Determinants of Infarct Size in Reperfusion Therapy for Acute Myocardial Infarction

Timothy F. Christian, MD; Robert S. Schwartz, MD; and Raymond J. Gibbons, MD

Background. Experimental animal studies have demonstrated that myocardium at risk, residual collateral flow, and duration of coronary artery occlusion are important determinants of final infarct size. The present study examined these variables in patients with acute myocardial infarction in relation to final infarct size.

Methods and Results. Myocardium at risk was assessed with hexakis(2-methoxyisobutyl isonitrile) technetium (I) $^{99m}$Tc sestamibi in 89 patients with first-time myocardial infarction (anterior, 48 patients; inferior, 41 patients). All patients had successful reperfusion therapy with either intravenous thrombolysis (32 patients) or primary coronary angioplasty (57 patients) within 24 hours of the onset of chest pain (4.7±3.9 hours; range, 0.5–21.5 hours) documented by coronary angiography. $^{99m}$Tc sestamibi was injected intravenously before reperfusion therapy, and tomographic imaging was performed 1–6 hours later. Myocardium at risk was quantitated for each patient and expressed as a percentage of the left ventricle: 35±19%; range, 2–73%. Collateral flow was estimated by both invasive and noninvasive methods. Fifty-three patients with TIMI grade 0 or 1 flow who underwent primary coronary angioplasty had collateral flow graded angiographically (0–3) before the first balloon inflation. All patients had collateral flow estimated noninvasively from the acute sestamibi short-axis profile curve by three methods that assess the severity of the perfusion defect. Each of these three methods was significantly associated with angiographic collateral grade. Final infarct size was determined at hospital discharge by a second sestamibi study (17±17%; range, 0–59%). Myocardium at risk ($r=0.61$, $p<0.0001$), angiographic collateral grade ($p=0.0003$), and radionuclide estimates of collateral flow ($r=0.69–0.70$, all $p<0.0001$) were all significantly associated with final infarct size. The time to reperfusion therapy was not significantly associated with final infarct size by univariate analysis ($r=0.18$, $p=0.10$). Two multivariate models were constructed to determine which variables were independently associated with final infarct size. In the invasive model, myocardium at risk, angiographic collateral grade with an interaction term for infarct location, and time to reperfusion were all independently significant and accounted for 70% of the variability in final infarct size. The noninvasive model, which substituted a radionuclide estimate of collateral flow for angiographic collateral grade, showed nearly identical results, accounting for 68% of the variability in infarct size in patients where the infarct artery was known to be occluded. When all patients were included (patients with and without acute angiography), the noninvasive model accounted for 59% of the variability in infarct size.

Conclusions. Myocardium at risk, collateral flow, and duration of coronary occlusion are each independently associated with final infarct size and account for most of its variability. Ideally, all three parameters should be examined in evaluation of the efficacy of new treatment strategies for acute myocardial infarction. (Circulation 1992;86:81–90)

Key Words • radionuclide imaging • collateral circulation

In a multicenter experimental animal protocol (AMPIM) in which the location and duration of coronary occlusion were constant, Reimer et al\textsuperscript{1} reported that angiographic area at risk, residual collateral flow to the infarct zone, and myocardial metabolic demand were independent determinants of infarct size after reperfusion. These findings were consistent with multiple previous reports. Myocardium at risk is highly variable for coronary occlusion at a given site and is an important determinant of infarct size.\textsuperscript{2–11} Collateral flow has been inversely correlated with final infarct size in multiple animal and clinical studies.\textsuperscript{7–10,12–16} The time-dependent nature of myocardial salvage has been clearly established in animal models of coronary artery occlusion/reperfusion.\textsuperscript{9,17}

Until recently, it has not been clinically feasible to measure myocardium at risk. Feiring et al\textsuperscript{2} were the first to measure myocardium at risk with the use of intracoronary radiolabeled microspheres. Hexakis(2-methoxyisobutyl isonitrile) technetium (I) $^{99m}$Tc sestamibi has been shown to be useful in both animal and clinical studies to accurately reflect myocardium at risk in acute myocardial infarction.\textsuperscript{3,11,18,19} Because of the minimal redistribution of this agent, tomographic imaging can be delayed until reperfusion therapy is complete.\textsuperscript{20} Reperfusion flow does not appear to alter the measurement of myocardium at
Myocardial risk at risk is significantly influenced by infarct location but is highly variable, even within infarct location subgroups. This measurement of jeopardized myocardium may help to explain much of the variability in final infarct size after reperfusion therapy.

99mTc sestamibi can also determine final infarct size in animal models of permanent occlusion and reperfusion. In clinical studies, infarct size estimated by 99mTc sestamibi has correlated with ejection fraction at discharge and 6 weeks and 1 year later. It has also correlated acutely with creatine kinase enzyme levels and with end systolic volume index up to 1 year after infarction.

Coronary collateral circulation is also a determinant of infarct size, but it requires acute invasive assessment; a noninvasive assessment of collateral flow is needed. Preliminary data have suggested that analysis of the 99mTc sestamibi profile curve can provide an estimate of collateral flow that correlates closely with angiographic collateral grade. The purpose of this study was to test the hypothesis that myocardial risk at risk, collateral flow assessed invasively and noninvasively, and time to reperfusion explain most of the variability in infarct size in patients with successful reperfusion therapy for acute myocardial infarction.

Methods

Study Group

The study group consisted of a consecutive series of patients enrolled in a prospective study of 99mTc sestamibi from February 1988 to December 1990 who met the following criteria: 1) chest pain of at least 30 minutes and less than 24 hours, 2) ECG ST segment elevation ≥0.1 mV in at least two contiguous leads in the same vascular territory (anterior, V1 through V4; inferior, II, III, aVF), 3) successful reperfusion therapy by either intravenous thrombolysis or coronary angioplasty as documented by restoration of TIMI grade II or III flow in the infarct-related artery on subsequent angiography, and 4) postmenopausal women or men >18 years of age. There were 109 patients who met the inclusion criteria. Nine patients were excluded because of evidence of a previous myocardial infarction or prior coronary artery revascularization. One patient died before acquisition of the sestamibi discharge image, and four patients' clinical instability precluded acute tomographic imaging. One patient had no apparent defect on the acute perfusion image despite enzymatic evidence of infarction, and in five patients the radionuclide data could not be retrieved from the optical disk for count profile analysis. The remaining 89 patients formed the study group: 74 men and 15 women (mean age, 60 ± 12 years; range, 28–80 years). Infarct location was anterior in 48 patients and inferior in 41 as determined by the acute ECG, coronary angiography, and contrast left ventriculography.

Thrombolytic Therapy

Intravenous thrombolysis was performed by previously described methods with either recombinant tissue-type plasminogen activator or streptokinase (two patients). The time to reperfusion therapy in these patients was taken from the onset of chest pain to the initiation of the infusion.

Direct Coronary Angioplasty

Successful coronary angioplasty was performed in 57 patients and was defined as restoration of TIMI grade II or III flow. The time to reperfusion therapy in this group was the time elapsed from the onset of chest pain to the first balloon inflation. In two patients, thrombolytic therapy was unsuccessful, but rescue coronary angioplasty performed within 24 hours of the onset of chest pain restored grade III flow in the infarct-related artery. Further treatment for both groups almost always included intravenous heparin and β-receptor blockers but was at the discretion of the attending physicians.

Coronary Angiography

All patients underwent coronary angiography with a standard femoral or brachial approach during the hospital stay. Patients undergoing primary coronary angioplasty underwent immediate coronary angiography. Patients receiving thrombolysis had angiography deferred until later in the hospital course (median 1.0 day, 25th percentile 0 days, 75th percentile 3 days). Collateral circulation to the infarct-related artery in 53 patients who underwent primary coronary angioplasty was blindly evaluated by a single observer and was graded before balloon inflation by the classification system proposed by Rentrop et al: 0, no collateral vessels visualized; 1, filling of the branches but not the main epicardial segment of the infarct-related artery; 2, filling of branches and a portion of the epicardial vessel; 3, filling of branches and the entire epicardial vessel. Collaterals were not graded in patients who received primary coronary angioplasty if grade II or III flow was present in the infarct-related artery before balloon inflation (four patients).

Radionuclide Studies

99mTc sestamibi (20–30 mCi) was injected in all patients before reperfusion therapy. Because of the minimal redistribution of this radionuclide agent, tomographic imaging was performed 1–6 hours later, after reperfusion therapy. A second injection and acquisition was performed at hospital discharge 7 ± 1.5 days from admission. Thirty images were acquired for 40 seconds over a 180° arc (45° right anterior oblique to 45° left posterior oblique) using a step-and-shoot method. 99mTc sestamibi images were processed by a previously described technique.

The left ventricular perfusion defect was quantitated by a previously described method. 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 representative apical, midventricular, and basal slices and two intermediate slices (midway between the apex and the midventricle and midway between the midventricle and the base) by identifying the peak counts every 6° around the left ventricle. The ventricle was assumed to consist of a hollow cylinder in all slices except the apex, which was assumed to be a hollow cone. The relative volume of each geometrical cylinder and cone was estimated using the radius of the representative slice and standard geometric formulas. The extent of the defect was determined by the number of radians (60 per slice) in the five count profiles less than 60% of maximal counts in the
slice weighted by the radius of the slice and/or apical location and was expressed as a percentage of the left ventricular myocardial volume.29 The extent of the defect on the acute image reflects myocardium at risk, and the extent of the defect on the predischARGE image reflects final infarct size. 

Collateral flow was estimated by three different techniques from the five short-axis sestamibi profile curves (Figure 1): 1) nadir: the lowest ratio of minimal counts per pixel over the maximum counts per pixel (B/A) of the short-axis slices; 2) severity index: the ratio of the cumulative area of the curve <60% maximal counts over the potential cumulative area for the extent of a defect [C/(C+D)] for all five short-axis slices; and 3) area: the cumulative area of the five curves <60% maximal counts (C).

All three of these methods directly or indirectly reflect the depth of the profile curve for a sestamibi defect. This approach hypothesizes that the depth of the profile curve is proportional to residual myocardial blood flow in the infarct territory, presumably from collateral circulation.

Statistics

Data are expressed as mean±SD or median with 25th and 75th percentiles when the distribution was not normal. Simple linear correlation was used to compare infarct size with myocardium at risk, time to reperfusion, and radionuclide estimates of collateral flow. An unpaired t test was used to compare angiographic radionuclide and time measurements by infarct location. A one-factor ANOVA was used to compare angiographic collateral grade with radionuclide estimates of collateral flow and infarct size.

We then used myocardium at risk, time to reperfusion, and either angiographic collateral grade or the best radionuclide estimate of collateral flow (nadir) to predict infarct size. The nadir measurement was selected over the other two methods used to determine radionuclide collateral flow because it correlated slightly better with infarct size and angiographic collateral grade and was the simplest to derive. When angiographic collateral grade was used, we used a one-factor ANOVA with myocardium at risk and time as covariates. Because the relation between angiographic collateral grade and infarct size depended on infarct location, the interaction between collateral grade and infarct location (anterior versus inferior) was also included as a covariate. When the radionuclide estimate of collateral flow (nadir) was used instead of angiographic collateral grade, we used multiple linear regression analysis. Because the relation between nadir and angiographic collateral grade depended on infarct location, the interaction between nadir and infarct location was also included in the analysis.

Results

Overall Results

See Table 1. Tomographic quantitation of infarct size was 17±17% of the left ventricle (range, 0–59%). Patients with anterior infarction had significantly greater final infarct size (22±20% versus 10±10%, p=0.0005) than patients with inferior infarction. Myocardium at risk was 35±19% of the left ventricle for the group. Patients with anterior myocardial infarction had significantly more myocardium at risk than patients with inferior infarction. Angiographically detectable collaterals were present in 43 of 53 patients (79%) before primary coronary angioplasty, and highly developed collateral vessels (grade 3) were present in 12 patients (22%). Angiographic collateral grade tended to be higher in patients with inferior infarction, but this finding did not reach statistical significance. However, radionuclide estimates of collateral flow were significantly influenced by infarct location. The mean time to reperfusion was 4.7±3.9 hours, and 21 patients were treated after 6 hours. There was a trend toward later reperfusion therapy in anterior infarction that did not reach statistical significance (p=0.15).
Comparison of Angiographic Collateral Grade and Radionuclide Estimates of Collateral Flow

See Table 2 and Figure 2. All three radionuclide estimates of collateral flow were significantly associated with angiographic collateral grade in the total group: nadir, \( p = 0.006 \); severity index, \( p = 0.02 \); area, \( p = 0.01 \), with more severe defects associated with less developed or absent angiographic collateral circulation. However, there was a clear difference in this association by infarct location. All three radionuclide estimates demonstrated a significant association with angiographic collateral grade in patients with anterior infarction but not in patients with inferior infarction. Myocardium at risk was associated with angiographic collateral grade \( (p=0.04) \) and significantly correlated with radionuclide estimates of collateral flow \( (\text{nadir}, r = -0.71, p<0.0001) \).

Univariate Predictors of Infarct Size

See Table 3 and Figures 3–6. There was a significant correlation of final infarct size with both myocardium at risk and radionuclide estimates of collateral flow \( (p<0.0001) \) and a significant association with angiographic collateral grade \( (p=0.0003) \). The relation between angiographic collateral grade and infarct size depended on infarct location (Figure 4). The correlation coefficients for the continuous variables \( (r=0.61 \text{ for myocardium at risk, and } r=0.69, 0.69, \text{ and } 0.70 \text{ for the radionuclide estimates of collateral flow}) \) indicated that each of these individual variables accounted for less than one half of the variability in infarct size. The variability in infarct size for any given value of each of these individual parameters was evident (Figures 3–5). Time to successful reperfusion was not significantly correlated with final infarct size, although there was a weak trend \( (p=0.10) \) toward greater infarct size with longer elapsed time to treatment (Figure 6). The addition of a constant of 1 hour to the time of initiation of infusion for only patients receiving thrombolytic therapy to correct for the presumed delay between the start of infusion and vessel recanalization did not improve this correlation.

Multivariate Models of Infarct Size

See Table 4. Myocardium at risk, angiographic collateral grade, and time to reperfusion were then examined in a multivariate analysis with infarct size as the dependent variable. An interaction term between collateral grade and infarct location was also considered. All four variables were independently associated with infarct size and accounted for 70% of the variability in final infarct size (Table 4A).

The alternative noninvasive model used the nadir as a radionuclide estimate of collateral flow instead of angiographic collateral grade. An interaction term between nadir and infarct location was considered. When the same 53 patients used in the invasive model were analyzed, the noninvasive model using radionuclide collateral flow instead of angiographic collateral grade accounted for 68% of the variability in final infarct size (Table 4B). When all patients were included (those with and without acute coronary angiography), the noninvasive model accounted for 59% of the variability in final infarct size (Table 4C). For both models, the addition of a time constant of 1 hour to the time to reperfusion for patients receiving thrombolytic therapy did not significantly alter the results.

Discussion

Infarct size in this study was quite variable and averaged about one half of the myocardium at risk. Patients with anterior infarction had significantly larger infarct size than patients with inferior infarction. Final infarct size measured by tomographic sestamibi imaging (the extent of the perfusion defect <60% maximal counts) has previously correlated closely with ejection fraction and end systolic volume after acute reperfusion.
models, area at risk, collateral flow, and rate/pressure product accounted for 80–90% of the variability in final infarct size. The most important parameter (which accounted for more than 70% of the variability of infarct size) was the amount of myocardium at risk. Collateral flow within the infarct zone was determined by radiolabeled microspheres injected during coronary occlusion and sampled postmortem. This measure of collateral flow was univariately associated with final infarct size and added significantly to myocardium at risk in a multivariate analysis. Rate/pressure product was used as an index of metabolic demand and was significantly associated with final infarct size only after adjustment for myocardium at risk and collateral flow. The duration of coronary occlusion in this study was held constant at 3 hours before reperfusion, and the same coronary artery at the same location was occluded for each dog.

The design of the present study is based on the AMPIM study, but there are several major differences between this prospective clinical series and the controlled environment of the animal laboratory. Most importantly, the duration of coronary occlusion was neither constant nor precise. The elapsed time is heavily dependent on an accurate description by the patient of the onset of chest pain, which is frequently problematic. The estimated duration of occlusion was incorporated in the study design as the time to reperfusion therapy. In addition, the metabolic demand of the myocardium could not be estimated at the time of occlusion, as the

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** *Scatterplots showing comparison of radionuclide collateral flow assessed by the nadir of the acute short-axis count profile curve and angiographic collateral grade before reperfusion.* Panel A: *All patients* (p=0.006). Panel B: *Anterior infarction* (p<0.0001). Panel C: *Inferior infarction* (p=NS).

Final infarct size estimated by sestamibi has also correlated with peak creatine kinase levels. Assessment of infarct size with sestamibi does not appear to be influenced by enhanced coronary flow into the infarct territory after successful reperfusion. When the flow is adequate, sestamibi myocardial uptake is dependent on sarcolemmal membrane integrity and, to a lesser extent, intact mitochondrial function.

The AMPIM study demonstrated that in carefully controlled experimental occlusion/reperfusion dog

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** *Scatterplot showing correlation of final infarct size and myocardium at risk: r=0.61, r²=0.38, p<0.0001.* Patients are dichotomized by time to reperfusion. LV, left ventricle.

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardium at risk</td>
<td>0.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Angiographic collateral grade</td>
<td>*</td>
<td>0.0003</td>
</tr>
<tr>
<td>Radionuclide collateral flow</td>
<td>Nadir</td>
<td>-0.70</td>
</tr>
<tr>
<td></td>
<td>Severity index</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Area</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Time to reperfusion</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*One-factor ANOVA was used because collateral grade is not a continuous variable.

### Table 3. Univariate Determinants of Infarct Size

<table>
<thead>
<tr>
<th></th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardium at risk</td>
<td>0.61</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Angiographic collateral grade</td>
<td>*</td>
<td>0.0003</td>
</tr>
<tr>
<td>Radionuclide collateral flow</td>
<td>Nadir</td>
<td>-0.70</td>
</tr>
<tr>
<td></td>
<td>Severity index</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Area</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>Time to reperfusion</td>
<td>0.18</td>
</tr>
</tbody>
</table>

*One-factor ANOVA was used because collateral grade is not a continuous variable.*
FIGURE 4. Scatterplots showing angiographic collateral circulation in 53 patients undergoing direct percutaneous transluminal coronary angioplasty in relation to infarct size. Panel A: There was a significant association between these parameters (p=0.0003) for all patients. Panel B: However, this association was seen primarily in patients with anterior infarction (p<0.0001). Panel C: There was no significant association between these parameters for patients with inferior infarction. LV, left ventricle.

patient was not under observation at that time. Finally, the occluded coronary artery and site of occlusion were variable.

In the present study, myocardium at risk correlated significantly with infarct size (r=0.61, p<0.0001). There was a broad range of myocardium at risk for the study group. There was also a broad range of myocardium at risk within infarct location subgroups, although patients with anterior infarction had considerably more myocardium at risk than patients with inferior infarction. Myocardium at risk for right coronary and left circumflex artery occlusion was similar to the values reported by Feiring et al. using radiolabeled intracoronary microspheres (18±8 in the present study versus 17.6±4.1 in Feiring et al's study). However, myocardium at risk
for patients with left anterior descending artery occlusion was somewhat larger in the present study (49 ± 14) than that reported by Feiring et al (39 ± 5.1). Feiring et al also noted considerable variation in myocardium at risk between individuals with similar occlusion sites in the same artery. This variability in area at risk has also been reported in animal experiments, including the AMPM study, in which the coronary artery and occlusion site were controlled.13,4 The importance of area at risk in determining final infarct size has been a consistent finding in multiple animal and clinical studies.1-11 Myocardium at risk determined by 99mTc sestamibi has correlated closely with postmortem area at risk in animal studies and in models of permanent occlusion18 and of reperfusion9 and has also been applied in clinical studies.11,21

**Table 4. Multivariate Model to Predict Infarct Size**

<table>
<thead>
<tr>
<th>A. Angiographic (n=53)*</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardium at risk</td>
<td>19.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Collateral grade</td>
<td>7.2</td>
<td>0.0005</td>
</tr>
<tr>
<td>Collateral grade and infarct location</td>
<td>4.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Time to reperfusion</td>
<td>4.5</td>
<td>0.04</td>
</tr>
<tr>
<td>$R^2$ of model=0.70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Radionuclide (n=53)†</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardium at risk</td>
<td>6.8</td>
<td>0.01</td>
</tr>
<tr>
<td>Nadir</td>
<td>28.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nadir and infarct location</td>
<td>8.9</td>
<td>0.005</td>
</tr>
<tr>
<td>Time to reperfusion</td>
<td>6.2</td>
<td>0.02</td>
</tr>
<tr>
<td>$R^2$ of model=0.68</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Radionuclide (n=89)‡</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardium at risk</td>
<td>12.3</td>
<td>0.0007</td>
</tr>
<tr>
<td>Nadir</td>
<td>21.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nadir and infarct location</td>
<td>10.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Time to reperfusion</td>
<td>6.6</td>
<td>0.01</td>
</tr>
<tr>
<td>$R^2$ of model=0.59</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Using angiographic collateral grade in patients with angiographic occlusion.
†Using radionuclide estimate of collateral flow in patients with angiographic occlusion.
‡Using radionuclide estimate of collateral flow in all patients.

The angiographic collateral grading system used in this study before reperfusion therapy has previously been shown to correlate with extent of regional wall motion hypokinesia and sum of ST elevation during coronary artery occlusion in the setting of coronary angioplasty.16 This classification has not been correlated directly with absolute measurements of collateral flow, however, and because the majority of collateral vessels in humans may not be angiographically detectable,31 this grading system provides only an estimate of collateral flow. There was a trend toward more developed collateral vessels in patients with inferior infarction, but it is unclear whether this is a true anatomic finding or an artifact related to the injection of a fixed volume of contrast into coronary arterial beds with different volume capacities. Despite these shortcomings, the angiographic estimate of collateral flow was univariately associated with final infarct size ($p=0.0003$) and added significantly to myocardium at risk in the multivariate analysis. Well-developed collaterals (grade 2 or 3) were present in 53% of patients, and some collaterals were present in 79%. Collateral flow has been reported in numerous studies to have significant impact on infarct size.1,3,6-9,12-16 Habib et al15 reported that infarct size determined by creatine kinase enzyme levels was 35% smaller and discharge ejection fraction higher in patients with than in those without significant collateral circulation, although there was a higher percentage of patients with inferior infarction in the group with collaterals. Saito et al14 reported higher ejection fractions at 6 weeks in patients with well-developed collateral circulation during acute myocardial infarction. Such a determination, however, requires invasive angiographic assessment.

This study has examined several measurements to assess noninvasively the residual collateral flow in the infarct territory. All of these measurements assess the severity of the perfusion defect by analyzing the depth of the short-axis count profile obtained from tomographic imaging. Such measurements assume that the severity of the perfusion defect is an indicator of residual coronary flow from collateral circulation to the infarct territory. All three noninvasive measurements of collateral flow correlated significantly with angiographically determined collateral grade. However, this correlation was found in patients with anterior infarction but not in patients with inferior infarction.

Experimental models examining coronary blood flow in the center of the area at risk during coronary occlusion have demonstrated a close correlation between postmortem microsphere blood flow and tissue 99mTc sestamibi uptake, although 99mTc sestamibi uptake was consistently higher.19,32 Because of the limited resolution of Anger cameras and the effects of scatter and attenuation, however, the correlation between tissue uptake and counts on tomographic imaging is imperfect.20 The effects should be more important for smaller perfusion defects. The absence of any association between radionuclide estimates of collateral flow and angiographic collateral grade in patients with inferior infarction may be related to the small amount of myocardium at risk in these patients. Alternatively, the trend toward higher angiographic collateral grade in patients with inferior infarction may reflect lower resistance in the right ventricle to left-to-right collateral flow.

**Figure 6. Scatterplot showing comparison of the time to reperfusion therapy as a continuous variable and final infarct size. There was no significant correlation between these parameters (p=0.10). LV, left ventricle.**
rather than collateral flow to the infarct territory within the left ventricle.

Noninvasive assessment of collateral flow correlated significantly with final infarct size using any of the three methods. Estimation of collateral flow, however, was significantly influenced by infarct location, presumably for the reasons already discussed. These estimates of residual flow also correlated with myocardium at risk. Sinusas et al.\(^3\) demonstrated that in vivo area at risk estimated by sestamibi was 29% less than postmortem area at risk, suggesting an influence of collateral circulation. Jugdutt et al.\(^8\) demonstrated a strong inverse correlation \((r = -0.80)\) between area at risk and collateral flow assessed in the center of the risk region. Murdock et al.\(^33\) found that similar rates of collateral flow resulted in a smaller ratio of final infarct size to area at risk in dogs with an absolute myocardial area at risk. It is apparent from these findings and the technical limitations of radionuclide imaging for small perfusion defects that the effects of collateral flow upon the extent of salvage are, in part, a function of the magnitude of area at risk and, consequently, infarct location. For these reasons, it is not surprising that the interaction terms between the estimates of collateral flow and infarct location were significant.

There is little doubt as to the importance of the duration of coronary occlusion in experimental models of final infarct size.\(^5,17\) The effect of collateral flow on infarct size has been shown to be influenced by the duration of coronary occlusion. Collateral flow has been shown to have little impact on infarct size when reperfusion occurred by 40 minutes but significant impact when reperfusion occurred after 3 hours.\(^33\) Smaller clinical studies have shown the time to therapy to be an important factor in patient outcome,\(^34,35\) but large randomized clinical trials have shown surprisingly inconsistent results with respect to the importance of the duration of coronary occlusion for treatment benefit.\(^27,36-38\) Unlike these previous studies, the present study analyzes the duration of coronary occlusion as a continuous variable rather than dichotomizing patients by an arbitrary time-point cut-off. As a univariate predictor of infarct size, time to reperfusion was not significant, although there was a trend toward larger infarct size with delayed reperfusion. When myocardium at risk, collateral grade, and infarct location were taken into consideration, however, the duration of coronary occlusion was significantly associated with final infarct size. Relatively few patients, however, had very early (≤2 hours) reperfusion therapy. The inclusion of more patients treated very early may significantly increase the importance of time to therapy in this model.

The results of the multivariate model for infarct size demonstrate the importance of assessing all three parameters—myocardium at risk, collateral flow, and time to reperfusion—in determining final infarct size. The substitution of the noninvasive method of determining collateral flow accounted for a similar variability in final infarct size when the same 53 patients in the invasive model were examined. In these patients, the status of the infarct-related artery was known to be occluded. When all patients were analyzed, however, the noninvasive model was slightly less predictive of final infarct size. This may be because of patency of the infarct artery, which was demonstrated in four of the 57 patients before direct coronary angioplasty. Presumably, a similar proportion of patients with patent arteries could be expected in the group receiving thrombolytic therapy who did not undergo acute coronary angiography. The adverse effect of arterial patency on angiographic detection of collaterals is well recognized.\(^28,39,40\) Arterial patency may also affect radionuclide estimates of collateral flow. Significant antegrade flow (TIMI grade II or III) to the infarct zone may influence the nadir of the short axis \(^99\)Tc sestamibi profile curve similarly to collateral flow. This may occur with spontaneous reperfusion of the infarct vessel. Whether maintained or resumed antegrade flow has an impact on final infarct size similar to that of collateral flow during coronary occlusion is unknown.

Both the models accounted for considerably less of the variability in final infarct size than the 90% value reported by the AMPIM study model. This is probably a result of several factors: 1) Myocardial metabolic demand at the time of occlusion, an independent determinant of infarct size in the dog model, was unknown in these patients. 2) Attenuation and scatter by the chest wall, which vary greatly between individuals, will affect radionuclide estimates of myocardium at risk and infarct size, as will patient motion during tomographic imaging. No attenuation or photon scatter correction was used in this study. 3) The site and duration of coronary occlusion are variable in clinical studies. 4) The angiographic or radionuclide estimation of collateral flow is clearly inferior to microsphere measurements.

All of these are limitations of this study, as is the frequent absence of follow-up angiography to confirm vessel patency before hospital discharge. Silent reocclusion may have gone undetected in these patients and altered final infarct size. The time to reperfusion was imprecise in patients receiving thrombolysis, although the addition of a time constant did not significantly influence the results. Furthermore, collateral grade was assessed only in patients undergoing primary coronary angioplasty with TIMI grade 0 or I flow before inflation, as collateral flow is infrequently detected in patients without total coronary artery occlusion.\(^28,39,40\) However, the time-dependent recruitment of collateral vessels after coronary artery occlusion is a well-recognized phenomenon\(^30,41\) and may have altered angiographic collateral grade. The effect of the recruitment of late collaterals on infarct size is unknown.

Mortality from acute myocardial infarction is low for patients who are eligible and receive acute thrombolytic therapy.\(^36,37\) Consequently, large randomized trials have turned to mechanical indices of left ventricular infarct size to evaluate new therapies of acute reperfusion. However, a paradox is apparent between the reduction in mortality and the demonstrable benefit in left ventricular function.\(^42\) Mechanical indices such as ejection fraction can be inaccurate in some patients after reperfusion, presumably because of myocardial stunning,\(^22\) and provide no information regarding initial myocardium at risk. From animal models of acute infarction, it is well established that myocardium at risk, collateral flow, and duration of occlusion are all independent determinants of final infarct size. Of these three, only duration of coronary occlusion has been routinely considered in clinical trials.
There are multiple determinants of final infarct size. The results of the present study suggest that myocardium at risk, collateral flow, and time to reperfusion each play a significant role. These factors should ideally be taken into account in any clinical trial that attempts to compare different reperfusion therapies or strategies.

Acknowledgments
We greatly appreciate the help of Dr. Bernard J. Gersh for his insightful review of the manuscript and Kay Knox for her expert secretarial assistance.

References
2. Feiring AJ, Johnson MR, Kioschos JM, Kirchner PT, Marcus ML, White CW: The importance of the determination of the myocardial area at risk to the evaluation of the outcome of acute myocardial infarction in patients. Circulation 1987;75:980–987
9. Reimer KA, Jennings RB: The waveform 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;40:633–644
in acute myocardial infarction: Final report of the GISSI study. 


Determinants of infarct size in reperfusion therapy for acute myocardial infarction.
T F Christian, R S Schwartz and R J Gibbons

Circulation. 1992;86:81-90
doi: 10.1161/01.CIR.86.1.81
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1992 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/86/1/81