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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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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.

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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 ≥30 min; 2) electrocardiographic (ECG) ST segment elevation of ≥0.1 mV in at least two consecutive anterior precordial leads (leads V_1 to V_4); and 3) successful reperfusion therapy with either PTCA (n = 32) or thrombolysis (n = 23), defined as restoration of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 on the coronary angiogram (17). Ninety-one patients met these inclusion criteria.

Patients were excluded because of 1) ECG or historic evidence of a previous myocardial infarction (n = 9); 2) clinical instability or death preventing transportation to the nuclear cardiology laboratory (n = 17); 3) anterograde flow in the IRA before direct PTCA (n = 5); 4) no measurable perfusion defect (myocardium at risk) on the early perfusion study (n = 1); 5) technical difficulties precluding radionuclide or angiographic collateral grading (n = 3); and 6) hypertrophic obstructive cardiomyopathy (n = 1). Thus, 55 patients formed the study group (42 men, 13 women; mean age 61 ± 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° right anterior oblique to the 45° left posterior oblique projection.

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 generated for apical, midventricular, basal and two intermediate slices (midway between the apical-midventricular and basal-midventricular slices).

Quantification of the extent of LV perfusion defect has been previously described (15) and validated in phantom models (18), animal models (19) and explanted human hearts (20). Briefly, pixels containing <60% of peak counts were considered abnormal and part of the perfusion defect. Assuming the ventricle consists of a hollow cylinder and hollow cone (for the apical slice), the relative volume of each geometric figure could be estimated using the radius of each representative slice and standard geometric formulas (18). The extent of the defect is expressed as a percentage of the left ventricular (LV) mass. The standard deviation of the difference between repeat measurements using this method is 3% of the left ventricle (21).

Myocardial salvage. The perfusion defect on the acute study represents the amount of myocardium at risk, and the discharge defect corresponds to the final infarct size. The difference between the acute and discharge defects is a measure of myocardial salvage. The salvage index is a measure of treatment efficacy, which allows for comparisons among infarcts of different sizes. It is derived by dividing the difference between the acute and discharge defect sizes (myocardial salvage) by the acute defect size (myocardium at risk) (22). A salvage index of 1.0 indicates an ideal treatment effect, whereas 0 indicates no treatment benefit.

Radionuclide assessment of residual blood flow. This was assessed using the nadir of the five short-axis Tc-99m sestamibi circumferential count–profile curves from the acute images. The nadir is the lowest ratio of minimal counts per pixel over the maximal counts per pixel in the five short-axis slices. 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 ± 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

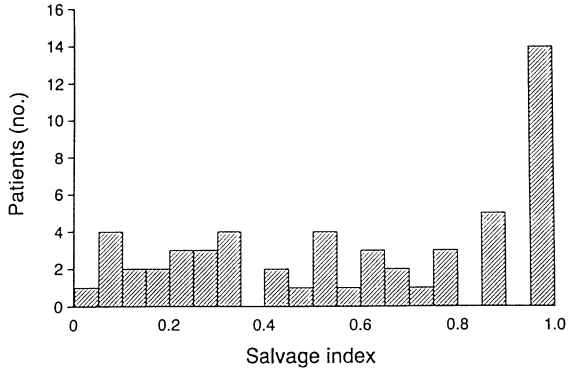

Figure 1. Histogram of salvage index for all 55 patients. The salvage index varied widely, with a dramatically skewed distribution.

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.

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

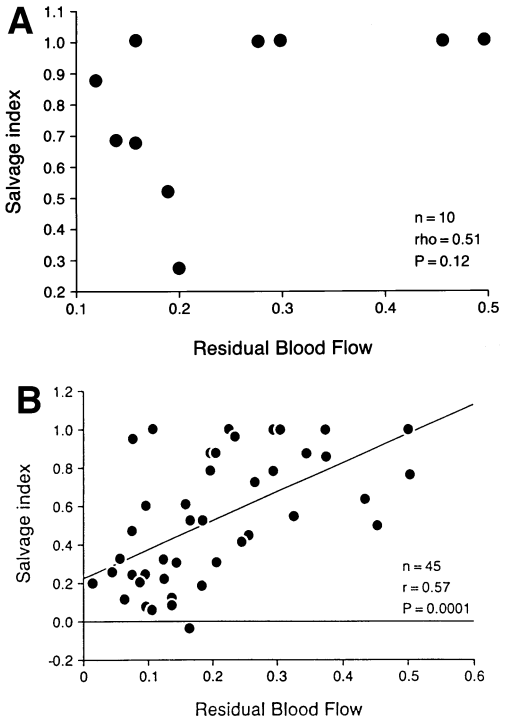

Figure 2. Relation of residual blood flow and salvage index for patients with reperfusion therapy initiated **(A)** within 2 h (n = 10, r = 0.48, p = 0.16) and **(B)** after 2 h (n = 45, r = 0.57, p = 0.0001).

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

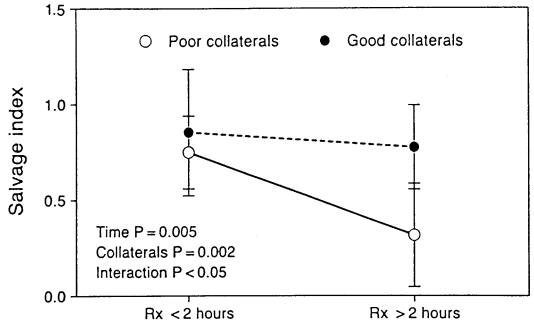

Table 2. Assessment of Historical and Hemodynamic Variables Potentially Associated With Residual Blood Flow and Myocardial Salvage

	p Value	
	Residual Blood Flow	Salvage Index
Age	0.56	0.96
Gender	0.98	0.95
Angina	0.38	0.33
Hypertension	0.91	0.57
Diabetes mellitus	0.20	0.45
Smoking	0.08	0.38
Beta-blockers (long term)	0.34	0.86
Acute HR	0.62	0.18
Acute SBP	0.12	0.02
Acute RPP	0.48	0.49

HR = heart rate; RPP = rate–pressure product; SBP = systolic blood pressure.

Timing and salvage. The finding that early reperfusion therapy is associated with improved myocardial salvage is conceptually consistent with the results from large clinical trials of reperfusion strategies in AMI (1–5). Clinical trials have clearly demonstrated a relation between early therapy and reduced mortality. More recently, this has been shown to be nonlinear, with a much greater mortality benefit if therapy is administered within 2 h of the onset of chest pain (16). A report from the Global Use of Strategies to Open occluded arteries (GUSTO) data base showed that the greatest benefit from thrombolytic therapy was experienced by patients receiving treatment within 2 h. At 2 h an inflexion point was apparent in the curve relating mortality to time to therapy (5).

Although the benefits of reperfusion therapy are greatest when administered early, experimental data have shown that other major determinants of infarct size include the amount of myocardial at risk, myocardial metabolic demand and degree of collateral blood flow to the infarct territory (6,24).

Our results confirm the importance of collateral blood flow in clinical infarction and suggest that adequate collateral flow to an infarct territory results in significant myocardial salvage. Conversely, in patients with poor collateral blood flow, unless reperfusion therapy was received within 2 h, myocardial salvage was extremely poor. Thus, the presence or absence of collateral blood flow explains both the skewed appearance of the salvage index, as seen in Figure 1, and the observation of extremes of salvage index seen in our patient group, as outlined in Table 1. Our data demonstrate that when reperfusion therapy is administered after 2 h, the major determinant

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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References

1. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomized trials of more than 1,000 patients. Lancet 1994;343:311–22.
2. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction: the Primary Angioplasty in Myocardial Infarction study. N Engl J Med 1993; 328:673–679.
3. The GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. N Engl J Med 1993;329:1615–22.
4. Michels KB, Yusuf S. Does PTCA in acute myocardial infarction affect mortality and re-infarction rates? A quantitative overview (meta-analysis) of the randomized clinical trials. Circulation 1995;91:476–85.
5. Newby LK, Rutsch WR, Califf RM, et al., for the GUSTO-I Investigators. Time from symptom onset to treatment and outcomes after thrombolytic therapy. J Am Coll Cardiol 1996;27:1646–55.
6. Reimer KA, Jennings RB, Cobb FR, et al. Animal models for protecting ischemic myocardium: results of the NHLBI cooperative study: comparison of unconscious and conscious dog models. Circ Res 1985;56:651–65.
7. Schaper W, Frenzel H, Hort W, Winkler B. Experimental coronary artery occlusion: II. Spatial and temporal evolution of infarcts in the dog heart. Basic Res Cardiol 1979;74:233–9.
8. Kloner RA, Ellis SG, Lange R, Braunwald E. Studies of experimental coronary artery reperfusion: effects on infarct size, myocardial function, biochemistry, ultrastructure, and microvascular damage. Circulation 1983;68 Suppl I:I-8–15.
9. Gibbons RJ, Holmes DR, Reeder GS, Bailey KK, Hopfenspirger MR, Gersh BJ. Immediate angioplasty compared with the administration of a thrombolytic agent followed by conservative treatment for myocardial infarction. N Engl J Med 1993;328:685–91.
10. Gibbons RJ, Verani MS, Behrenbeck T, et al. Feasibility of tomographic Tc-99m-hexakis-2-methoxy-2-methylpropyl-isonitrile imaging for the assessment of myocardial area at risk and the effect of acute treatment in myocardial infarction. Circulation 1989;80:1277–86.
11. Behrenbeck T, Pellikka PA, Huber KC, Bresnahan JF, Gersh BJ, Gibbons RJ. Primary PTCA in myocardial infarction: assessment of myocardial salvage with Tc-99m sestamibi. J Am Coll Cardiol 1991;17:365–72.
12. Christian TF, Gibbons RJ, Gersh BJ. Effect of infarct location on myocardial salvage assessed by technetium-99m-isonitrile. J Am Coll Cardiol 1991;17: 1303–8.
13. DeCoster PM, Wijns W, Cauwe F, Robert A, Beckers C, Melin JA. Area at risk determination by technetium-99m-hexakis-2-methoxy-isobutyl-isonitrile in experimental reperfused myocardial infarction. Circulation 1990;82:2151–62.
14. Sinusas AJ, Trautman KA, Bergin JD, et al. Quantification of "area at risk" during coronary occlusion and degree of myocardial salvage after reperfusion with technetium-99m-methoxyisobutyl-isonitrile. Circulation 1990;82:1424–37.
15. Christian TF, Schwartz RS, Gibbons RJ. Determinants of infarct size in reperfusion therapy for acute myocardial infarction. Circulation 1992;86:81–90.
16. Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. Lancet 1996;384:771–5.
17. The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings. N Engl J Med 1985;312:932–6.
18. O'Connor MK, Hammell T, Gibbons RJ. In vitro validation of a simple tomographic technique for estimation of percentage myocardium at risk using methoxyisobutyl isonitrile technetium-99m (sestamibi). Eur J Nucl Med 1990;17:69–76.
19. Verani MS, Jeroudi MO, Mahmarian JJ, et al. Quantification of myocardial infarction during coronary occlusion and myocardial salvage after reperfusion using cardiac imaging with technetium-99m-hexakis-2-methoxyisobutyl isonitrile. J Am Coll Cardiol 1988;12:1573–81.
20. Medrano R, Lowry RW, Young JB, et al. Assessment of myocardial viability with ^{99m}Tc-sestamibi in patients undergoing cardiac transplantation: a scintigraphic-pathologic study. Circulation 1996;94:1010–7.

21. Gibbons RJ, Verani MS, Behrenbeck T, et al. Feasibility of tomographic ^{99m}Tc-hexakis-2-methoxy-2-methylpropyl-isonitrile imaging for the assessment of myocardial area at risk and the effect of treatment in acute myocardial infarction. Circulation 1989;80:1277–86.
22. Christian TF, Gibbons RJ, Gersh BJ. Effect of infarct location on myocardial salvage assessed by technetium-99m isonitrile. J Am Coll Cardiol 1991;17: 1303–8.
23. Christian TF, O'Connor MK, Schwartz RS, Shepherd FJ, Gibbons RJ, Ritman EL. Technetium-99m MIBI to assess coronary collateral flow during acute myocardial infarction in two closed chest animal models. J Nucl Med 1997;38:1840–6.
24. Reimer KA, Jennings RB. The "wavefront phenomenon" of myocardial ischemic cell death: II. Transmural progression of necrosis within the framework of ischemic bed size (myocardium at risk) and collateral flow. Lab Invest 1979;40:633–44.
25. Habib GB, Heibig J, Forman SA, et al., and the TIMI Investigators. Influence of coronary collateral vessels on myocardial infarct size in humans: results of phase I Thrombolysis in Myocardial Infarction (TIMI) trial. Circulation 1991;83:739–46.
26. Murdock RH, Chu A, Grubb M, Cobb FR. Effect of re-establishing blood flow on extent of myocardial infarction in conscious dogs. Am J Physiol 1985;249:H783–91.
27. National Heart Foundation of Australia Coronary Thrombolysis Group. Coronary thrombolysis and myocardial salvage by tissue plasminogen activator given up to 4 hours after onset of myocardial infarction. Lancet 1988;1:203–8.
28. Goldstein RE, Stinson EB, Scherer JL, Senigen RP, Grehl TM, Epstein SE. Intraoperative coronary collateral function in patients with coronary occlusive disease: nitroglycerin responsiveness and angiographic correlations. Circulation 1974;49:298–308.