 0.27).

Clinical variables. Age, gender, previous angina, hypertension, diabetes mellitus, smoking status, long-term beta-blocker

| Table 1. Comparison of Variables of 19 Patients With Extreme Myocardial Salvage (<10% vs. >90% salvage index) |
|--------------------------------------|------------------|------------------|-----------------|
|                                    | Salvage Index    |                  |
|                                    | <0.10 (n = 5)    | >0.90 (n = 14)   | p Value         |
| Discharge LVEF (%)                 | 30 ± 14          | 55 ± 8           | 0.0004          |
| Infarct size (%) of LV             | 49 ± 3           | 1 ± 1            | 0.0001          |
| Angioplasty                        | 60%              | 42%              | NS              |
| Time to treatment (h)              | 4.6              | 4.3              | 0.90            |
| Reperfusion therapy <2 h           | 0/5              | 5/14             | 0.17            |
| Good residual blood flow           | 0/5              | 11/14            | 0.005           |
| Good residual blood flow or reperfusion <2 h | 0/5              | 12/14            | 0.002           |

*Data presented are mean value ± SD, median or number or percent of patients. LV = left ventricle; LVEF = left ventricular ejection fraction.
use, acute heart rate or acute rate–pressure product were not found to be associated with the myocardial salvage index or collateral grade (Table 2). Acute systolic blood pressure weakly correlated \( r = 0.32, p = 0.02 \) with the salvage index, but this finding is of doubtful significance given the 30 comparisons that were performed. Of all 55 patients, the discharge LVEF was 44 ± 12% (range 16% to 69%). The discharge LVEF was significantly higher among those patients treated within 2 h (52 ± 9% vs. 42 ± 12%, \( p = 0.03 \)).

### Discussion

This study lends insight into the variable clinical outcomes of patients who receive successful reperfusion therapy for AMI. In such patients, myocardial salvage is optimal in the presence of either extremely early therapy (<2 h from symptom onset) or adequate residual blood flow (collateral blood flow or anterograde flow) to the infarct-related territory. In patients treated after 2 h, the most powerful predictor of myocardial salvage was the presence of good residual blood flow, as assessed by radionuclide angiography. No historic or hemodynamic factors accurately predicted myocardial salvage.

**Figure 2.** Relation of residual blood flow and salvage index for patients with reperfusion therapy initiated (A) within 2 h \((n = 10, r = 0.48, p = 0.16)\) and (B) after 2 h \((n = 45, r = 0.57, p = 0.0001)\).

**Figure 3.** Relation between time to reperfusion therapy (Rx) and residual blood flow on myocardial salvage index. Each variable, including their interaction, was significant.

**Table 2.** Assessment of Historical and Hemodynamic Variables Potentially Associated With Residual Blood Flow and Myocardial Salvage

<table>
<thead>
<tr>
<th>Variable</th>
<th>Residual Blood Flow</th>
<th>Salvage Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.56</td>
<td>0.96</td>
</tr>
<tr>
<td>Gender</td>
<td>0.98</td>
<td>0.95</td>
</tr>
<tr>
<td>Angina</td>
<td>0.38</td>
<td>0.33</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.91</td>
<td>0.57</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.20</td>
<td>0.45</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.08</td>
<td>0.38</td>
</tr>
<tr>
<td>Beta-blockers (long term)</td>
<td>0.34</td>
<td>0.86</td>
</tr>
<tr>
<td>Acute HR</td>
<td>0.62</td>
<td>0.18</td>
</tr>
<tr>
<td>Acute SBP</td>
<td>0.12</td>
<td>0.02</td>
</tr>
<tr>
<td>Acute RPP</td>
<td>0.48</td>
<td>0.49</td>
</tr>
</tbody>
</table>

HR = heart rate; RPP = rate–pressure product; SBP = systolic blood pressure.
of salvage is the extent of residual blood flow to the infarct zone.

The nonlinear relation between time to reperfusion therapy and mortality, as recently reported in a meta-analysis of 22 placebo-controlled trials, may be interpreted based on our findings in Figure 3 (16). Of all patients with acute MI, those with good residual blood flow to the infarct zone will have a low rate of loss of viable myocardium. In contrast, those with poor collateral vessels will show an early and rapid loss of myocardium.

None of the clinical variables in this study were predictive of therapeutic efficacy. Although this may be due to a lack of statistical power, this finding is similar to data from the TIMI phase I trial in which numerous variables failed to correlate with angiographic collateral vessels in the initial hours of infarction (25). Time to therapy was dichotomized a priori at 2 h in this study, based on previous animal (26) and clinical (27) studies. Because all patients in this study had “successful” reperfusion, any comparison of an open versus closed artery could not be made. Our study supports the importance, however, of residual blood flow in patients with AMI who are treated successfully with reperfusion therapy.

**Study limitations.** Only survivors of anterior infarcts with successful reperfusion therapy were examined. This group was chosen to minimize the effects of measurement error, as anterior infarcts have greater myocardium at risk (22,23), and because Tc-99m estimates of residual flow are more closely correlated with angiographic grading of collateral vessels in anterior infarcts (15). Both radionuclide and angiographic estimates of residual blood flow are crude, although angiographic grading systems have correlated closely with intraoperative measurements of collateral flow and retrograde perfusion pressure (28). In addition to collateral artery blood flow, radionuclide angiography may also reflect anterograde flow in the IRA.

The exact timing of successful reperfusion cannot be known with certainty in the 23 patients who underwent thrombolysis. Intermittent spontaneous reperfusion and the effects of aspirin and heparin on infarct–vessel patency are difficult to assess. In addition, silent reocclusion may be undetected in some patients and may have affected the final infarct size. Finally, because only 55 patients were examined, the study lacks the statistical power of a larger trial.

Despite these limitations, these data reinforce the importance of very early (<2 h) reperfusion and demonstrate that the efficacy of late reperfusion is primarily determined by the extent of residual blood flow to the infarct territory. Current investigations directed toward understanding the development of collateral circulation may ultimately help to limit infarct size and thereby improve long-term clinical outcome.

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