Serial Myocardial Lactate Metabolic Changes After Intracoronary Thrombolysis in Evolving Myocardial Infarction

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To investigate whether early reperfusion (≤ 3 hours) preserves aerobic myocardial metabolism in acute myocardial infarction, we examined serial changes in trans-cardiac lactate extraction after thrombolysis in 43 patients with acute antero-septal myocardial infarction. In the chronic phase, we also determined abnormally contracting segments as an index of infarct size and regional ejection fraction as an index of chronic regional cardiac function. In the early reperfusion group (≤ 3 hours), positive lactate extraction was restored and there were small abnormally contracting segments and a high regional ejection fraction. The intermediate reperfusion group (3–5 hours), however, had sustained anaerobic lactate extraction, large abnormally contracting segments and a low regional ejection fraction. The late reperfusion (> 5 hours) group showed apparently aerobic lactate extraction, but had large abnormally contracting segments and a low regional ejection fraction. Thus, early reperfusion preserves aerobic lactate metabolism and good chronic ventricular function.

EXPERIMENTAL studies have clearly demonstrated that infarction progresses through the myocardial wall from subendocardium to subepicardium with increasing duration of coronary artery occlusion¹ and that reperfusion must take place within 2 to 3 hours of the occlusion in order to salvage the myocardium.² In clinical studies of thrombolytic therapy, patients who were treated by reperfusion early after the onset of symptoms of infarction had significantly greater improvement in ventricular function than reperfused later.^{3–11} In this study of 43 patients with acute antero-septal myocardial infarction, we report the dynamic changes in lactate metabolism before and after successful thrombolysis. The purpose of this study is to evaluate the effects of thrombolytic therapy on acute myocardial metabolic changes, infarct size and

left ventricular function, measured by ventriculography at follow-up.

METHODS

Recanalization group

Thirty five patients admitted with acute antero-septal myocardial infarction (29 men and 6 women with a mean age of 59 years old, range 41 to 83), in whom the left anterior descending artery was recanalized by intracoronary urokinase therapy, were included in this study. They were selected from a consecutive series of 107 patients with acute transmural antero-septal myocardial infarction who had undergone coronary angiography within 6 hours of the onset of chest pain, between March 1982 and February 1987. All 35 patients fulfilled the following criteria: 1) informed consent for cardiac catheterization and administration of intracoronary medication was obtained; 2) the time from onset of chest pain to hospital admis-

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sion was less than 6 hours' duration; 3) total occlusion of the proximal portion of the left anterior descending artery was present at the time of initial angiographic visualization; 4) at the end of the urokinase infusion there was prompt antegrade filling of the initially occluded vessel; and 5) angiography was repeated during the chronic stage of infarction.

The remaining 72 patients were excluded from this analysis on the basis of the following exclusion criteria: 1) history of previous myocardial infarction; 2) cardiogenic shock; 3) clinical signs of infarct extension or recurrent infarction during the study period; 4) demonstration of reocclusion of the infarct vessel at repeat angiography in the chronic stage; 5) inadequate number of blood samples or blood flow measurement in the coronary sinus; 6) previous cerebrovascular accident; 7) surgery in the preceding 10 days; and 8) history of acute peptic ulcer and other bleeding problems. Elapsed time, or time from onset to recanalization, was ≤ 3 hours in 15 patients (early recanalization group), > 3 but ≤ 5 hours in 10 patients (intermediate recanalization group) and > 5 hours in the remaining 10 patients (late recanalization group).

Comparison group

For comparison, a group was selected from 24 consecutive patients with acute antero-septal myocardial infarction who underwent initial angiography as part of the protocol of urokinase therapy. In all of these patients, thrombolysis by urokinase administration was unsuccessful and the left anterior descending artery remained totally occluded at the end of the urokinase infusion. No further attempt was made to reopen the infarct vessel. Of these 24 patients, who met the same criteria as the study group with the exception of the fourth item, 8 formed the comparison group.

Diagnosis of acute myocardial infarction

The diagnosis of acute myocardial infarction was determined on the basis of a history of chest pain lasting more than 30 min and electrocardiographic changes suggestive of acute ischemia occurring in at least 2 leads. The diagnosis was confirmed retrospectively in all patients by an increase of creatine kinase to at least twice the upper limit of normal.

Catheterization and thrombolysis

Coronary angiography was carried out by the

percutaneous femoral approach. After total occlusion of the involved vessel had been confirmed, intracoronary nitroglycerin 0.1 mg was administered to exclude spastic angina and angiography was again performed. If no change in the angiographic appearance of the vessel was noted, 240,000 units of urokinase were administered as a bolus through a catheter and followed by coronary angiography. We added another 240,000 units of urokinase into the affected coronary artery every 15 min until the artery reopened or a total dose of 960,000 units was given. The infarct vessel was visualized soon after each infusion of urokinase, using a small amount of contrast medium, to see whether reperfusion was established. Elapsed time was determined at the point when restoration of antegrade flow in the infarct vessel was angiographically confirmed.

Blood sampling and measurements of lactate extraction ratio

Blood samples for measurements of lactate were obtained simultaneously from the ascending aorta and great cardiac vein through catheters. Blood sampling was performed after the first visualization of the left anterior descending artery (sample "before"). Blood was also sampled immediately after reperfusion in the recanalization group, and soon after the end of the thrombolysis trial in the control group (sample "after"). In all patients, blood was consecutively sampled at 6 hours (sample "6h"), 12 hours (sample "12h"), 18 hours (sample "18h") and 24 hours (sample "24h") after the onset of symptoms.

For sampling from the great cardiac vein and measurement of great cardiac venous flow, a 7F multithermistor flow catheter (Wilton Webster Laboratories, Altadena, CA) was inserted through the left basilic or brachial vein and advanced to the great cardiac vein. One milliliter of heparinized blood samples for lactate measurements was centrifuged for 5 min at 2000g. The supernatant was withdrawn, and the plasma level of lactate was measured in duplicate samples by an enzyme system assay kit¹² (Determina LA, Kyowa Medics Corporation, Tokyo) employing lactate oxidase combined with N-ethyl-N(3-methylphenyl)-N'-acetyl ethylenediamine on an autoanalyzer (HITACHI type 705). The data showed an extremely favorable correlation with those obtained by the enzymatic ultraviolet absorption method which is widely used at

%ACS and REF vs Elapsed Time

Fig.1. Only early reperfusion group (< 3 hours) had significantly smaller abnormally contracting segments and greater regional ejection fraction.

Lactate Extraction Ratio (LER) after Recanalization

Fig.2. Elapsed time showed in hours. "3 hrs" indicates early reperfusion group. "3-5 hrs" indicates intermediate reperfusion group. "5 hrs" indicates late reperfusion group. "failure" corresponds to unsuccessful thrombolysis.

present.¹³ The coefficient of variance of this method was 2.1% in our laboratory. The lactate extraction ratio (LER) was calculated as follows:

$$\text{LER (\%)} = ((\text{La} - \text{Lg}) / \text{La}) \times 100$$

where La and Lg represent oxygen saturation in the aortic and great cardiac venous blood, respectively.

Measurements of great cardiac venous flow and regional myocardial oxygen consumption

Great cardiac venous flow (GCVF) was measured by the continuous thermodilution technique,¹⁴ at an infusion rate of 40 ml 5% glucose per minute for 30 sec, with an angiographic injector (MEDRAD Mark IV, MEDRAD, Pittsburgh PA), a 2-thermistor flow catheter (Wilton Webster Laboratories, Model CCS-8/7U-90K), and a flow meter (Thermo Flow RF,

Goodman co. ltd. Nagoya JAPAN). At the beginning of the investigation, the position of the distal thermistor in the great cardiac vein was confirmed fluoroscopically by small injections of contrast medium. Aortic and great cardiac venous blood samples were drawn simultaneously for the measurement of hemoglobin, hematocrit and oxygen saturation at the time of sampling for the lactate assay. Oxygen partial pressure and saturation were determined with a blood gas analyzer (Corning 2500 CO-oximeter, Corning Medical and Scientific, Medfield MA). Arterio-venous (AVDO₂) difference in oxygen saturation was calculated as follows:

$$\text{AVDO}_2 (\text{mlo}_2 / \text{dl}) = 1.34 \times \text{Hb} \times (\text{SaO}_2 - \text{SgO}_2) / 100$$

where Hb is hemoglobin (g/dl) and SaO₂ and SgO₂ are oxygen saturation (%) in aortic blood

Arterio-Venous Oxygen Difference (AVDO₂) after Recanalization

Fig.3.

Great Cardiac Venous Flow (GCVF) after Recanalization

Fig.4.

and great cardiac venous blood, respectively.

Assessment of left ventricular function and infarct size

All patients underwent angiographic reevaluation 4 weeks later (chronic stage). All medications were discontinued at least 24 hours before catheterization. Coronary angiography was performed by the femoral approach. Left ventriculography was also performed in all patients. As an index of infarct size, abnormally contracting segments (ACS) or the length of any akinetic or dyskinetic segment in end-diastolic ventricular circumference was measured using the method of Feild.¹⁵ ACS was expressed as a percentage:

$$\text{ACS (\%)} = \left(\frac{\text{akinetic or dyskinetic length of end-diastolic circumference}}{\text{total end-diastolic circumference}} \right) \times 100$$

Regional ejection fraction was calculated from left ventriculogram using the area method of Gelberg,¹⁶ in which systolic changes were mea-

sured as a percent reduction of end-diastolic area and area changes corresponding to the perfusion area of the left anterior descending artery (area 2 and 3 in AHA coding of LVG) were averaged. And this volume was defined as regional ejection fraction.

Statistics

All values are expressed as mean $\pm$ standard deviation. Significance of difference between the mean values of LER and GCVF was assessed by analysis of variance and a multiple comparison method. Differences between the groups in terms of underlying diseases and other conditions were compared by means of the chi-square test with the Yates correction. A probability value of 0.05 or less was considered significant.

RESULTS

Clinical information

Elapsed Time and Myocardial Metabolism

Fig.5.

The 3 subgroups and control group were comparable in age, sex, medication before hospital admission, duration of symptoms before angiography, extent of coronary artery disease, presence of collateral circulation, the occluded site of the infarct vessel (segment 6 of the left anterior descending artery), residual stenosis after successful thrombolysis and interval between the initial and repeat angiography.

Effects of time to recanalization on infarct size and regional left ventricular performance (Fig. 1)

Mean percentage of ACS in the early group was $12.0 \pm 14.4\%$ and this was significantly smaller than in the intermediate, late and control groups ($p < 0.05$), in which it was 36.7 ± 15.9 , 34.8 ± 6.7 , and $35.0 \pm 13.6\%$, respectively. There were no significant differences in ACS between these 3 groups. Regional ejection fraction in the early group was $52.4 \pm 24.2\%$ which was significantly greater than in the intermediate, late and control groups, in which it was 24.6 ± 16.0 , 19.2 ± 13.0 and $24.0 \pm 14.1\%$, respectively. Again there were no significant differences in regional ejection fraction among these 3 groups. For residual stenosis and collateral flow in each group, there were no significant differences. The factor having the most influence on infarct size and regional ventricular function after successful thrombolysis was the time to recanalization from onset of myocardial infarction.

Serial changes in lactate extraction (Fig. 2)

The early and late groups did not demonstrate lactate production (great cardiac venous lactate level greater than arterial lactate level) after 6 hours from onset, and the control group did not demonstrate lactate production at any time during the study. Only in the intermediate group was lactate production, or negative lactate extraction ratio, observed up to 12 hours from onset, and these values were significantly lower

than in the control group ($-5.3 \pm 19.7\%$ vs $7.3 \pm 15.6\%$, respectively, $p < 0.05$). Compared with control group ($19.4 \pm 14.0\%$), mean lactate extraction soon after the recanalization were significantly lower in the early group ($-2.1 \pm 35.0\%$, $p < 0.05$), intermediate group ($-22.4 \pm 27.9\%$, $p < 0.01$) and late group ($-2.8 \pm 26.3\%$, $p < 0.05$). These relative decreases in lactate extraction suggest a washout of regionally accumulated lactate. The intermediate group showed positive values of lactate extraction more than 18 hours from onset and these were significantly greater than the lactate extraction before and after recanalization. All groups had positive LER at 18 hours and 24 hours from onset.

Changes in arterio-venous differences in oxygen saturation and great cardiac venous flow (Fig. 3, 4)

Arterio-venous difference in oxygen saturation gradually but insignificantly decreased in every group. Great cardiac venous flow was almost constant in the early and control groups. In the intermediate and late groups, it decreased slightly in the course of time but there were no significant differences.

DISCUSSION

Time-dependent thrombolytic efficacy

Several studies have shown recently that myocardial salvage and a reduction in mortality after thrombolysis for evolving myocardial infarction are time dependent. Rentrop¹⁷ described a reperfusion time of 4 hours as the cut-off point for significant salvage and others^{3,18,19} have suggested 2 or 3 hours. Koren²⁰ in a recent study, reported better preservation of left ventricular function in patients receiving therapy within 90 min of the onset of symptoms. The GISSI study⁸ has clinched the argument by showing the greatest reduction in early mortality

in patients who received streptokinase within 3 hours of the onset of symptoms. Several authors^{4,21,22} found that, whereas the extent of salvage is much less when therapy is started more than 4 hours after the onset of symptoms, late recanalization may still result in some improvement, particularly in patients who have collateral flow demonstrable by acute angiography. Schroder et al³ found a correlation between infarct size, measured from the circumferential extent of hypokinesia, and the time to treatment with intravenous streptokinase. Schwartz et al⁴ observed that the infarct size measured from peak CK activity was smaller and the ejection fraction at follow-up was higher in patients whose coronary arteries were reperfused 4 hours versus 4 hours after onset of symptoms. Mathey et al^{5,6} found that improvement in wall motion at the infarct site was significantly greater if reperfusion was achieved 2.5 hours after onset of symptoms, or if thrombolytic therapy using either intracoronary streptokinase or intravenous urokinase was begun 2 hours after symptom onset, compared with later reperfusion or treatment. Serruys et al¹⁰ reported significantly greater recovery of regional wall motion in patients treated with intracoronary or intravenous streptokinase within 3 hours of symptom onset than in those treated later. In other studies, few or no patients treated 2 hours after symptom onset failed to demonstrate a significant relation between time to treatment and left ventricular function.^{7,9,11}

Three stages of ischemic damage to a myocyte

We believe that there are various degrees of vulnerability to ischemia in myocardial cell components. Mitochondria are the most sensitive organella to myocardial ischemia and mitochondrial dysfunction leads to the impairment of aerobic metabolism. The Embden-Myerhof glycolytic pathway in cytosol is maintained for a short duration of ischemia and anaerobic lactate metabolism or lactate production is sustained until the destruction of the cell membrane. So, there may be 3 stages of ischemic damage to the myocyte: 1) reversible ischemic insults to mitochondria, which allow restoration of aerobic lactate metabolism; 2) irreversible changes in mitochondrial respiration and impairment of aerobic metabolism, and barely maintained anaerobic glycolysis, as demonstrated by lactate production; 3) damage to the whole structure and function of the myocyte, with cessation of

lactate metabolism.

Patterns of myocardial metabolism in each group (Fig. 5)

Only in the early group was aerobic lactate metabolism restored. These patients showed excellent left ventricular performance before discharge from hospital. Only the intermediate group demonstrated prolonged anaerobic lactate metabolism, which indicated that successful thrombolysis salvaged only the glycolytic pathway; they showed poor left ventricular function at follow-up. The late group demonstrated a transient lactate production, which indicated a washout, and a constant level of lactate extraction in the perfused non-infarct area; they also demonstrated chronic poor ventricular performance. The control group demonstrated aerobic lactate metabolism in the perfused non-infarct area.

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