Prevalence of spontaneous reperfusion and associated myocardial salvage in patients with acute myocardial infarction

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This study sought to determine the prevalence of spontaneous reperfusion of an infarct-related artery (IRA) and associated myocardial salvage in the absence of thrombolysis or angioplasty. Twenty-one patients with acute myocardial infarction received only heparin and aspirin. At a median of 18 hours after presentation, 12 patients (57%) had angiographic patency of the IRA. Technetium-99m sestamibi was injected acutely on presentation and again at hospital discharge. Acute and final perfusion defect sizes were measured. Their difference, myocardial salvage, was calculated along with salvage index (myocardial salvage/acute defect). Comparing patients with a patent versus occluded IRA, myocardium at risk was similar (16% ± 12% vs 12% ± 9% left ventricle, p = NS); however, myocardial salvage (9% ± 9% vs −2% ± 7% left ventricle, p = 0.01), and salvage index (0.62 ± 0.37 vs 0.19 ± 0.33, p = 0.01) were greater in patients with spontaneous reperfusion. Resolution of chest pain was greater in patients with a patent IRA (100% vs 55%, p = 0.003). Spontaneous reperfusion of the IRA occurs frequently in patients with acute myocardial infarction and is associated with significant myocardial salvage. (Am Heart J 1998;135:421-7.)

Thrombolytic therapy and direct coronary angioplasty are effective therapy for acute myocardial infarction (AMI).[1-3] When performed early, both methods of reperfusion have been associated with salvage of approximately half the myocardium at risk in clinical studies.[4] The Second Interventional Study of Infarct Survival (ISIS-2) trial of therapy in AMI has demonstrated a beneficial impact on survival in patients treated with aspirin in the absence of thrombolytic therapy, presumably through an effect on patency of the infarct-related artery.[1] DeWood et al.[5] demonstrated that 20% of patients diagnosed with AMI did not have occlusive thrombi at the time of acute coronary angiography, suggesting spontaneous reperfusion. Patency of the infarct-related artery has been shown to occur in 16% to 24% of patients receiving intravenous heparin infusion within the first 24 hours.[6] Subsequent patency rates during heparin infusion range from 57% to 64% after 3 days.[6] The purpose of this study was to determine the prevalence of spontaneous reperfusion of an infarct-related artery (in the absence of thrombolysis or angioplasty) and its effect on myocardial salvage among patients with AMI. The measurement of myocardial salvage by technetium-99m sestamibi perfusion imaging[7-11] was therefore performed in patients with AMI treated with aspirin and heparin.

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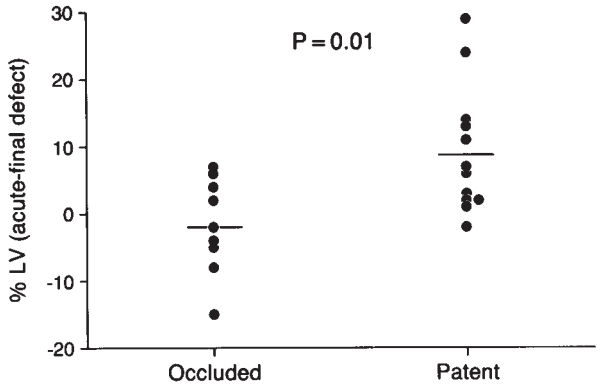
Methods

The study group was selected from a consecutive series of 199 patients who received ^{99m}Tc sestamibi during acute myocardial infarction between November 1988 and September 1993. Myocardial infarction was defined on the basis of the finding of chest pain for ≥30 minutes duration and positive serum CK-MB enzyme elevation consistent with myocardial necrosis. Acute reperfusion therapy, either primary angioplasty or lytic therapy, was given to 157 patients (79%) in the study group. The results of studies pertaining to this group have been reported previously.[7-9,12] The remaining 42 patients (21%) received heparin and aspirin. Patients were excluded from the study if they had a history of prior myocardial infarction (n = 11), underwent a revascularization procedure between the two ^{99m}Tc sestamibi injections (n = 5), or did not undergo angiography (n = 5). Therefore 21 patients formed the study group.

Aspirin and heparin therapy

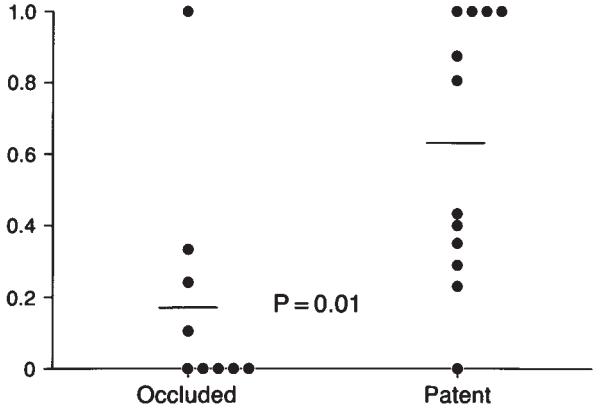
All patients received aspirin 325 mg on admission and daily thereafter. In addition, all patients were given a bolus

Figure 1



Myocardial salvage as percent of LV determined by change in ^{99m}Tc sestamibi tomographic defect size (acute-discharge) for all patients. Myocardial salvage is significantly greater in patients with patent arteries.

Figure 2



Salvage index (proportion of myocardium at risk salvaged) for all patients. Patients with patent infarct-related vessels had significantly greater salvage of myocardium at risk.

of intravenous heparin 5000 U followed immediately by a continuous infusion of 1000 U/hr adjusted to maintain an activated partial thromboplastin time of 60 to 90 seconds. Heparin infusion was continued for at least 2 days and then discontinued at the discretion of the attending physician. Treatment with other medications, including β-blockers, was at the discretion of the attending physician. Chest pain severity was graded at the time of admission as mild (1 to 3), moderate (4 to 7), or severe (8 to 10) on a 10-point scale; and chest pain resolution within 12 hours of admission was graded as none, partial, or complete.[12]

Coronary angiography

Coronary angiography was performed during hospitalization (median 18 hours, range 0 to 13 days). The infarct-related artery was determined from the electrocardiogram, left ventriculogram, and coronary angiogram. Antegrade flow was assessed by use of Thrombolysis in Myocardial Infarction (TIMI) Trial criteria.[13] Patency was defined as any antegrade flow (TIMI 1 to 3). This definition was based on a previous study from this laboratory on a different patient population demonstrating that TIMI 1 and 2 flow before reperfusion therapy were associated with significantly greater myocardial salvage than TIMI 0 flow.[14]

Radionuclide assessment of myocardium at risk and final infarct size

All 21 patients received an injection of ^{99m}Tc sestamibi (20 to 30 mCi) on presentation. Tomographic imaging was performed 1 to 6 hours later to determine the initial perfusion pattern. A second injection and acquisition were performed 5 days after admission or later (6 ± 2 days, range 5 to 15 days). Tomographic images were acquired and processed with a previously described technique.[9]

The left ventricular perfusion defect was quantified by use of a previously described threshold method.[15] Briefly, five short-axis slices were selected from apex to base. Circumferential count profiles were generated for each slice from 60 radians every 6 degrees. Perfusion defect size was determined from the number of radians with less than 60% of maximal counts for that slice adjusted for the radius of the slice or apical location. The size of the acute perfusion defect is a measure of myocardium at risk, and the size of the discharge perfusion defect is a measure of infarct size; both are expressed as a percentage of the left ventricle. Myocardial salvage is derived from the difference between the acute and final perfusion defect (myocardium at risk – final infarct size). The salvage index is the proportion of myocardium at risk that is salvaged and is equal to myocardial salvage/myocardium at risk.[9] When the value of myocardial salvage was a negative number, the salvage index was set equal to zero. Perfusion defect severity (nadir) was calculated with the lowest ratio of minimal/maximal counts from the five short-axis slices.[16] This measure has been shown to be highly associated with acute angiographic collateral vessels during coronary artery occlusion and is an independent determinant of infarct size.[16] Infarct location was designated on the basis of the location on the short-axis radionuclide image by use of quantitative criteria.[16]

Statistical analysis

Data are expressed as mean ± standard deviation. Differences between patients with patent versus occluded arteries were assessed with an unpaired *t* test or a chi-square contingency table analysis for nominal variables such as chest pain response. To test whether patency was independently associated with benefit, a one-factor analysis of variance, with infarct size as the dependent variable, patency as

Table I. Summary of clinical, angiographic and radionuclide results

Pt	Sex	MI location	ST segment	Time to angiography	Infarct artery	Patency	MAR (% LV)	IS (% LV)	Salvage (% LV)	Salvage index
1	M	Inf	Elevation	56 hrs	RCA	Patent	15	9	6	0.40
2	M	Ant	Isoelectric	51 hrs	LAD	Patent	16	2	14	0.87
3	M	Inf	Elevation	144 hrs	LCX	Patent	30	17	13	0.43
4	F	Lat	Depression	120 hrs	LCX	Patent	24	0	24	1.0
5	M	Inf	Elevation	120 hrs	RCA	Patent	13	10	3	0.23
6	M	Inf	Isoelectric	20 hrs	RCA	Patent	38	27	11	0.29
7	F	Lat	Depression	312 hrs	RCA	Patent	2	0	2	1.0
8	M	Ant	Elevation	1 hrs	LAD	Patent	1	0	1	1.0
9	F	Lat	Isoelectric	168 hrs	RCA	Patent	20	13	7	0.35
10	M	Inf	Elevation	2 hrs	RCA	Patent	0	2	−2	0
11	M	Ant	Isoelectric	144 hrs	LAD	Patent	36	7	29	0.81
12	M	Ant	Isoelectric	27 hrs	LAD	Patent	2	0	2	1.0
13	M	Ant	Elevation	1 hrs	LAD	Occluded	18	12	6	0.33
14	F	Lat	Elevation	6 hrs	RCA	Occluded	0	15	−15	0
15	F	Lat	Depression	18 hrs	LCX	Occluded	4	6	−2	0
16	M	Inf	Depression	2 hrs	LCX	Occluded	29	22	7	0.24
17	M	Inf	Isoelectric	10 hrs	LCX	Occluded	19	17	2	0.10
18	M	Inf	Elevation	18 hrs	RCA	Occluded	13	21	−8	0
19	M	Inf	Isoelectric	10 hrs	LCX	Occluded	4	0	4	1.0
20	M	Inf	Isoelectric	2 hrs	SVG	Occluded	10	15	−5	0
21	M	Ant	Elevation	1 hrs	LAD	Occluded	12	16	−4	0

Pt, Patient; *MI*, myocardial infarction; *MAR*, myocardium at risk; *IS*, infarct size; *Inf*, inferior; *RCA*, right coronary artery; *Ant*, anterior; *LAD*, left anterior descending artery; *LCX*, left circumflex artery; *Lat*, lateral; *SVG*, saphenous vein graft.

a dichotomous factor (TIMI 0 vs 1-3), and myocardium at risk as a covariate, was performed (Superanova 2.0, Abacus software). Two other models were analyzed with patency defined by different criteria (TIMI 3 flow vs 0-2 flow and TIMI flow as a monotonic integer [0 to 3]).

Results

The study group consisted of 21 patients (16 men and 5 women) with a mean age of 64.5 ± 10.5 years (Table I). Six patients had anterior infarction, 10 had inferior infarction, and five had lateral infarction. Only nine patients (43%) had ST elevation on the presenting electrocardiogram. The remainder had ST segment depression (n = 4) or nondiagnostic changes (n = 8). Of those patients with ST elevation, five had perceived contraindications to thrombolytic therapy (recent cerebrovascular accident, trauma, elderly age). Chest pain severity was mild in three patients, moderate in 11, and severe in seven. The four remaining patients with ST elevation did not receive reperfusion therapy because of perceived low clinical risk. Chest pain resolved completely within 12 hours in 16 of 21 patients (76%) and partially in the remaining 5 patients (24%).

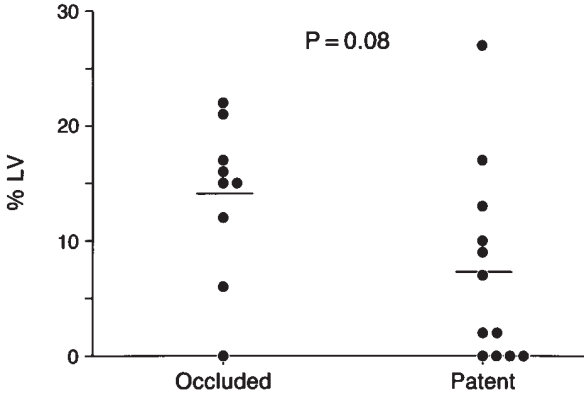
Coronary angiography/chest pain

Twelve patients had evidence of antegrade flow (TIMI 3 flow [n = 6], TIMI 2 [n = 5], TIMI 1 [n = 1]) and nine patients remained occluded (TIMI 0). Chest pain resolution within 12 hours was significantly different between patients with patent versus occluded arteries. Complete resolution of chest pain occurred in 100% of patients (12 of 12) with patent arteries (TIMI 1 to 3) versus 55% (5 of 9) in those with occluded arteries (p = 0.003).

Radionuclide measures

For all 21 patients myocardium at risk (as reflected by the size of the acute ^{99m}Tc sestamibi perfusion defect) was 16% ± 12% of the left ventricle (LV). Final infarct size was 10% ± 10% of the LV, which was significantly (p = 0.01) smaller than the myocardium at risk. Myocardial salvage was 6% ± 11% of the LV. The proportion of myocardium at risk salvaged (salvage index) was 0.46 ± 0.42; five patients had a salvage index of 1.0 corresponding to complete resolution of acute defect. Table II shows the 12 patients with patent (TIMI 1 to 3) arteries compared with the nine with occluded arteries (TIMI 0). Myocardium at risk was similar (16% ± 12% vs 12% ± 9% LV, p = NS). Myocardial salvage was significantly greater in those patients with patent infarct-related arteries (9% ± 9% vs –2% ± 7% LV, p = 0.01)(Fig. 1). In patients with occluded infarct-related arteries, there was no evident salvage. Patients with patent arteries also demonstrated

Figure 3



Infarct size as percent of LV for patients with patent versus occluded arteries. Patients with patent infarct-related vessels tend to have smaller infarcts. This analysis does not account for differences in myocardium at risk.

significantly greater salvage index than those with persistently occluded arteries (0.62 ± 0.37 vs 0.19 ± 0.33, p = 0.01) (Fig. 2). Infarct size at discharge was smaller in patients with a patent infarct-related artery (7% ± 8% vs 14% ± 7% LV, p = 0.008) (Fig. 3).

Multivariate analysis

Multivariate analysis was performed to assess the impact of infarct artery patency on infarct size after adjustment for the covariates of myocardium at risk and collateral vessel blood flow (Table III). Infarct-related artery patency examined both as a categorical and dichotomous variable (TIMI 1 to 3) was independently associated with infarct size after adjustment for myocardium at risk.

Discussion

Spontaneous reperfusion of the infarct-related artery has been described in a consistent minority of patients during myocardial infarction where acute coronary angiography has been performed. Patency of the infarct-related artery before thrombolytic therapy or direct coronary artery angioplasty in the absence of heparin or aspirin has ranged from 9% to 28%, and similar prevalence rates have been demonstrated at 90 minutes during heparin infusion.[17-19] By 3 days the patency rate during heparin infusion without other reperfusion therapy has ranged from 36% to 78%, with an overall 61% prevalence of patent arteries by pooled data from eight studies.[6,20,21] This phenomenon is a confounding variable when the benefit from a reperfusion strategy, such as a new thrombolytic agent, is analyzed.

One method of analyzing the impact on a patient population of spontaneous reperfusion is to assess myocardial salvage. ^{99m}Tc sestamibi is a unique radiopharmaceutical that is taken up in proportion to coronary artery blood flow and sequestered within the mitochondria of cardiac myocytes as a result of its large positive charge.[22,23] Consequently, distribution within the myocardium is little changed over time after acute administration.[22] The distribution is relatively unaffected by subsequent fluctuations in coronary artery blood flow.[10] The tracer can be injected in the emergency department, and scanning can be delayed for up to 8 hours to obtain a measure of myocardium at risk. A subsequent injection and scanning performed 5 days later provide an accurate assessment of infarct size. The change between the two measures is therefore a measure of myocardial salvage. This approach has been used in multiple previous studies and allows an estimate of the benefit a patient receives from a given therapy.[4,7-9,16]

The data from this study add to the large body of literature that arterial patency in acute myocardial infarction should be the goal of therapy to preserve functioning myocardium. Patients with patent infarct-related arteries had improved myocardial salvage. This benefit persisted in spite of adjustments for differences in myocardium at risk and collateral vessel flow between these two subgroups. Furthermore, restoration of the infarct-related artery patency either spontaneously or by means of angioplasty or thrombolytic therapy, seems to result in similar degrees of salvage. The proportion of myocardium at risk that was salvaged (salvage index) was nearly identical to values obtained by Gibbons et al.[4] in a randomized trial comparing thrombolysis and direct coronary artery angioplasty.

The ISIS-2 Trial demonstrated a significant reduction in the mortality rate in patients receiving aspirin without concomitant thrombolytic therapy.[1] Several trials of acute infarction have suggested that intravenous heparin therapy results in higher coronary artery patency rates than either placebo or aspirin when used in conjunction with a thrombolytic agent.[24,25] The ISIS-3 and GISSI-2 trials have demonstrated a lower mortality rate in patients treated with heparin while the infusion was maintained, but this benefit was not apparent by 35 days.[26,27] These studies suggest that heparin and aspirin can reduce mortality rates. This study suggests that the

Table II. Comparison of patients based on infarct artery status

	Patent (n = 12)	Occluded (n = 9)	p Value*
Myocardium at risk (%LV)	16 ± 14	12 ± 9	NS
Infarct size (%LV)	7 ± 8	14 ± 7	0.008†
Myocardial salvage (%LV)	9 ± 9	−2 ± 7	0.01
Salvage index	0.62 ± 0.3	0.19 ± 0.3	0.01
Residual flow (nadir)	0.43 ± 0.3	0.40 ± 0.1	NS

%LV, Percent of left ventricle.
*Patent versus occluded.
†p = 0.005 after adjustment for myocardium at risk.

Table III. Multivariate analyses of infarct size

	F	P
Myocardium at risk	16.3	0.0008
Patent vs occluded		
R^2 = 0.56	10.4	0.005
Myocardium at risk	14.8	0.001
TIMI flow (0,1,2, or 3)		
R^2 = 0.58	5.0	0.02

mechanism of the benefit seen in these large trials results from significant myocardial salvage and, consequently, a smaller final infarct size.

For six patients, the final infarct size was greater than the acute defect size. Because lysis and thrombosis are dynamic processes, this finding may reflect the clinical spectrum of unstable angina progressing toward myocardial infarction. The acute injection may have occurred at a point when the occlusive thrombus was in flux and relatively more perfusion to the ischemic area was present. Subsequently, irreversible damage occurred as a result of infarct-related artery occlusion, and a larger infarct size resulted. In support of this concept, five of the six patients had occluded infarct-related arteries on angiography.

A second possibility is that infarct expansion and LV remodeling occurred in these six patients, resulting in a final defect size greater than the acute defect size. This seems unlikely because infarct and defect sizes were expressed as percent of total LV area. Thus LV expansion tends to decrease the percent area of the infarct size.

Myocardium at risk was the most powerful multivariate predictor of final infarct size (Table III). This finding is consistent with previous work from our group in which we described the determinants of infarct size among 89 patients with AMI undergoing successful reperfusion therapy with either coronary angioplasty or thrombolysis.[16]

Chest pain resolution was more prevalent in patients with patent versus occluded infarct-related arteries (100% vs 55%). Chest pain resolution during thrombolytic therapy infusion has previously been shown to be a predictor of myocardial salvage with the method used in this study.[12]

Limitations

The timing of angiography was at the discretion of the attending physicians and was consequently variable. Although most patients underwent angiography within 24 hours of presentation, treatment for some patients was delayed for several days. The prevalence of an open versus closed artery at any specific time point is therefore difficult to assess with certainty. Furthermore, it is unknown whether the patency status of an infarct-related artery (open vs closed) remained static after angiography. Spontaneous lysis or rethrombosis may have subsequently occurred. Nonetheless, patency of the infarct-related artery at angiography was associated with a significant reduction in ^{99m}Tc sestamibi perfusion defect size. Thus it is likely that for most patients, patency occurred during a time period where myocardial salvage was possible.

The issue of selection bias must be considered in nonrandomized studies. Patients in this study tended to have small infarcts and therefore were treated conservatively, particularly when relative contraindications to acute reperfusion therapy existed. Most of the patients in this study did not have ST segment elevation that met accepted criteria for the administration of a thrombolytic agent, although creatine kinase isoenzyme elevations diagnostic for infarction developed in all patients. The proportion of patients with ST elevation in this study (42%) more closely reflects the prevalence of ST elevation in a large unselected population of patients (45%) with chest pain who were subsequently found to have myocardial infarction.[28] The mortality rate in patients without ST elevation is significantly higher than in patients with ST elevation who receive thrombolytic therapy.[29] The differences in myocardial salvage demonstrated in this study may have an impact on clinical outcome in this group of patients.

In spite of these limitations, the major findings of this study are that in patients with acute myocardial infarction who are not treated with reperfusion therapy, an open infarct-related artery is found with a relatively high frequency (57% of patients). Furthermore, a patent

infarct-related artery is associated with significant myocardial salvage and a higher frequency of resolution of chest pain.

The relatively high prevalence of reperfusion and myocardial salvage with only heparin and aspirin therapy for patients with acute myocardial infarction has important implications for trials of reperfusion strategies. This is of particular importance for patients without ST segment elevation, because most of these patients do not receive acute reperfusion therapy. Frequent spontaneous reperfusion may be a substantial confounding variable in any trial of thrombolytic therapy, because a number of patients will have had patency restored and myocardium salvaged in the absence of a thrombolytic agent.

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