Progressive Decreases in Coronary Vein Flow During Reperfusion in Acute Myocardial Infarction: Clinical Documentation of the No Reflow Phenomenon After Successful Thrombolysis

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Objective. This study was undertaken to examine the effects of coronary flow dynamics after thrombolytic infarct size limits-

Background. It has been commonly accepted that early thrombolytic therapy does not necessarily salvage infarcted myocardium. Plausible causes for myocardial necrosis include such factors as elapsed time to reperfusion, residual stenosis, collateral vessels, hemodynamic loads, preconditioning and reperfusion injury. Recently, the no reflow phenomenon has been elucidated to be associated with infarct extension in clinical studies employing contrast echocardiography or thallium scintigraphy.

Methods. Nineteen patients with early reperfusion in acute anterior myocardial infarction and comparable clinical background were studied. The patients were classified into two groups on the basis of pattern of thallium perfusion measurements of great cardiac vein flow after reperfusion: group A, 9 patients with a progressive decrease in great cardiac vein flow during the first 24 h of the onset of infarction; and group B, 10 patients without this observation. Left ventricular ejection fraction and thallium-201 index were compared between the two groups at follow-up.

Results. There were no significant differences in systemic hemodynamic variables between groups A and B, and neither group had recurrent ischemic events suggesting reocclusion or restenosis during the study. In group A, both great cardiac vein flow (mean ± SD 44 ± 17% reduction) and oxygen extraction (38 ± 15% reduction) were progressively decreased after the onset of reperfusion. Compared with group B, this group showed a lower left ventricular ejection fraction (36 ± 7% vs. 63 ± 15%, p < 0.01) and a larger thallium-201 defect severity index (1,091 ± 366 U vs. 247 ± 261 U, p < 0.01) at follow-up. Although other patient characteristics were comparable between the two groups, antecedent angina occurred in 90% of group B patients in contrast to only 33% of group A patients.

Conclusions. Salvage of myocardium from infarction by successful thrombolysis was not observed in the patients demonstrating progressive decreases in great cardiac vein flow (group A). In those patients, inadequate myocardial reperfusion on a microvascular basis might be associated with a much larger myocardial infarction. Antecedent angina may protect against a progressive decrease in coronary flow and may have beneficial effects on infarct size limitation.

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fully perfuse the ischemic myocardium and, hence, may not recover the processes of cellular injury. In the present study, we tested the hypothesis that there is a correlation between indexes of infarct size at follow-up and progressive decreases in coronary vein flow during the early phase of complete reperfusion. To examine this idea, we serially measured coronary vein flow in patients with early reperfusion in transmural anterior infarction and assessed infarct size by left ventriculography and thallium-201 scintigraphic study at follow-up.

Methods

Study patients. One hundred seven consecutive patients with evolving anteroseptal myocardial infarction were enrolled into the thrombolysis and rescue coronary angioplasty protocol of our hospital. All gave written informed consent for diagnostic and therapeutic catheterization as well as for participation in this study protocol, which was approved by the Osaka Police Hospital Ethical Committee. Coronary recanalization was successful in 80 of the 107 patients. The study group comprised the 19 patients (17 men, 2 women; mean age ± SD 57 ± 12 years) with successful coronary revascularization who fulfilled the following criteria: 1) no history of previous myocardial infarction; 2) total occlusion of the proximal portion of the left anterior descending coronary artery at initial angiography and no significant (>75% diameter reduction) stenosis in the remaining coronary arteries; 3) no opacifiable collateral vessels on initial and follow-up angiography; 4) performance of all studies when arterial partial pressure of oxygen [Pao2] pH and hemoglobin concentration were normal; 5) no use of inotropic agents, beta-adrenergic blocking agents or calcium channel blockers during the study; 6) recanalization by ≤5 h of the onset of symptoms with Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow (17) without high grade (>90%) residual diameter stenosis; 7) neither reocclusion nor restenosis of the infarct-related vessel on follow-up angiography; 8) no observed clinical events, such as recurrent ischemic pain, cardiac arrest, congestive heart failure, reinfarction, revascularization by bypass surgery or in-hospital death.

The diagnosis of acute myocardial infarction was determined on the basis of a history of chest pain that lasted >30 min, was associated with electrocardiographic (ECG) changes suggestive of acute ischemia in at least two leads and did not respond to nitroglycerin administration. The diagnosis was subsequently confirmed by evolutionary ECG changes and elevation of plasma creatine kinase activity.

Electrocardiographic assessment of risk area. The ST segment–predicted risk area was determined from the initial in-hospital ECG recording. The following formula based on the number of ST segment elevations ≥0.1 mV (nST) in the standard 12 leads was used for prediction (18,19): ECG risk area = 31.5(nST) − 0.4 (%). This formula was validated in the Second International Study of Infarct Survival (18,20).

Catheterization and recanalization. Eligible patients underwent cardiac catheterization by the percutaneous femoral approach and received intravenous heparin, 5,000 U. After angiographic confirmation of total occlusion of the left anterior descending coronary artery, intracoronary nitroglycerin, 0.1 mg, was subsequently administered to exclude vasospasm and intracoronary urokinase, 960,000 U, was administered during 45 to 60 min; if necessary, rescue angioplasty was performed. The time of recanalization was confirmed by angiography every 15 min, and the corresponding perfusion status after recanalization was identified with the use of an adequate amount of contrast material. Successful recanalization was defined as TIMI grade 3 perfusion (17). Coronary angioplasty was performed when TIMI perfusion grade was <3 or percent residual diameter stenosis was >90%. Minimal percent diameter stenosis was expressed using the methods of Ad Hoc Committee of the American Heart Association (21).

Measurements of systemic hemodynamic variables and great cardiac vein flow. The standard hemodynamic measurements, including systemic and pulmonary artery catheterization, were monitored throughout the procedures with catheters introduced percutaneously by way of the femoral artery and vein. The hemodynamic subset of Forrester et al. (22) at hospital admission was determined. The 7F coronary vein multithermistor thermodilution catheter (Wilton Webster Laboratories) was inserted percutaneously from the left arm by cutdown of antecubital vein and advanced to the great cardiac vein. Catheter position was monitored by injection of a small volume of contrast medium, and the stable catheter position was frequently confirmed by fluoroscopy using a minimal amount of contrast agent during the whole procedure. Great cardiac vein flow was measured by continuous thermodilution technique (23,24), infusing 5% dextrose in water at a rate of 40 ml/min for 30 s with an angiographic injector (Medrad Mark IV). Systemic and coronary hemodynamic status was determined before thrombolysis, 60 min after the first angiogram and at follow-up. The time of reperfusion was within 60 min after the first angiogram. We chose postreperfusion flow as baseline flow because 1) confirmation of reperfusion took ≤60 min after the first angiogram, when the peak time of reactive hyperemic flow might be over; 2) great cardiac vein flow before reperfusion did not reflect nonoccluded baseline flow but represented coronary vein flow from nonischemic areas.

Measurements of myocardial oxygen extraction. Oxygen partial pressure and saturation were determined with a blood gas analyzer (Corning 2500 CO-oximeter, Corning Medical and Scientific). Blood from the aorta and great cardiac vein were sampled simultaneously before thrombolysis, 60 min after the first angiogram and at 6, 12 and 24 h after the onset of symptoms.
Ventricular performance at follow-up catheterization. Follow-up catheterization was performed 46 ± 13 days after the onset of infarction. Global ejection fraction was calculated by the standard method of Sandler and Dodge (25) from traced silhouettes of single-plane left ventriculograms in the 30° right anterior oblique view.

Thallium-201 perfusion defect at follow-up. Thallium-201 scintigraphy was performed 38 ± 11 days of the onset of infarction by a technique previously described (26,27). Briefly, 32 projections of thallium-201 single-photon emission computerized tomography over 180° were obtained 3 h after intravenous administration of 3 mCi of thallium-201. The left ventricle was sliced at equidistant intervals perpendicular to its long axis, and the tomograms were quantitated by maximal count: circumferential profiles at each slice; results were compared with normal limit profiles derived from 60 normal control subjects. Defect areas were defined as the areas at each slice in which thallium counts decreased ≥2 SD below the count distribution in normal control subjects. These defect areas were weighed for the average counts in each area, and the sum of these defect areas was defined as the extent of damaged myocardium in the left ventricle, that is, “defect severity index.”

Study protocol. Systemic hemodynamic and great cardiac vein flow measurements at baseline and collection of arterial and great cardiac vein blood samples were made before thrombolysis. All patients were treated with continuous infusion of nitroglycerin (0.1 to 0.3 μg/min) for hemodynamic stabilization and with small-dose heparin infusion (3 to 7 U/min) for prevention of reocclusion during the 1st 24 h after admission. Inotropic agents were not administered. In all patients with successful recanalization, systemic and coronary hemodynamic measurements and blood sampling were repeated 60 min after the first angiogram and at 6, 12 and 24 h of the onset of symptoms. The time of reperfusion when angiography showed TIMI grade 3 flow was 30 to 60 min after the first angiogram. All patients underwent follow-up catheterization 46 ± 13 days after the onset of infarction. Neither reocclusion nor restenosis of the infarct-related vessel was proved at follow-up catheterization. Patients were classified into two groups according to the pattern of thermodilution measurements of great cardiac vein flow; group A included 9 patients with a decrease in great cardiac vein flow >30% of baseline flow during the 1st 24 h of the onset of infarction; Group B included 10 patients without this observation (Table 1).

Calculations. Myocardial oxygen extraction (EO2) was calculated as EO2 = C(A - G)O2/CAO2, where C(A - G)O2 and CAO2 represent arterial–great cardiac vein oxygen content difference and arterial oxygen content, respectively. Coronary vessel resistance (CVR) was calculated as CVR (mm Hg-min/ml) = Mean arterial pressure/Great cardiac vein flow.

Statistical analyses. All data were expressed as mean value ± SD. An unpaired Student t test was used to compare values of age, elapsed time, time interval between initial and repeat angiography, ECG risk area, systemic hemodynamic variables and indexes of infarct size between the two groups of patients. We used regression equations to analyze the statistical significance of sequential changes in great cardiac vein flow, oxygen extraction and coronary vessel resistance over time between the two groups: y = b0 + b1t + b2Dt, where t = time; D = 0 if group A, 1 if group B; b0 = “after” value; b1 = slope (over time) for group A; b2 = change in slope for group B. If b2 is significant, we can judge that one of the groups evolves over time differently from the other. A chi-square analysis with the Yates correction was used to determine qualitatively differences between the two groups (i.e., gender, hemodynamic subsets of Forrester et al. and associated rescue angioplasty or antecedent angina). The Mann-Whitney U test was used to determine qualitative differences for residual stenosis in the acute and chronic phases of infarction. Results were considered significant at p < 0.05.

Results

Clinical characteristics of the patients (Table 2). Age, gender, hemodynamic subset on admission and time interval between the initial and repeat angiography were comparable in the two groups of patients, as were the elapsed time from the onset of infarction to reperfusion and residual coronary stenosis after reperfusion and at follow-up. Three of 10 patients in group B and 4 of 9 patients in group A were treated by rescue coronary angioplasty after thrombolysis.

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<th>Table 1. Great Cardiac Vein Flow (ml/min) in the 19 Study Patients</th>
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Aft = 60 min after the first angiogram; Pt = patient; 6 h; 12 h and 24 h = 6, 12 and 24 h, respectively, after the onset of infarction.
In both groups, the thrombi were located at the proximal segment of the left anterior descending coronary artery, and there were no opacifiable collateral vessels on initial or follow-up angiography. The ECG risk area on admission did not differ between the two groups. Only the prevalence of antecedent angina, defined as recurrent ischemic chest pain beginning > 7 days before admission (28), differed between the two groups (90% in group B patients in contrast to 33% in group A patients). After reperfusion, no patient had recurrent infarction or prolonged angina, congestive heart failure or cardiac arrest during the in-hospital period.

Systemic hemodynamic changes (Table 3). Table 3 summarizes the changes in hemodynamic variables in the two groups during the study. Heart rate and systolic and mean arterial blood pressures in both groups were unchanged throughout the study, and there was no significant difference between the two groups in each variable at any time point. Pulmonary capillary wedge pressure decreased significantly (p < 0.05) after reperfusion in both groups, and thereafter it was unchanged during the study. There was no difference in capillary wedge pressure between the two groups. At follow-up left ventriculography, systemic hemodynamic variables were also similar between the two groups.

Changes in great cardiac vein flow (Fig. 1). In group B, mean great cardiac vein flow did not change during the study. However by definition, in group A, great cardiac vein flow gradually decreased by 26 ± 13 ml/min (mean ± SD) or 44 ± 17% from the postreperfusion flow (58 ± 15 ml/min) during the 1st 24 h of the onset of infarction. Regression equation for analysis of significance over time between the two groups was y = 60.7 - 1.32t + 1.05Dt, where t = time; D = 0 if group A, 1 if group B (see Statistical analyses under Methods). Coefficient of 1.05Dt was significant (p < 0.0001), indicating that great cardiac vein flow evolved over time differently in group A than in group B.

Regional oxygen extraction (Fig. 2). Figure 2 demonstrates that mean myocardial oxygen extraction was gradually decreased in group A by 0.25 ± 0.13 or 38 ± 15% from the postreperfusion value of 0.64 ± 0.11. Regression equation for analysis of significance over time between the two groups was y = 0.622 - 0.0104t + 0.00616Dt, where t = time; D = 0 if group A, 1 if group B (see Statistical analyses under Methods). Coefficient of 0.00616Dt was significant (p < 0.0001), indicating that oxygen extraction in group A evolved over time in a manner different from that in group B. In group B, oxygen extraction did not change during the study.

Coronary vessel resistance (Fig. 3). After reperfusion in
group B, mean coronary vessel resistance remained unchanged throughout the study. Group A demonstrated gradual increases in coronary vessel resistance by 1.60 ± 1.59 from 1.52 ± 0.28 mm Hg-min/ml during the 1st 24 h of the onset of infarction. Regression equation for analysis of significance over time between the two groups was $y = 1.31 + 0.0774t - 0.0664Dt$, where $t = time; D = 0$ if group A, 1 if group B. Coefficient of $-0.0664Dt$ was significant ($p < 0.0001$), indicating that coronary vessel resistance in group A evolved over time in a manner different from that in group B.

Ventricular wall motion and scintigraphic analyses at follow-up (Fig. 4). Group B showed a significantly ($p < 0.01$) higher global ejection fraction (63 ± 15%) than that of group A (36 ± 7%). Ejection fraction was measured at follow-up catheterization, when systemic hemodynamic variables were comparable between the two groups (Table 2). Group B had a significantly ($p < 0.01$) smaller defect severity index than that of group A (247 ± 261 U vs. 1,091 ± 366 U, $p < 0.01$).

**Discussion**

The major finding of this study was that limitation of myocardial infarct size was attenuated in the patients who demonstrated progressive decreases in great cardiac vein flow even after successful early recanalization. In the patients who did not show progressive decreases in great cardiac vein flow, infarct size was smaller. Except for a
Figure 3. Serial changes in coronary artery resistance in groups A and B. The solid line represents the linear regression for group A, the dashed line that for group B. The regression equation for analysis of significance over time between the two groups was \( y = 1.31 + 0.0774t - 0.0064D, \) where \( t = \) time; \( D = 0 \) if group A, 1 if group B. The time course in group A was significantly different from that in group B (\( p < 0.0001 \)). Abbreviations as in Figure 1.

much greater frequency of antecedent angina in group B, the two groups of patients had apparently homogeneous clinical characteristics (i.e., left anterior descending coronary artery occlusion with no collateral flow, moderate size of ECG risk area and complete reperfusion within 5 h of the onset of infarction).

Possible mechanisms of reduction in great cardiac vein flow and failure of infarct size limitation despite early successful recanalization. There are several possible mechanisms of decreased great cardiac vein flow after reperfusion. 1) Metabolic demand of reperfused myocardium might decrease because disappearance of ischemia may attenuate sympathetic nerve stimulation. However, heart rate and aortic pressure did not change in either patient group throughout the study. 2) Epicardial coronary spasm after recanalization may decrease coronary blood flow. In this case, oxygen extraction might have increased (29). However, oxygen extraction after recanalization was decreased in our patients, and there was no evidence of recurrent ischemia during the study. 3) Coronary microvascular injury in reperfused myocardium may decrease great cardiac vein flow. In pathologic studies of myocardial infarction, leukocyte plugging (30) and platelet aggregation (31) are often observed during reperfusion and are suggested to cause the disturbances of microcirculation. In experimental obstruction of coronary microcirculation (32), microvascular embolization decreased oxygen extraction with massive releases of lactate and decreased coronary blood flow. These situations correspond well with our observations. Functional microvascular disturbances, such as capillary compression by myocardial tissue edema (33), myocardial ischemic contracture (34), endothelial cell swelling (35) and increases in vasomotor tone (36), are also possible causes of microvascular injury after reperfusion.

In previous clinical studies (15,16), myocardial imaging by contrast echocardiography or thallium-201 scintigraphy was used to prove the presence of a no reflow zone. In the present study, we used no index of myocardial perfusion in the acute phase of infarction and measured only coronary venous flow and coronary vessel resistance. Ambrosio et al. (13) have shown that no reflow zones are characterized by abrupt vascular occlusion at both small arteriolar and venular levels and absence of capillary filling. Kloner and colleagues (37) revealed progressive microvascular damage after reperfusion characterized by neutrophil migration into the vessel wall and erythrocyte stasis. Furthermore, these abnormalities were associated with reduced vasodilator reserve. Another pathologic study (38) demonstrated progressive infarct extension during reperfusion. Experimental

Figure 4. Differences in left ventricular ejection fraction (left panel) and thallium-201 defect severity index (right panel) between groups A and B. Group A had a significantly (**) lower (\( p < 0.01 \)) ejection fraction and a larger (\( p < 0.01 \)) defect size compared with group B.
studies (14,32) of no reflow demonstrated a progressive decrease in myocardial perfusion. Our results are consistent with those findings. The progressive reduction in great cardiac vein flow strongly suggests progressive impairment of anterograde flow. Because we did not measure white blood cell count in the coronary venous blood, we could not confirm that there was leukocyte plugging in the ischemic myocardium. However, white blood cell count in the peripheral blood was higher in group A than in group B (15,667 ± 2.872 vs. 11,300 ± 2.177/µl, p < 0.05), raising the possibility that the inflammatory response to ischemia might be one difference between the two groups.

Study limitations. Although thermodilution measurements of great cardiac vein flow have been previously validated in humans and widely used in clinical studies (23,39), this procedure has some technical limitations (40,41). However, changes >30% in great cardiac vein flow can be considered significant (24,42,43). In the present study, extreme care was taken to stabilize and document the catheter position when great cardiac vein flow was measured repeatedly. We found that patients in group A showed decreases in great cardiac vein flow of 44% or 26 ml/min, indicating that in a particular subset of patients, great cardiac vein flow substantially decreases during the acute phase of infarction. It is possible that decreases in myocardial perfusion are attributable to decreases in collateral flow from nonischemic regions (44). However, this possibility does not seem likely, because no opacifiable collateral vessels were observed during coronary angiography.

Nicklas et al. (45) showed a mean increase of 12.9% in great cardiac vein flow after recanalization in myocardial infarction in humans. Our patients had a mean hyperemic increase in great cardiac vein flow of 7.2%. Possible causes for the decreased hyperemia are 1) we measured the post-reperfusion flow after confirmation of TIMI grade 3 flow, which took ≤60 min after the first angiogram, indicating that the peak time of reactive hyperemia might be over; 2) the great cardiac vein flow measurement before reperfusion should have reflected coronary vein flow from nonischemic areas; hence, reactive hyperemia in the present study might not be similar to that in the experimental studies.

It is difficult to estimate infarct size by means of wall motion abnormality in the follow-up period, because stunned myocardium (46) may be assessed as infarct area even though impaired contractile dysfunction in stunned myocardium is reversible. Because myocardial stunning is reported to restore its basic contractile function 10 to 16 days after reperfusion (47,48) and we estimated ventricular wall motion 46 ± 13 days after recanalization, our estimation of infarct size may not include reversibly injured myocardium. In addition, differences in loading conditions in the acute and chronic phases of infarction may cause erroneous estimates of ventricular wall motion. However, the assessment of infarct size by ventricular wall motion in the two comparable loading conditions is reported to cause minimal errors (49). Furthermore, we assessed infarct size with thallium-201 defect severity, which is not affected by abnormal wall motion of salvaged myocardium. Taken together, the estimation techniques of infarct size in the present study seem to provide a precise extent of necrotic area.

Ischemic preconditioning is believed to limit infarct size in reperfused myocardium experimentally (50) and also clinically (51). Various plausible mechanisms of this phenomenon such as free radical generation and scavenging (52) or endogenous adenosine (53) are proposed. Our definition of antecedent angina is different from that of experimental ischemic preconditioning. However, most of our study patients without clinical demonstration of the no reflow phenomenon had antecedent angina. Because no established data have linked preconditioning to the no reflow phenomenon, we need to further investigate the general aspect of microvascular disturbances in acute myocardial infarction.

Conclusions. Salvage of myocardial infarction by early successful thrombolysis could not be observed in the patients demonstrating progressive decreases in great cardiac vein flow. Those patients appeared to have inadequate myocardial reperfusion on a microvascular basis, which is associated with a much larger infarction. Antecedent angina may have beneficial effects on the no reflow phenomenon or infarct size limitation, or both.

References

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