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CLINICAL INVESTIGATIONS

# Early reperfusion therapy improves left ventricular function after acute inferior myocardial infarction associated with right coronary artery disease

**Quantitative global and regional ventriculographic analysis was performed acutely and 1 week later in 46 patients undergoing reperfusion procedures within 6 hours of acute inferior myocardial infarction due to right coronary artery disease. While serial improvement in global left ventricular ejection fraction was not demonstrated for the group, infarct zone regional wall motion did improve (−2.7 ± 0.9 vs −2.3 ± 1.4 SD/chord, $p < 0.007$). Serial improvement in global ejection fraction was demonstrated in the subgroup of patients treated within 2 hours of symptom onset (55 ± 10 vs 62 ± 10%; n = 5; $p < 0.03$). Infarct zone regional wall motion improved serially only in the subgroup of patients treated within 3 hours of symptom onset (−2.4 ± 1.1 vs −1.3 ± 1.7 SD/chord; n = 11; $p < 0.007$). Patients with initially patent arteries had a higher ejection fraction on follow-up catheterization than did those with initially occluded vessels (61 ± 11 vs 55 ± 7%; $p < 0.02$), and patients with patent arteries at follow-up had a higher ejection fraction than did those whose arteries were occluded (60 ± 9 vs 48 ± 4%; $p < 0.0001$). We conclude that significant improvement in global and regional left ventricular function in patients with inferior myocardial infarction is possible when reperfusion therapy is begun early or when arterial patency is achieved. (Am Heart J 1987;114:261.)**

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Prognosis following inferior myocardial infarction is significantly better than prognosis following anterior myocardial infarction.[1-3] Inferior infarction is associated with a smaller enzyme release[1-3] and a higher left ventricular ejection fraction,[4,5] suggesting that less myocardial damage occurs. This is reflected clinically by a lower incidence of congestive heart failure[2-4] and death.[1-3] A major goal of reperfusion therapy is to preserve left ventricular function by reperfusing ischemic myocardium. It has been suggested[6,7] that improvement in ventricular function is inversely proportional to the extent of initial dysfunction. Since global left ventricular function may be relatively normal following inferior infarction,[4,5] the extent of myocardial salvage to be expected from reperfusion therapy in these patients may not justify the risk and expense.

The purpose of this study was to determine the effect of acute reperfusion therapy on global and regional left ventricular function in patients with acute inferior myocardial infarction due to right coronary artery disease who were treated within 6 hours of symptom onset. Patients with circumflex coronary artery disease constitute a small minority of patients with inferior infarction undergoing reperfusion therapy and were excluded from this study because myocardial salvage cannot be adequately assessed from single-plane 30-degree right anterior oblique ventriculograms.[8]

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**Table I.** Coronary arteriographic results by treatment group

| | *PTCA (n = 19)* | *SK/PTCA (n = 10)* | *t-PA (n = 11)* | *t-PA/PTCA (n = 6)* | *Total (n = 46)* |
|---|---|---|---|---|---|
| Age | 57 ± 10 | 54 ± 12 | 55 ± 8 | 50 ± 11 | 52 ± 10 |
| Initial arterial patency | 3 (16%) | 6 (60%) | 6 (55%) | 3 (50%) | 18 (39%) |
| Final arterial patency | 18 (95%) | 10 (100%) | 11 (100%) | 5 (83%) | 44 (96%) |
| Follow-up arterial patency | 15 (79%) | 9 (90%) | 8 (73%) | 4 (67%) | 36 (78%) |
| Initial arterial % stenosis | 99 ± 2 | 92 ± 10 | 85 ± 19 | 97 ± 4 | 94 ± 11 |
| Final arterial % stenosis | 46 ± 21 | 35 ± 10 | 79 ± 16 | 36 ± 29 | 50 ± 26 |
| Follow-up arterial % stenosis | 52 ± 30 | 41 ± 24 | 71 ± 29 | 58 ± 31 | 55 ± 30 |

PTCA = percutaneous transluminal coronary angioplasty; SK = intravenous streptokinase; t-PA = intravenous tissue-type plasminogen activator.

## METHODS

**Patient selection.** From May, 1984, to February, 1986, 148 patients with acute myocardial infarction by enzymatic criteria were prospectively enrolled in reperfusion therapy protocols at the University of Michigan Medical Center. All underwent cardiac catheterization both acutely and 7 to 10 days later. Inclusion criteria were: (1) chest pain of greater than 20 minutes' duration, but of less than 6 hours' duration, consistent with ischemia and unrelieved by sublingual nitroglycerin; (2) at least 1 mm ST segment elevation in two contiguous ECG leads; (3) age less than 75 years. Exclusion criteria for this study were: (1) recent history of trauma, surgery, stroke, bleeding or prolonged cardiopulmonary resuscitation: (2) previous coronary bypass surgery or transmural infarction; (3) cardiogenic shock. The right coronary artery was identified as the infarct-related artery in 64 patients. Eighteen patients were subsequently excluded for the following reasons. Follow-up catheterization was not performed in three patients who died shortly after reperfusion therapy, in three patients who refused the follow-up study, and in three patients who underwent immediate coronary bypass surgery because of severe triple-vessel disease. Two patients were excluded because of previous myocardial infarction, while seven others had ventriculograms that were inadequate for analysis. Thus, 46 patients had acute and follow-up contrast ventriculograms suitable for quantitative analysis and they constitute the study group. Nineteen were treated with percutaneous transluminal coronary angioplasty alone, 10 were treated with intravenous streptokinase followed by immediate angioplasty, 11 were treated with intravenous tissue-type plasminogen activator alone, and six were treated with tissue-type plasminogen activator followed by immediate angioplasty. These protocols were approved by the University of Michigan Institutional Review Board. Informed consent was obtained from each patient.

**Interventional protocols**

*1. Intravenous lytic therapy.* Patients receiving streptokinase were premedicated with intravenous hydrocortisone, 200 mg, and were then given a total of 1.5 million U of streptokinase over 30 minutes, following a test dose. Patients receiving tissue-type plasminogen activator were given 0.75 mg/kg over 1 hour and 0.5 mg/kg over the subsequent 2 hours, for a total dose of 1.25 mg/kg over 3 hours. The recombinant tissue-type plasminogen activator was predominately a single-chain preparation (Genentech, San Francisco, Calif.)

*2. Angiography.* Vascular sheaths were placed in a femoral artery and vein and 5000 U of intravenous heparin was administered. By means of the Judkins technique, selective coronary arteriography was performed in multiple projections and then ventriculography was performed in the 30-degree right anterior oblique projection.

*3. Angioplasty.* Patients receiving angioplasty were given an additional 5000 U of intravenous heparin. The procedure was performed only in the infarct vessel with a steerable guidewire and balloon catheter system.

*4. Hospital course.* Therapeutic heparin infusion was continued until repeat angiography was performed 7 to 10 days later, except for a few hours on the second hospital day when the vascular sheaths were removed. Patients were also treated with aspirin, 325 mg one to three times per day, dipyridamole, 75 mg three times per day, and diltiazem, 30 mg four times per day.

**Analysis of left ventricular function.** To measure left ventricular function, end-diastolic and end-systolic outlines were independently projected and traced by two blinded experienced angiographers from a non-postpremature normal sinus beat. Global ejection fraction was determined by means of the area-length method.[9] When results obtained by the two determinations differed by more than 5%, a joint determination of outlines was performed. Regional wall motion was determined by the centerline method.[10,11] Briefly, 100 equally spaced chords are constructed perpendicular to a centerline drawn midway between the end-diastolic and end-systolic outlines. Motion along the perpendicular lines is normalized for centerline length and is expressed in units of standard deviation of mean wall motion obtained from ventriculographic analysis of 64 normal subjects.[10] Regional wall motion is calculated as the mean motion of chords lying in the most hypokinetic 50% of the infarct zone or the most hyperkinetic 50% of the non-infarct zone, and is expressed in standard deviations per chord. Negative and positive values are respectively hypokinetic and hyperkinetic compared with normal mean wall motion.

**Statistical analysis.** Results are expressed as mean ±

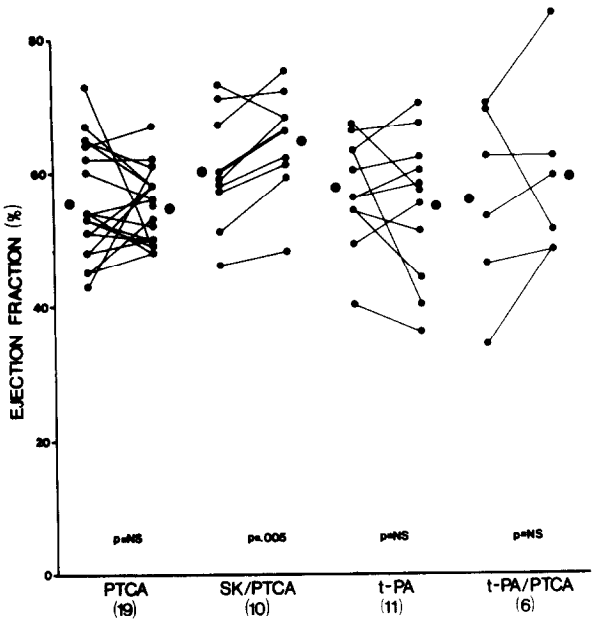


**Fig. 1.** Change in ejection fraction in acute and follow-up studies in each patient group. *PTCA* = percutaneous transluminal coronary angioplasty; *SK* = intravenous streptokinase; *t-PA* = intravenous tissue-type plasminogen activator.

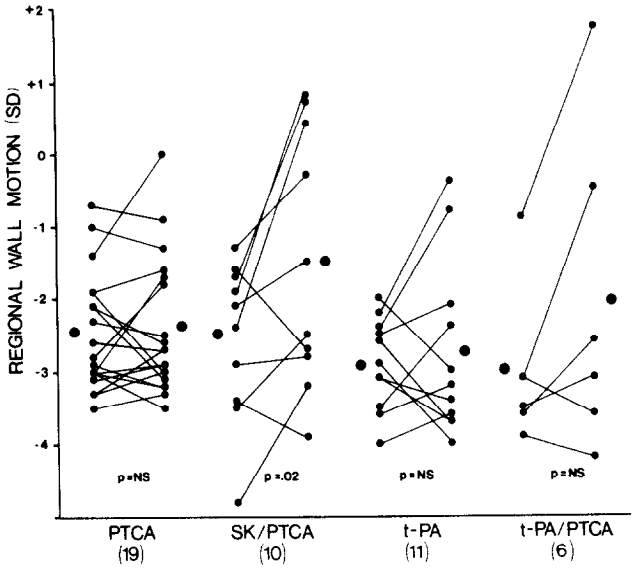


**Fig. 2.** Change in regional wall motion in the infarct zone in acute and follow-up studies in each patient group. Abbreviations as in Fig. 1.

SD. Paired *t* tests were performed to compare initial and follow-up values. Unpaired *t* tests were used for intergroup comparisons. A probability *(p)* value of less than 0.05 was considered statistically significant.

## RESULTS

**Coronary arteriography (Table I).** The initial arteriogram revealed right coronary artery patency with good visualization of the distal vessel in 18 of 46 (39%) patients. Those studied after intravenous lytic therapy had a higher initial patency rate than those who had not received lytic therapy (15 of 27 vs 3 of 19, $p < 0.007$). The last arteriogram following completion of reperfusion therapy demonstrated arterial patency in 44 of 46 (96%) patients. Patency 1 week later was demonstrated in 36 of 46 (78%) patients.

Arterial percent stenosis of the infarct-related artery was significantly less following reperfusion therapy in patients treated with angioplasty compared to patients treated only with lytic therapy ($41 \pm 21$ vs $79 \pm 16$, $p < 0.03$). Arterial percent stenosis 1 week later increased slightly in each group due to inclusion of patients with arterial reocclusion.

**Ventricular function by treatment group (Figs. 1 and 2, Table II).** No significant serial improvement in ejection fraction between the initial and follow-up studies was found for the total group. However, patients treated with streptokinase plus angioplasty did experience an improvement in ejection fraction ($60 \pm 8\%$ vs $65 \pm 7\%$, $p < 0.005$). Importantly, time to treatment in this group was at least 93 minutes sooner than treatment in the other groups.

Regional wall motion in the infarct zone improved significantly only in the streptokinase plus angioplasty group ($-2.6 \pm 1.0$ vs $-1.5 \pm 1.7$ SD/chord, $p < 0.02$) and in the total group ($-2.7 \pm 0.9$ vs $-2.3 \pm 1.4$ SD/chord, $p < 0.007$). Regional wall motion in the non-infarct zone did not change in any group.

**Ventricular function by time to treatment (Table III).** Patients treated less than 2 hours from symptom onset had serial improvement in ejection fraction ($55 \pm 10$ vs $62 \pm 10\%$, $p < 0.03$), while those treated after 2 hours did not. Improvement in infarct zone regional wall motion was found only in patients treated within 3 hours of symptom onset ($-2.4 \pm 1.1$ vs $-1.3 \pm 1.7$ SD/chord, $p < 0.007$).

**Ventricular function by patency status (Table IV).** Neither initial nor follow-up arterial patency were associated with serial improvement in ejection fraction. On follow-up catheterization, however, patients with initially patent arteries had a higher ejection fraction than did those with initially occluded arteries ($61 \pm 11$ vs $55 \pm 7\%$, $p < 0.02$), and patients with persistently patent arteries had a higher ejection fraction than did those whose arteries were occluded ($60 \pm 9$ vs $48 \pm 4\%$, $p < 0.0001$).

Serial improvement in infarct zone regional wall

**Table II.** Global and regional left ventricular function by treatment group

| | *PTCA (n = 19)* | *SK/PTCA (n = 10)* | *t-PA (n = 11)* | *t-PA/PTCA (n = 6)* | *Total (n = 46)* |
|---|---|---|---|---|---|
| Ejection fraction (%) | | | | | |
| Acute | 55 ± 8 | 60 ± 8 | 57 ± 8 | 56 ± 13 | 57 ± 9 |
| Follow-up | 55 ± 5 | 65 ± 7 | 55 ± 10 | 59 ± 12 | 57 ± 9 |
| Delta | −0.5 ± 8 | 4.5 ± 4 | −2.5 ± 8 | 3 ± 11 | 0.5 ± 8 |
| *p* Value | NS | 0.005 | NS | NS | NS |
| Regional wall motion (SD/chord) infarct zone | | | | | |
| Acute | −2.5 ± 0.8 | −2.6 ± 1.0 | −2.9 ± 0.6 | −3.0 ± 1.0 | −2.7 ± 0.9 |
| Follow-up | −2.4 ± 0.9 | −1.5 ± 1.7 | −2.8 ± 1.1 | −2.1 ± 2.0 | −2.3 ± 1.4 |
| Delta | 0.1 ± 0.7 | 1.1 ± 1.3 | 0.1 ± 1.0 | 1.0 ± 1.2 | 0.4 ± 1.1 |
| *p* Value | NS | 0.02 | NS | NS | 0.007 |
| Regional wall motion (SD/chord) non-infarct zone | | | | | |
| Acute | 1.1 ± 1.4 | 1.9 ± 1.1 | 0.3 ± 1.6 | 0.1 ± 1.3 | 1.0 ± 1.5 |
| Follow-up | 0.8 ± 1.1 | 1.8 ± 1.1 | 0.2 ± 1.4 | 0.4 ± 1.6 | 0.8 ± 1.4 |
| Delta | −0.4 ± 1.3 | −0.1 ± 0.4 | −0.1 ± 1.2 | 0.2 ± 1.0 | −0.2 ± 1.1 |
| *p* Value | NS | NS | NS | NS | NS |
| Time to treatment (min) | 254 ± 59 | 135 ± 68 | 228 ± 44 | 257 ± 44 | 222 ± 74 |

Delta = difference between acute and follow-up values; NS = not significant; other abbreviations as in Table I.

**Table III.** Global and regional left ventricular function by time to treatment

| | *<2 hr (n = 5)* | *<3 hr (n = 11)* | *≥3 hr (n = 35)* |
|---|---|---|---|
| Ejection fraction (%) | | | |
| Acute | 55 ± 10 | 59 ± 10 | 56 ± 9 |
| Follow-up | 62 ± 10 | 63 ± 9 | 56 ± 9 |
| Delta | 7.5 ± 6 | 3.5 ± 7 | −0.5 ± 9 |
| *p* Value | 0.03 | NS | NS |
| Regional wall motion (SD/chord) infarct zone | | | |
| Acute | −2.0 ± 0.6 | −2.4 ± 1.1 | −2.7 ± 0.8 |
| Follow-up | −0.2 ± 1.5 | −1.3 ± 1.7 | −2.5 ± 1.2 |
| Delta | 1.9 ± 1.1 | 1.1 ± 1.2 | −0.2 ± 1.0 |
| *p* Value | 0.01 | 0.007 | NS |
| Regional wall motion (SD/chord) non-infarct zone | | | |
| Acute | 1.3 ± 0.9 | 1.4 ± 1.5 | 0.8 ± 1.5 |
| Follow-up | 0.8 ± 1.1 | 1.4 ± 1.5 | 0.6 ± 1.3 |
| Delta | −0.5 ± 0.5 | 0 | 0.2 ± 1.2 |
| *p* Value | NS | NS | NS |

Abbreviations as in Table II.

motion occurred in patients with both initially patent (−2.2 ± 0.9 vs −1.3 ± 1.7 SD/chord, $p < 0.006$) and persistently patent arteries (−2.6 ± 0.9 vs −2.0 ± 1.5 SD/chord, $p < 0.003$). No improvement occurred in patients with initially occluded or persistently occluded arteries. Patients with initially patent arteries had better infarct zone regional wall motion than did those with initially occluded arteries, both initially (−2.2 ± 0.9 vs −3.0 ± 0.8 SD/chord, $p < 0.002$) and at follow-up (−1.3 ± 1.7 vs −2.9 ± 0.8 SD/chord, $p < 0.0001$). Patients with persistently patent arteries had better infarct zone regional wall motion than did those with persistently occluded arteries at follow-up (−2.0 ± 1.5 vs −3.1 ± 0.4 SD/chord, $p < 0.01$).

## DISCUSSION

**Global ejection fraction.** Although the Western Washington randomized, controlled trial demonstrated no improvement in left ventricular ejection fraction when streptokinase therapy was given approximately 5 hours after symptom onset in acute myocardial infarction,[12,13] a more recent trial by Serruys et al.[14] with streptokinase administered within 3 hours of symptom onset in patients without previous infarction did show a significant improvement in ejection fraction compared to the control group, both in patients with inferior infarction and anterior infarction.

More controversial is whether streptokinase therapy results in further improvement in ejection fraction on serial testing following the acute ejection fraction determination. While analysis of patients with persistently patent arteries in uncontrolled studies have shown serial improvement in ejection fraction,[15-18] patients analyzed by the intention-to-treat principle[14,19,20] have not. Additionally, studies that used the area length method of contrast ventriculographic analysis employed in this study[11,21] have not shown serial improvement in ejection fraction. This discrepancy is not explained by the route of streptokinase administration or by time to treatment differences. No serial improvement in ejection fraction following inferior infarction has previously been demonstrated.[14,22,23]

A severe residual stenosis following thrombolysis has been shown[7] to limit functional recovery. Restricted blood flow or rethrombosis and reinfarction may explain why serial improvement in ejection fraction is not consistently found after lytic thera-

**Table IV.** Global and regional left ventricular function by patency status

| | *Initial status* | | | *Follow-up status* | | |
|---|---|---|---|---|---|---|
| | *Patent (n = 18)* | *Occluded (n = 28)* | p *Value* | *Patent (n = 36)* | *Occluded (n = 10)* | p *Value* |
| Ejection fraction (%) | | | | | | |
| Acute | 59 ± 10 | 56 ± 8 | NS | 59 ± 9 | 51 ± 8 | 0.008 |
| Follow-up | 61 ± 11 | 55 ± 7 | 0.02 | 60 ± 9 | 48 ± 4 | 0.0001 |
| Delta | 2 ± 9 | −1 ± 8 | NS | 1 ± 8 | −2.5 ± 10 | NS |
| *p* Value | NS | NS | | NS | NS | |
| Regional wall motion (SD/chord) infarct zone | | | | | | |
| Acute | −2.2 ± 0.9 | −3.0 ± 0.8 | 0.002 | −2.6 ± 0.9 | −3.0 ± 0.5 | NS |
| Follow-up | −1.3 ± 1.7 | −2.9 ± 0.8 | 0.0001 | −2.0 ± 1.5 | −3.1 ± 0.4 | 0.01 |
| Delta | 0.9 ± 1.4 | 0.1 ± 0.7 | 0.005 | 0.6 ± 1.2 | −0.1 ± 6 | 0.04 |
| *p* Value | 0.006 | NS | | 0.003 | NS | |
| Regional wall motion (SD/chord) non-infarct zone | | | | | | |
| Acute | 0.8 ± 1.7 | 1.2 ± 1.4 | NS | 1.1 ± 1.6 | 0.5 ± 1.3 | NS |
| Follow-up | 0.4 ± 1.5 | 1.1 ± 1.3 | NS | 0.9 ± 1.5 | 0.4 ± 1.0 | NS |
| Delta | −0.3 | −0.1 | NS | −0.2 ± 1.2 | −0.2 ± 0.8 | NS |
| *p* Value | NS | NS | | NS | NS | |

Abbreviations as in Table II.

py.[7, 24, 25] Interestingly, preliminary evidence suggests that when angioplasty[14, 26, 27] or coronary bypass surgery[28] follows lytic therapy, serial ejection fraction *does* improve. Our data also show that early lytic therapy followed by angioplasty can result in serial ejection fraction improvement in inferior infarction, while late treatment with lytic therapy and/or angioplasty does not. Regardless of whether or not serial improvement in ejection fraction occurs, it should be emphasized, both in our own and previous studies, that successful reperfusion with a documented patent vessel prior to hospital discharge results in a higher ejection fraction than is found with an occluded infarct-related artery.

**Regional wall motion.** As reported for ejection fraction, regional wall motion was not improved by reperfusion therapy in the Western Washington Study, in which streptokinase was given approximately 5 hours after symptom onset,[12, 13] while it was improved in the study by Serruys et al.,[14] in which streptokinase was administered within 3 hours of symptoms. All the nonrandomized studies that reported either presence or absence of serial improvement in ejection fraction following reperfusion therapy reported serial improvement in regional wall motion.[15-21] Those that did not find serial improvement in ejection fraction found that compensatory hyperkinesia in the non-infarct zone often preserved initial ejection fraction despite severe hypokinesia in the infarct zone, thus masking potential global improvements.[11, 19, 21] Serial improvement in infarct zone regional wall motion after inferior infarction has been reported for patients with patent arteries[7, 15, 23] and for patients receiving streptokinase.[14] Our data also show improvement in infarct zone regional wall motion, particularly in patients treated with streptokinase plus angioplasty. Time to treatment and patency staus were strong predictors of improvement.

**Limitations.** This study is limited by the fact that small groups of patients were treated by different interventions and that treatment was delayed in patients treated by angioplasty alone or by tissue-type plasminogen activator. These limitations reflect the rapid evolution of reperfusion therapy in our catheterization laboratory from direct angioplasty[20] to intravenous streptokinase followed by immediate angioplasty[29] to intravenous tissue-type plasminogen activator with subsequent randomization to delayed angioplasty or immediate angioplasty.[30] While patients treated with streptokinase received early therapy in their local emergency rooms, patients receiving direct angioplasty or tissue-type plasminogen activator had to be sent by ground or helicopter transport to our catheterization laboratory before treatment could be instituted, thus explaining the differences between groups in time to treatment. In spite of these limitations, improvement in ventricular function by reperfusion therapy in inferior infarction was demonstrated by this study. Earlier therapy would be expected to produce more dramatic improvement.[11, 15-17, 21, 22, 31]

Not enough patients were treated with tissue-type plasminogen activator plus angioplasty to demonstrate a statistically significant improvement in ventricular function, although the serial changes obtained were similar to those in the streptokinase plus angioplasty group. Time to treatment was 2

hours later, however, and was equivalent to patients treated only with either tissue-type plasminogen activator or with angioplasty who did not show improvement in ventricular function. More patients will have to be studied to determine if this form of sequential therapy provides a longer time frame within which reperfusion therapy can be applied with expectation of myocardial salvage.

Three patients died before the follow-up study could be obtained. All were clinically stable before reperfusion of a proximal arterial occlusion and then deteriorated rapidly, dying within 24 hours of hospitalization. This course of events has not occurred in our experience with reperfusion therapy in proximal left anterior coronary arteries. The hemodynamic sequelae of right ventricular infarction probably result from interruption of proximal right coronary artery blood flow to the crista supraventricularis.[32] It is possible that the right ventricle is particularly susceptible to reperfusion injury[33] and that this contributed to the demise of these patients.

**Clinical implications.** It is increasingly clear that reperfusion therapy in acute myocardial infarction has the potential to preserve left ventricular function[14-23, 26-31] and decrease mortality.[22, 34] Data from this study and others demonstrate that myocardial salvage is critically dependent upon time to treatment and upon restoring arterial patency, and is not related to location of infarction. It is also probable that early angioplasty after lytic therapy is important in salvaging myocardium by preventing arterial reocclusion or by achieving acute arterial patency in arteries not reperfused by lytic therapy.

The effort and expense required to apply reperfusion therapy to all patients with acute infarction would require a major allocation of additional resources to the cardiac catheterization laboratory and regionalization of health care delivery. If treatment could be limited to subgroups of patients most likely to benefit from this form of therapy, the risk and expense could be reduced. Unfortunately, such subgroups have not yet been clearly defined. While therapy is better given earlier than later, intermittent coronary occlusion or the presence of collateral blood flow cannot be predicted noninvasively and extend the time frame within which myocardial salvage can be achieved. Although it has been suggested that ECG criteria[23, 35] or initial reduced ejection fraction[36] predict larger infarct size and patients with inferior infarction more likely to benefit from lytic therapy, we could not confirm those findings in our patients, most of whom had angioplasty. Until more rigorous selection criteria can be formulated based upon mortality data in prospective randomized trials, the data from the current study suggest that reperfusion therapy in patients with inferior myocardial infarction who present within 3 hours of symptom onset with ST segment elevation in at least two contiguous ECG leads will improve left ventricular function. Additional data are required to determine whether patient survival is also increased.

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