Influence of Coronary Collateral Vessels on Myocardial Infarct Size in Humans

Results of Phase I Thrombolysis in Myocardial Infarction (TIMI) Trial

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Background. The influence of coronary collateral vessels on infarct size in humans remains controversial, partly because no previous study has examined the impact of collaterals present at the onset of acute myocardial infarction on infarct size.

Methods and Results. The present study used the data base of the Thrombolysis in Myocardial Infarction (TIMI) Phase I trial to correlate the presence or absence of angiographically documented collaterals in the initial hours of myocardial infarct evolution with the size of the infarct as assessed by serial measurements of serum creatine kinase (CK). To avoid the confounding effects of reperfusion on enzymatic estimates of infarct size, this report is limited to those 125 patients who failed to recanalize at 90 minutes after administration of tissue plasminogen activator or streptokinase. Patients with angiographically documented collaterals (group A, n=51) had significantly lower values of peak serum CK than patients without collaterals (group B, n=74) (1,877±216 versus 2,661±212 IU/l, respectively [mean±SEM], p=0.004). Similarly, CK-derived infarct size estimates were significantly lower in group A than in group B (20.6±2.5 versus 31.4±2.8 CK gram equivalents, p=0.001). The infarct size observed in patients with collaterals was less for anterior infarctions as well as for infarctions of other locations; thus, the beneficial effects of collaterals were independent of the site of the infarct. In 65 of the 125 patients who failed to reperfuse, left ventricular ejection fraction (LVEF) was assessed by contrast ventriculography both at initial cardiac catheterization (before thrombolytic therapy) and at hospital discharge. Among the patients who had both studies, global LVEF tended to increase from pretreatment to hospital discharge in group A (from 50.6±1.8% to 53.4±1.8%, p=0.10) but decreased in group B patients (from 50.3±1.8% to 47.8±1.7%, p=0.02). At hospital discharge, global LVEF was greater in patients with coronary collaterals (53.5±1.7% versus 49.6±1.7%, p=0.01).

Conclusions. The results demonstrate that, in patients in whom thrombolytic therapy fails to induce reperfusion, the presence of coronary collateral vessels at the onset of myocardial infarction is associated with limitation of infarct size as assessed enzymatically and with improved ventricular function on discharge as assessed by LVEF. (Circulation 1991;83:739–746)

It is well established that coronary collateral blood flow is a major determinant of the extent of necrosis after coronary artery occlusion in experimental animals. However, the role of coronary collaterals in modulating infarct size in humans remains speculative. The uncertainty stems in large part from limitations of previous clinical studies, including delay in the assessment of collaterals after the onset of myocardial infarction, use of enzymatic estimates of infarct size despite the alter...
ation of kinetics of creatine kinase (CK) release by reperfusion,\textsuperscript{13–16} and reliance on global left ventricular function parameters despite the poor correlation between recovery of regional wall motion in the infarct site and improvement in global left ventricular ejection fraction after thrombolytic therapy.\textsuperscript{17} No previous study has examined the impact of collateral vessels present at the onset of acute myocardial infarction on infarct size, estimated enzymatically, in the absence of any confounding effect due to reperfusion.

The Thrombolysis in Myocardial Infarction (TIMI) Phase I trial provided a unique opportunity to investigate the functional significance of coronary collaterals present during the first few hours of myocardial infarction. In this trial, patients with evolving myocardial infarction underwent coronary angiography immediately after enrollment and had serial measurements of serum CK throughout the subsequent 72 hours. Acute coronary angiography made it possible to determine 1) whether the infarct-related artery was completely occluded in the early phase of myocardial infarction, 2) whether angiographically detectable collateral vessels were present at this time, and 3) whether the thrombolytic agent was effective in inducing thrombolysis. Given that intravenous thrombolytic therapy is now recommended in acute myocardial infarction, it is unlikely that it would be feasible to repeat this study presently or in the future. Accordingly, the objective of the present study was to correlate the presence or absence of coronary collaterals in the acute phase of myocardial infarction with the size of the infarct as assessed by serial measurements of serum CK. To avoid the interference of reperfusion on CK kinetics,\textsuperscript{13–16} the analysis was limited to those 125 patients who failed to recanalize at 90 minutes after the administration of recombinant tissue-type plasminogen activator (t-PA) or streptokinase.

**Methods**

The TIMI Phase I trial was a multicenter randomized prospective trial, sponsored by the National Heart, Lung, and Blood Institute and designed to compare the efficacy of intravenous t-PA and streptokinase in achieving reperfusion in patients with acute myocardial infarction. Phase I began on August 15, 1984, and was stopped prematurely on February 5, 1985, because the reperfusion rate after treatment with t-PA was significantly greater than that with streptokinase. The results of TIMI Phase I have been published elsewhere.\textsuperscript{18,19}

**Thrombolytic Therapy**

Patients were enrolled and treated at 13 clinical sites. Patients were eligible if they experienced at least 30 minutes of ischemic chest pain and ST segment elevation of 0.1 mV or more in at least two electrocardiographic leads reflecting one zone of infarction. Exclusion criteria were as follows: duration of chest pain over 7 hours; age over 75 years; uncontrolled hypertension; cerebrovascular events, severe streptococcal infection, previous streptokinase infusion, or severe trauma within the last 6 months; current oral anticoagulant therapy; past or present bleeding disorder or significant gastrointestinal bleeding; surgery or cardiopulmonary resuscitation within the previous 2 weeks; prior coronary artery bypass graft surgery; presence of left bundle branch block, prosthetic heart valve, or dilated cardiomyopathy; shock unresponsive to volume expansion and vasopressor therapy; or other advanced illness.

After informed consent was obtained, eligible patients had immediate cardiac catheterization. A 5,000-unit bolus of heparin was given intravenously. Left ventriculography was performed in the 30° right anterior oblique projection; after this procedure, angiograms of the noninfarct- and infarct-related coronary arteries were obtained. Patients with less than 50% diameter reduction in the infarct-related artery before or after 200 µg intracoronary nitroglycerin did not receive thrombolytic therapy. The remaining patients were randomly assigned to receive t-PA (preparation No. G11021, Genentech, Inc., Somerville, N.J., or KabiVitrum, Inc., Alameda, Calif.) or streptokinase (Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J., or KabiVitrum, Inc., Alameda, Calif.). Recombinant t-PA was given at a dose of 80 mg i.v. over 3 hours (40 mg, 20 mg, and 20 mg in the first, second, and third hours, respectively). Streptokinase was given at a dose of 1.5 million units i.v. for 1 hour. Each patient received both an active drug and a placebo in concomitant 1-hour and 3-hour infusions through separate intravenous lines. This was done in all randomized patients to ensure blinding. Angiograms of the infarct-related artery were repeated 10, 20, 30, 45, 60, 75, and 90 minutes after initiating thrombolytic therapy. Patients were then transferred to the coronary care unit, where they received routine care and intravenous heparin (1,000 units/hr) adjusted to maintain the partial thromboplastin time at 1.5 to two times control.

**Data Analysis**

The perfusion status of the infarct-related artery was assessed by the radiographic core laboratory using standardized TIMI criteria.\textsuperscript{18,19} Successful reperfusion was defined as TIMI perfusion grade 2 or 3 at 90 minutes after initiation of thrombolytic therapy. Collaterals to the infarct-related artery were evaluated from the acute pretreatment coronary angiogram. Collaterals were analyzed by the radiographic core laboratory and graded on a three-point scale as absent (grade 1), minimal (grade 2), or well developed (grade 3), respectively. Grade 1 was defined as the absence of any collaterals to the occluded vessel supplying the area of infarction. Grade 2 collaterals were defined as collaterals resulting in faint opacification to a diameter not exceeding 1 mm in the occluded vessel or its branches, visualized distal to the obstruction in the
Well-developed collaterals (grade 3) were defined as collaterals resulting in full opacification to a diameter greater than 1 mm in the occluded vessel or its branches, visualized distal to the obstruction in the occluded vessel that supplies the area of the infarction. A patient was considered to have collaterals to the infarct-related artery if the collateral perfusion grade was 2 or 3. Collaterals were graded in this manner only in the acute pretreatment film. Two hundred ninety patients were enrolled in TIMI Phase I. Of these 290 patients, 57 (20%) had pretreatment TIMI perfusion grade 2 or 3 in the infarct-related artery. One patient did not have the 90-minute reading. Among the remaining 232 patients with pretreatment perfusion grade 0 or 1 in the infarct-related artery, successful reperfusion at 90 minutes after thrombolytic therapy occurred in 107 patients (70 of 113 patients treated with t-PA and 37 of 119 patients treated with streptokinase). Thus, 125 patients had TIMI perfusion grade 0 or 1 both before and 90 minutes after initiation of thrombolytic therapy. These patients who had initial coronary occlusion and failed to exhibit reperfusion form the basis of the present report.

**CK Enzyme Determination and Estimation of Infarct Size**

All patients enrolled had serial serum CK enzyme levels measured at 4-hour intervals for the first 48 hours after randomization at each of the participating clinical sites. Total serum CK activity was assessed by the Rosalki method.\(^2\) Infarct size was estimated from changes in serum CK, as previously described.\(^2\) Peak serum CK and estimates of infarct size were compared in patients with collaterals (group A) and in those without collaterals (group B). Infarct size could not be estimated in 11 of 125 patients because of incomplete serum CK data.

**Statistical Methods**

All values are expressed as mean±SEM. Differences in means between groups A and B were analyzed with Student's *t* tests for unpaired observations if the data followed a normal distribution. Differences in peak serum CK levels and CK-derived infarct size were analyzed by nonparametric statistics (Wilcoxon's rank-sum test),\(^2,2\) because these data did not follow a normal distribution.\(^2,2\) Pretreatment and predischarge measurements of left ventricular ejection fraction were compared with Student's *t* tests for paired observations.

**Results**

Well-developed coronary collaterals (grade 3) were rare, being present in only four (3%) of 125 patients who failed to recanalize at 90 minutes, whereas minimal (grade 2) collaterals were more common (47 [38%] of 125 patients) (Table 1). Overall, 51 (41%) of the patients who did not reperfuse at 90 minutes had angiographically detectable collaterals (group A).

**Baseline Characteristics**

In Table 1, the clinical and angiographic baseline characteristics of patients who failed to reperfuse at 90 minutes are compared in the cohort with angiographically documented collaterals (group A) and in the cohort without collaterals (group B). For comparison, data for all TIMI I patients are also presented. There was no significant difference between groups A and B in any of these variables that could influence infarct size, indicating that the two groups were comparable except for collateral status.

**Late Reperfusion**

As indicated above, all patients included in this analysis had TIMI perfusion grade 0 or 1 at 90 minutes of thrombolytic therapy. The occurrence of late reperfusion (defined as infarct-related artery TIMI perfusion grade 2 or 3 at discharge) was assessed in 78 patients who underwent coronary angiography before leaving the hospital. Of 29 patients with collaterals who had pre-discharge coronary angiography, 15 (52%) exhibited late reperfusion. Of 49 patients without collaterals who had pre-discharge coronary angiography, 26 (53%) had late reperfusion. Thus, there was no relation between the presence of angiographically detectable coronary collateral vessels and the occurrence of late reperfusion. Furthermore, the time from the first serum CK measurement to the highest CK measurement was similar in patients with collaterals (981±45 minutes) and without collaterals (934±59 minutes).

**Enzymatic Estimates of Infarct Size**

Group A had significantly lower values of peak serum CK activity and enzymatic estimates of infarct size as compared with patients in group B (Figure 1). These differences in serum CK activity and infarct size were highly significant (*p*=0.004 and 0.001, respectively). Infarct size in group A was approximately 35% less than infarct size in group B.

The beneficial effect of collaterals on infarct size was independent of infarct location (Figure 2). In patients with anterior wall infarcts, angiographically documented collaterals were associated with lower values of peak serum CK activity (2,257±439 versus 3,077±327 IU/l, *p*=0.045) and infarct size (23.2±4.8 versus 34.2±3.9 CK gram equivalents, *p*=0.027). A similar reduction in both peak serum CK activity and infarct size was noted in patients with infarcts in other locations (1,589±174 versus 2,267±261 IU/l, *p*=0.06 and 18.5±2.3 versus 28.7±4.0 CK gram equivalents, *p*=0.044, respectively). Thus, infarct size was approximately 35% less in all subgroups of patients with collaterals, irrespective of site of infarction.

In three patients who died within 24 hours of symptom onset (one in group A and two in group B), serum CK data were not sufficient to measure CK-derived infarct size or peak serum CK. An
TABLE 1. Clinical and Angiographic Data

<table>
<thead>
<tr>
<th></th>
<th>All treated TIMI patients (n=290)</th>
<th>Group A (n=51)</th>
<th>Group B (n=74)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>57±1</td>
<td>58±1</td>
<td>58±1</td>
</tr>
<tr>
<td>Male (%)</td>
<td>80</td>
<td>74</td>
<td>81</td>
</tr>
<tr>
<td>Infarct location (%)</td>
<td>Anterior 48</td>
<td>43</td>
<td>49</td>
</tr>
<tr>
<td></td>
<td>Inferior 52</td>
<td>57</td>
<td>51</td>
</tr>
<tr>
<td>History (%)</td>
<td>Prior infarction 18</td>
<td>20</td>
<td>24</td>
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<tr>
<td></td>
<td>Angina 48</td>
<td>49</td>
<td>55</td>
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<td>Medications</td>
<td>Long-acting nitrates 17</td>
<td>16</td>
<td>20</td>
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<td></td>
<td>Short-acting nitrates 26</td>
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<td></td>
<td>β-Blockers 20</td>
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<td></td>
<td>Calcium antagonists 13</td>
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<td>14</td>
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<tr>
<td>Baseline HR (beats/min)</td>
<td>78±1</td>
<td>78±2</td>
<td>78±2</td>
</tr>
<tr>
<td>Baseline SBP (mm Hg)</td>
<td>134±1</td>
<td>135±3</td>
<td>133±3</td>
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<tr>
<td>Baseline DBP (mm Hg)</td>
<td>83±1</td>
<td>86±2</td>
<td>82±2</td>
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<tr>
<td>Infarct-related artery (%)</td>
<td>RCA 45</td>
<td>55</td>
<td>43</td>
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<tr>
<td></td>
<td>LAD 43</td>
<td>41</td>
<td>39</td>
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<tr>
<td></td>
<td>LCx 12</td>
<td>4</td>
<td>18</td>
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<tr>
<td>Collateral grade 2 or 3 (%)</td>
<td>32</td>
<td>100</td>
<td>0</td>
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<tr>
<td>Collateral grade 3 (%)</td>
<td>2</td>
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<td>0</td>
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<td>Thrombolytic therapy (%)</td>
<td>t-PA 49</td>
<td>33</td>
<td>35</td>
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<td></td>
<td>SK 51</td>
<td>67</td>
<td>65</td>
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<tr>
<td>LVEF (%)</td>
<td>Pretreatment 48.4±0.7</td>
<td>47.2±1.6</td>
<td>49.7±1.6</td>
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<tr>
<td></td>
<td>(n=248)</td>
<td>(n=48)</td>
<td>(n=61)</td>
</tr>
<tr>
<td>Hospital discharge</td>
<td>49.7±0.8</td>
<td>53.5±1.7</td>
<td>46.9±1.7*</td>
</tr>
<tr>
<td></td>
<td>(n=182)</td>
<td>(n=26)</td>
<td>(n=46)</td>
</tr>
<tr>
<td>Time, pain to treatment (min)</td>
<td>285±5</td>
<td>301±12</td>
<td>286±11</td>
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<tr>
<td>Recurrent inhospital ischemic pain (%)</td>
<td>45</td>
<td>57</td>
<td>42</td>
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<tr>
<td>Late reperfusion† (%)</td>
<td>Present 52</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>Absent 20</td>
<td>27</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>Not assessed 28</td>
<td>43</td>
<td>34</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>Within 6 weeks 7.2</td>
<td>11.8</td>
<td>9.5</td>
</tr>
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<td></td>
<td>Within 6 months 8.6</td>
<td>15.7</td>
<td>10.8</td>
</tr>
</tbody>
</table>

Continuous variables are expressed as mean±SEM. Group A, patients with angiographically documented collaterals (collateral perfusion grade 2 or 3) at pretreatment catheterization; group B, patients without angiographically documented collaterals (collateral perfusion grade 1); HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; t-PA, tissue-type plasminogen activator; SK, streptokinase; LVEF, left ventricular ejection fraction. "Baseline" hemodynamic values were measured before administration of thrombolytic therapy.

* † p = 0.01 vs. hospital discharge in group A (unpaired t test).
† Late reperfusion is defined as an infarct-related artery TIMI perfusion grade 2 or 3 at hospital discharge.

effort was made to take into account these missing data. Since these patients presumably had large infarctions, they were assigned the largest peak CK and infarct size values observed in the present study. When the analysis of peak CK and infarct size was repeated after including these three patients, the results were similar to those described above; that is, peak serum CK and CK-derived infarct size were significantly lower in group A than in group B.

Since only four patients in group A had well-developed (grade 3) collaterals, a statistical analysis...
of the relation between collateral perfusion grade and infarct size is not possible.

Left Ventricular Systolic Function

In 65 of the 125 patients who failed to reperfuse, left ventricular ejection fraction was assessed both at initial cardiac catheterization (before treatment) and before hospital discharge. (In the remaining 60 patients, comparison of predischarge and initial assessments of left ventricular ejection fraction was not possible because of death [n=10], percutaneous transluminal coronary angioplasty or coronary bypass surgery [n=7], patient or physician refusal of repeat cardiac catheterization [n=22], other unspecified reasons for failing to repeat cardiac catheterization [n=6], or inadequate quality of predischarge or initial left ventriculogram [n=15]). As shown in Table 2,

<table>
<thead>
<tr>
<th>Table 2. Paired Left Ventricular Ejection Fraction Measurements</th>
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<tr>
<td>Pretreatment LVEF (%)</td>
</tr>
<tr>
<td>----------------------</td>
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<tr>
<td></td>
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<tr>
<td>Difference</td>
</tr>
</tbody>
</table>

Values are expressed as mean±SEM. Table includes only patients with left ventricular ejection fraction measurements taken both before thrombolytic therapy and at discharge (n=65). Group A, patients with angiographically documented collaterals (collateral perfusion grade 2 or 3) at pretreatment catheterization; group B, patients without angiographically documented collaterals (collateral perfusion grade 1); LVEF, left ventricular ejection fraction. *p=0.02 vs. group B pretreatment (paired t test). †p=0.006 vs. group A (unpaired t test).

left ventricular ejection fraction increased from pretreatment to hospital discharge in group A patients (from 50.6±1.8% to 53.4±1.8%, p=0.10 by paired t test), whereas it decreased in group B patients (from 50.3±1.8% to 47.8±1.7%, p=0.02 by paired t test). Unpaired statistical analysis confirmed that the changes in left ventricular ejection fraction differed in groups A and B: at initial cardiac catheterization, the ejection fraction was virtually identical in the two cohorts (50.6±1.8% and 50.3±1.8%), but at the time of discharge it was greater in group A as compared with group B (p=0.04 by unpaired t test). Similar results were obtained when the analysis was extended to include all patients who failed to reperfuse at 90 minutes, regardless of whether contrast ventriculography was performed only once or twice (Table 1): at initial catheterization (n=109), left ventricular ejection fraction was similar in groups A and B (47.2±1.6% versus 49.7±1.6%, respectively), but at the time of discharge (n=72), it was significantly greater in group A than in group B (53.5±1.7% versus 46.9±1.7%, respectively, p=0.01 by unpaired t test). In conclusion, with either analysis, patients with angiographically detectable collaterals (group
A) had better predischarge left ventricular ejection fraction than patients without collaterals (group B).

**Discussion**

This study demonstrates that, in patients in whom thrombolytic therapy fails to effect reperfusion, the presence of angiographically detectable collaterals in the initial hours of acute myocardial infarction is associated with a significant reduction in infarct size and a significant increase in predischarge left ventricular ejection fraction. Although well-developed collaterals were rare, the presence of any angiographically detectable collateral circulation was sufficient to decrease infarct size by approximately 35%, a difference that is likely to be clinically significant. These results indicate an important role of coronary collaterals in limiting the extent of myocardial necrosis in the absence of reperfusion in humans. Previous reports on the functional significance of coronary collateral vessels in humans have been conflicting. To our knowledge, this is the first study to correlate myocardial infarct size with the presence or absence of collaterals in the acute phase of myocardial infarction in humans.

In TIMI Phase I, successful reperfusion occurred in 62% of the patients treated with t-PA and in 31% of those treated with streptokinase. Thus, over a third of the patients treated with t-PA and two thirds of the patients treated with streptokinase did not experience early recanalization. The present results suggest that, in these patients, adjunctive mechanical or pharmacological interventions aimed at improving collateral blood flow in the early hours of infarct evolution could be beneficial by limiting the final extent of myocardial necrosis.

**Use of Serum CK to Estimate Infarct Size**

Myocardial infarct size, estimated enzymatically using serial serum CK determinations, is an objective end point for assessing interventions in patients with acute myocardial infarction and correlates with acute and long-term morbidity and mortality. However, reperfusion is associated with altered kinetics of CK release, both experimentally and clinically. In experimental animals, early reperfusion is associated with higher serum CK levels that peak earlier than those associated with sustained occlusion, reflecting a more rapid release of CK from myocardial tissue. A similar pattern is observed in patients. For example, in the 272 patients enrolled in TIMI Phase I, reperfusion was associated with peaking of serum CK levels within 4 hours after thrombolytic therapy: 82% of patients with peaking of CK levels within 4 hours had angiographic evidence of reperfusion compared with 19% of those with peaking of CK levels 16 hours or more after thrombolytic therapy. In view of these alterations of CK kinetics, the validity of CK-derived measurements of infarct size in the setting of reperfusion remains to be established. Consequently, in the present study, we have limited the analysis to those patients who had no angiographic evidence of reperfusion (as defined by TIMI perfusion grade 0 or 1) at 90 minutes after initiation of thrombolytic therapy. Peak serum CK enzyme levels and CK-derived infarct size in these patients are likely to accurately reflect the extent of myocardial necrosis.

Reperfusion occurring after 90 minutes of thrombolytic therapy but before 48–72 hours from the onset of symptoms could still affect enzymatic estimates of infarct size. However, time to peak CK and incidence of late recanalization (as assessed by predischarge coronary angiography) did not differ in patients with and without coronary collaterals, indicating that the occurrence of reperfusion between 90 minutes and hospital discharge was similar in both groups. The similarity of time to peak CK between groups A and B also indicates that the presence of collateral circulation did not result in faster “wash-out” of CK from infarcted myocardium.

**Previous Studies**

Two prior studies have examined the relation between presence of coronary collaterals and regional and global left ventricular function in the TIMI Phase I trial. In the report by Sheehan et al, left ventricular global and regional wall motion were evaluated by contrast ventriculography before treatment and at hospital discharge in 145 patients. Overall, global left ventricular ejection fraction increased (from 48.7±1.7% to 50.9±1.6%, p=0.06) in 43 patients with collaterals (collateral perfusion grade 2 or 3) but remained unchanged in 102 patients without collaterals (from 48.6±1.0% to 48.9±1.1%). These findings are in agreement with our present results obtained in the subset of TIMI I patients who failed to reperfuse at 90 minutes.

In that previous report, the higher global left ventricular ejection fraction at hospital discharge in TIMI patients with coronary collaterals was not attributed to differences in the degree of recovery of wall motion in the infarct site. One possible interpretation of this finding is that coronary collaterals did not limit infarct size. In the present study, however, enzymatic estimates of infarct size in the cohort of TIMI patients in whom thrombolytic therapy did not effect reperfusion showed a significantly smaller infarct size in patients with coronary collaterals. The apparent discrepancy between this prior report and the present study may be related to the different populations examined (all treated patients, regardless of the occurrence of reperfusion, in the report by Sheehan et al, versus patients who failed to reperfuse in the present study). It is possible that the beneficial effect of collaterals can be more readily demonstrated in the presence of sustained coronary occlusion. In patients in whom the extent of necrosis is limited by reperfusion, the impact of collaterals may be less important. Furthermore, the analysis of regional wall motion in the infarct territory used by Sheehan et al is an indirect means of assessing infarct size.
In the second report, Wackers et al used quantitative radionuclide angiography to assess left ventricular function in 229 TIMI I patients. No difference in global left ventricular ejection fraction was found between patients with and without collaterals. Regional left ventricular ejection fraction in the infarct territory was also similar in both groups. This study, however, did not selectively analyze global or regional left ventricular function in the cohort of TIMI patients who failed to reperfuse after thrombolytic therapy. In contrast, the present study was designed to evaluate the role of coronary collaterals in that specific cohort of TIMI patients. As mentioned above, it is conceivable that collaterals limit infarct size in patients in whom thrombolytic therapy fails to produce reperfusion but not in patients who experience early recanalization.

Other investigators have evaluated the role of coronary collaterals in the recovery of global and regional left ventricular function after various acute reperfusion interventions such as intravenous or intracoronary streptokinase, percutaneous transluminal coronary angioplasty, or emergency coronary artery bypass surgery. Despite the small number of patients reported and the variable modalities of reperfusion used, patients with well-developed coronary collaterals had a significant improvement in global left ventricular ejection fraction, whereas those without collaterals had no improvement. A recent preliminary report suggests that the presence of coronary collaterals may reduce the development of postinfarction aneurysm.

A protective effect of coronary collaterals in acute myocardial infarction in humans was also suggested in a postmortem study of 16 hearts using labeled microspheres to visualize collaterals and quantify collateral blood flow. Hearts with subendocardial infarcts had more collaterals and a larger lateral zone of viable myocardium at risk than hearts with transmural infarcts. The authors concluded that coronary collaterals may limit the extension of the wave front of necrosis from the subendocardial to the subepicardial layers during the acute evolution of myocardial infarction.

Reasons for Controversy on the Role of Collaterals

The conflicting results on the significance of collaterals in humans are at least partly due to the variability in the interval between onset of myocardial infarction and coronary arteriography. Indeed, coronary collateral visualization has been previously reported to vary greatly depending on the timing of cardiac catheterization. Schwartz et al performed coronary arteriography at variable intervals in 116 patients with persistent occlusion of the infarct-related artery. Well-developed collaterals were rarely visualized in 42 patients who had coronary arteriography within 6 hours after the onset of symptoms but became increasingly evident in patients studied over the next 45 days. The TIMI Phase I study circumvents this limitation by enrolling all patients within 7 hours of symptom onset, thereby eliminating the potential disparity in collateral visualization due to variable timing of coronary arteriography after myocardial infarction.

In experimental animals, it is well established that coronary collateral blood flow is a major determinant of the extent of necrosis after acute coronary artery occlusion. However, the influence of collaterals on infarct size, left ventricular global and regional systolic function, and clinical outcome after acute myocardial infarction in humans remains unsettled. A beneficial effect of coronary collaterals on infarct size has been suggested by many clinical investigators but not by others. This apparent controversy may be related to one of the following factors: different techniques used to visualize coronary collaterals, variable timing of coronary arteriography after acute myocardial infarction, limitations of enzymatic estimates of infarct size in patients with spontaneous or induced reperfusion, use of indirect means of assessing infarct size (such as regional wall motion or ejection fraction), and inclusion of patients with previous manifestations of myocardial ischemia such as angina or healed myocardial infarction.

The TIMI Phase I study addresses many of these limitations. All patients included in this report had a persistently and totally occluded infarct-related artery despite thrombolytic therapy, thus making angiographic visualization of coronary collaterals more feasible. Moreover, enzymatic estimates of myocardial infarct size using serial serum CK levels are more reliable in the absence of reperfusion. All patients in this report were enrolled within 7 hours after the onset of symptoms of acute myocardial infarction and underwent coronary arteriography immediately thereafter. The present results, together with previous studies that focused specifically on the early phase of acute myocardial infarction, provide strong evidence that coronary collaterals do indeed limit ischemic injury.

Implications

The present analysis of data from this large multicenter double-blind trial is the first study to demonstrate a protective effect of coronary collateral vessels on enzymatically estimated infarct size. These findings should stimulate further research to investigate the role of various pharmacological interventions aimed at salvaging myocardial tissue by increasing coronary collateral blood flow or by enhancing collateral growth.

Acknowledgment

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References


KEY WORDS: creatine kinase • thrombolysis • infarct size • coronary collaterals
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