TIME LIMIT FOR EARLY CORONARY ARTERY REVASCULARIZATION

Restoration of Contractility in Reperfused Myocardium in Dogs

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NORIKATSU SHINZATO, M.D., AND TATSUO TANABE, M.D.

The present study was undertaken to establish the time limit until the beginning of reperfusion that would permit restoration of contractility in acute myocardial infarction, and to confirm the delayed recovery of dyskinesis in ischemic area followed by reperfusion. Studies were carried out in 31 dogs of which 29 had temporary (20 min to 5 hours) occlusion of the left anterior descending coronary artery with short or long term reperfusion, and 2 had permanent occlusion. Dyskinesis was detected with tension curve obtained using a strain gauge arch. In the short term reperfusion study, dyskinesis disappeared if reperfusion was begun within 20 min of ischemia. However, dyskinesis remained after one hour of reperfusion, if reperfusion was done after 40 min of ischemia. Reperfusion for 10 days after 3 and 4 hours of occlusion resulted in recovery of regional myocardial contractility. However in 2 of 5 animals with 5 hours of coronary occlusion, the reperfused area remained dyskinetic even after 10 days of reperfusion. It is concluded that revascularization of myocardium that has been kept ischemic for less than 4 hours may lead to disappearance of dyskinesis. These findings also indicate that early coronary revascularization does not always provide an immediate recovery of dyskinesis of the revascularized area.

The main cause of death in patients with acute myocardial infarction was life threatening arrhythmia or power failure. Although arrhythmic deaths have become less with the development of the coronary care unit, deaths due to power failure have not decreased. Accordingly attention has turned toward efforts to improve power failure. Power failure of acute myocardial infarction is closely related to the amount of irreversibly damaged myocardial cells and abnormal wall motion. Various interventions to salvage reversibly damaged ischemic myocardium have been studied experimentally and clinically by many investigators. Aorto-coronary bypass grafting performed soon after the onset of acute myocardial infarction is one of these. Many investigators reported that reduction of infarct size and restoration of contractility could be obtained after early coronary artery revascularization. However, the maximal period permitting the restoration of the contractility of ischemic myocardium was not established. The purpose of the present study is to clarify the time limit for early coronary revascularization

Key Words:
- Acute myocardial infarction
- Coronary reperfusion
- Regional myocardial contractility

(Received July 1, 1980; accepted July 10, 1981)
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This paper was presented at the Thirtieth Annual Meeting of the Japanese Association for Thoracic Surgery, September 23–25, 1977, Tokyo, Japan.
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Japanese Circulation Journal Vol. 45, December 1981 1355
to recover the regional contractility after coronary occlusion.

METHODS

Experiments were performed on 31 mongrel dogs weighing 12–20 kg. The animals were anesthetized with sodium pentobarbital (25 mg/kg, intravenously) and respiration was maintained through an oral endotracheal tube using a Bird artificial respirator. A left thoracotomy was then performed at the fifth intercostal space and the pericardium was opened vertically along the phrenic nerve. The left anterior descending coronary artery (LAD) was isolated from adjacent tissues so as to clamp it. Experimental models of infarction were made by clamping the LAD for various periods just distal to the first diagonal branch, followed by short or long term reperfusion. Dyskinesia of ischemic wall was detected by tension curve recordings using a strain gauge arch. Reperfusion was initiated by declamping after various periods of coronary occlusion. In long term reperfusion studies, the chest was closed after one hour of reperfusion and opened again after 10 days of reperfusion to study the regional contractility under general anesthesia. We used Student’s \( t \)-test to test the significance of the differences in the percent change of peak tension among studied groups.

1. Short Term Reperfusion Studies (Fig. 1A)

The experiments were divided into 2 groups.

Group 1 (7 dogs): reperfusion for 1 hour after 20 minutes of coronary occlusion.

Group 2 (7 dogs): reperfusion for 3 hours after 40 minutes of coronary occlusion.

Regional myocardial contractility: Strain gauge arch (Nihonkoden, HT-IT) was sutured rectangulaarily to the LAD. The distance between two feet of strain gauge arch was 10 mm. There was a linear relationship between the load and output (Fig. 2). Circuit diagram of strain gauge is shown in Fig. 2.

ECG was monitored by lead II.

Hemodynamic measurements: Left ventricular and aortic pressures were monitored through stiff walled catheters directly connected to Nihonkoden MPU-0.5 transducer system. Ascending aortic flow was measured by Nihonkoden MF-26 electromagnetic flowmeter. Left
Fig. 3. Serial effects of reperfusion after 20 min of coronary occlusion on myocardial contractility. Curve of tension development in preocclusion state is inscribed in upward direction. The curve is inverted during coronary occlusion indicating dyskinesis. After reperfusion the curve returned to preocclusion contraction pattern. \( P(t) \) = curve of tension development.

Fig. 4. Serial effects of reperfusion after 40 min of coronary occlusion on myocardial contractility. Systolic upward curve in control state is inverted during coronary occlusion and after 3 hours reperfusion.

<table>
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<th>TABLE 1 PERCENT CHANGE OF PEAK TENSION IN SHORT TERM REPERFUSION STUDIES</th>
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<tr>
<td>Control (%)</td>
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<tr>
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<tr>
<td>Group 1 (n = 7)</td>
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<td>Group 2 (n = 7)</td>
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Values are mean ± SEM; \( N \) = number of dogs.

* \( p < 0.01 \): statistically significant difference in values between Group 1 and Group 2 after 1 hour of reperfusion.
ventricular end-diastolic pressure was measured using high gain amplification. All hemodynamic and ECG tracings except central venous pressure were recorded on a Nihonkoden R-1000 polygraph. Central venous pressure was measured by glass column.

Electron microscopy: At the end of each experiment, the heart was excised and myocardial specimens were obtained for electron microscopy from the center of the reperfused area and non-ischemic area. Formalin was used for the initial fixation and osmic acid for the second fixation. Sections were cut and stained with acetic uranyl and acetic lead.

Lactate balance was expressed by (A-V difference / A) x 100, where A: arterial, V: venous lactate levels. Lactate levels were determined by Barker-Summerson technique. Blood samples for measuring lactate content were taken from the left anterior interventricular vein and aortic root before occlusion of the LAD and just before and after reperfusion.

2. Long Term Reperfusion Studies (Fig. 1B)

The experiments were divided into the following 4 groups:

Group 3 (5 dogs): reperfusion for 10 days after 3 hours of coronary occlusion.

Group 4 (5 dogs): reperfusion for 10 days after 4 hours of coronary occlusion.

Group 5 (5 dogs): reperfusion for 10 days after 5 hours of coronary occlusion.

Control group (2 dogs): coronary occlusion for 10 days without reperfusion.

Regional myocardial contractility: Strain gauge arch was sutured parallel to the direction of myocardial fiber of the ischemic area perfused by the LAD and non-ischemic area perfused by the left circumflex coronary artery. Tension curve was recorded just before coronary occlusion and reperfusion, and after 10 days of reperfusion.

ECG was monitored by lead II.

Hemodynamic measurements: Left ventricular pressure was measured and recorded by the same method as described in short term reperfusion studies.

Histology: Myocardial specimens were obtained from the center of the revascularized area and non-ischemic area. The specimens were fixed in a solution of 10 percent formalin and stained with hematoxylin and eosin, van Gieson and Mallory azan.
Time Limit for Early Coronary Artery Revascularization

ISCHEMIA (3 hours)  ISCHEMIA (4 hours)

Fig. 7. Effect of long term reperfusion after 3 and 4 hours of coronary occlusion on the curve of myocardial contractility. Dyskinesis observed during coronary ischemia returned to preischemic pattern after reperfusion. The curve in animals after 4 hours of coronary occlusion showed downward inscription in only early systole after 10 days of reperfusion.

ISCHEMIA (5 hours)  ISCHEMIA (10 days)

Fig. 8. Effect of reperfusion after 5 hours of coronary occlusion and permanent occlusion. Release of coronary occlusion failed to restore myocardial contractility. Tension curve of permanent occlusion animals remained dyssynergic after 10 days of occlusion.

RESULTS

1. Short Term Reperfusion Studies

Regional myocardial contractility: The systolic curve of myocardial contraction is inscribed upward and the diastolic curve downward. Normal pattern of tension development is shown in Fig. 3. The change of developed tension in ischemic area occurred uniformly within 30 sec after occlusion of the LAD. In systole, tension curve inverted due to paradoxical systolic outward motion of the ischemic wall. In Group 1, reperfusion after 20 min of coronary occlusion produced an immediate
TABLE II  PERCENT CHANGE OF PEAK TENSION IN LONG TERM REPERFUSION STUDIES

<table>
<thead>
<tr>
<th></th>
<th>Control (%)</th>
<th>Reperfusion (%)</th>
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<td></td>
<td></td>
<td>Immediately before</td>
</tr>
<tr>
<td>Group 3 (n = 5)</td>
<td>100.0 ± 0.0</td>
<td>-136.0 ± 54.8</td>
</tr>
<tr>
<td>Group 4 (n = 5)</td>
<td>100.0 ± 0.0</td>
<td>-101.8 ± 45.6</td>
</tr>
<tr>
<td>Group 5 (n = 5)</td>
<td>100.0 ± 0.0</td>
<td>-94.2 ± 48.8</td>
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Values are mean ± SEM; N = number of dogs. NS: statistically no significant difference. * p < 0.02: statistically significant difference in values between Group 3 and Group 5 after 10 days of reperfusion. ** p < 0.01: statistically significant difference in values between Group 4 and Group 5 after 10 days of reperfusion.

Fig. 9. Microscopic sections from ischemic myocardium.
A: Myocardial tissue with 10 days of reperfusion after 3 hours of coronary occlusion showed scattered focal necrosis. B: After 4 hours of coronary occlusion followed 10 days of reperfusion. Focal necrosis was found in myocardial tissue. C: Greater part of the section in animals with 5 hours of coronary occlusion was occupied with extensive myocardial necrosis and fibrosis. D: Section of permanent coronary occlusion also showed extensive myocardial necrosis and granulation tissue (hematoxylin and eosin stain, ×100).

recovery of the abnormal tension curve (Fig. 3). In Group 2, however, reperfusion for 3 hours after 40 min of coronary occlusion could not restore normal tension curve (Fig. 4), and dyskinesis in ischemic area remained. Dyskinesis did not occur in non-ischemic area in either
groups. The mean values of the percent change of peak tension after one hour of reperfusion showed significant difference between these 2 groups (Table I) (t = 6.9, p < 0.01).

Hemodynamic measurements: In both groups, the mean value of each hemodynamic parameter showed no significant difference from the control value throughout the whole experimental period.

Lactate balance: Lactate balance before LAD occlusion was $27.7 \pm 4.8\%$ (mean $\pm$ S.E.M.) in Group 1 and $27.6 \pm 5.2\%$ in Group 2. Lactate balance just before reperfusion decreased to $37.3 \pm 8.9\%$ in Group 1 and to $62.0 \pm 12.0\%$ in Group 2 (Fig. 5). After one hour of reperfusion, Group 1 exhibited a balance of $31.7 \pm 4.4\%$. After 3 hours of reperfusion, Group 2 showed a balance of $23.0 \pm 8.2\%$. These results showed lactate production in ischemic area during coronary occlusion and lactate extraction after reperfusion.

Electron microscopy: The structure of myocardial cells and myofibrillars (mitochondria, cristae and nucleus) remained normal in Group 1 (Fig. 6A). In Group 2, we found only a small change such as slight swelling of the mitochondria and increased density of the mitochondrial matrix (Fig. 6B).

2. Long Term Reperfusion Studies

Regional myocardial contractility: Although contraction pattern of ischemic wall was dyskinetic in each group, recovery of contractility occurred after 10 days of reperfusion in Groups 3 and 4 (Fig. 7). In Group 5, however, 2 of 5 dogs with 5 hours of coronary occlusion did not return to normal contraction even after the same period of reperfusion (Fig. 8). Of course, the pattern of myocardial contraction remained dyskinetic in both control dogs (Fig. 8). Tension curves in the non-ischemic area were normal in almost all studied groups, except for some animals exhibiting dyskinesis or early systolic bulge.

The mean values of peak tension just before reperfusion showed no significant differences among Groups 3, 4 and 5. After 10 days of reperfusion, however, those in Group 5 decreased significantly as compared with in Group 3 ($t = 3.86, p < 0.02$) and Group 4 ($t = 4.70, p < 0.01$) (Table II).

Hemodynamic measurement: There were no significant changes in hemodynamic parameters throughout the study.

Histology: Histologic examinations of non-ischemic area revealed no significant abnormalities. In animals with 3 and 4 hours of coronary occlusion, there was scattered focal myocardial infarction in the section of ischemic areas. In animals with 5 hours of coronary occlusion and in the control animals without reperfusion, the section showed extensive myocardial infarction (Fig. 9A–D).

DISCUSSION

Since the major causes of power failure in myocardial infarction are extensive loss of myocardium$^{10,12}$ and asynergy of the ischemic wall$^{13,14}$ many studies have been carried out to reduce the extent of infarction and to restore regional myocardial contractility. Sobel et al$^{10}$ reported that infarct size assessed by analysis of serial serum CPK changes was closely related to prognosis, i.e., 8 of 12 patients with infarct size exceeding 65 CPK-g-Eq died, while only one of 21 patients with infarct size less than 65 CPK-g-Eq died due to causes other than power failure. In the clinical studies of Mathey et al.$^{11}$ 89% of patients with left heart failure had an average infarct size of 99 grams calculated from serial determination of CPK. These results indicated that the extent of infarct was closely related to the complication of power failure and prognosis in acute myocardial infarction.

In an attempt to reduce the quantity of infarcted tissue, many interventions were studied experimentally and a few of them were applied clinically, i.e., 1) decreasing myocardial oxygen demand, 2) increasing oxygen supply, 3) augmentation of anaerobic metabolism and 4) reduction of edema and inflammation of ischemic myocardium. Early myocardial revascularization can now save jeopardized myocardium. In animal experiments, Maroko et al.$^{3}$ and Ginks et al.$^{4}$ reported a reduction of infarct size by coronary artery reperfusion carried out within 3 hours after coronary occlusion. Costantini et al.$^{5}$ and Bolooki et al.$^{6}$ also reported the same results. In clinical studies, many authors$^{15–22}$ reported a decrease in mortality by early myocardial revascularization within 12 hours after the onset of myocardial infarction. They concluded that early coronary bypass grafting could reduce the mortality rate in patients with acute myocardial infarction, and that the extension of infarct size could be prevented by salvaging ischemic myocardium in twilight zone around severe ischemic area, resulting in restoration of mechanical and
metabolic function. However, coronary bypass grafting must be done within a limited time after the onset of myocardial infarction to improve myocardial contractility and rescue ischemic myocardial cells. Thus, establishment of the time limit for early revascularization has become of clinical importance.

Abnormal wall motion also plays an important role in occurrence of power failure. Dyskinesis of ventricular wall is usually determined by ventriculography, segment length measurement by mercury strain gauge or ultrasonic crystals. Yoshida and Parmley showed that dyskinesis could also be determined by tension curve by strain gauge arch. Using this tension curve, we also studied the time limit until the beginning of reperfusion that could make recovery of dyskinesis of ischemic wall, and evaluated whether or not there was a delayed recovery of regional myocardial contractility after several hours of coronary occlusion.

Jennings et al. studying electronmicroscopic changes in the posterior papillary muscle of the left ventricle showed that all myocardial cells survived if coronary ischemia were less than 18 min but almost all cells died if coronary ischemia exceeded 60 min. As this study was performed on the left ventricular posterior papillary muscle which lacked collateral blood supply, caution should be paid to applying these results to areas having good collateral circulation. Therefore, the effectiveness of early coronary revascularization must be studied in areas in which acute myocardial infarction occurs frequently such as anterior and posterior wall of the left ventricle. After reperfusion for 6 hours, fine structure of myocardial cell was restored in animals with 40 min of occlusion, but myocardial necrosis was found in reperfused myocardial tissue in those with 45 min of occlusion. These results indicated that irreversible myocardial cell necrosis might begin to occur after 40 min of coronary ischemia. Concerning the reduction of infarct size, coronary reperfusion after 3 hours of occlusion could salvage ischemic but reversibly damaged myocardial tissue. Costantini et al. reported that infarct size estimated histopathologically after 3 hours of the LAD occlusion was 31.6% in the control group without reperfusion but was 14.3% in the group reperfused for 7 days.

In all our animals with 20 min of coronary occlusion, dyskinesis disappeared immediately after one hour reperfusion. On the other hand, all animals with 40 min of coronary occlusion exhibited persisting dyskinesis even after 3 hours reperfusion. Electron microscopic examination of the ischemic and non-ischemic area in Group 1 (coronary occlusion for 20 min) revealed no significant abnormalities. In Group 2 (coronary occlusion for 40 min), swelling of mitochondria and increased density of mitochondrial matrix were found in the section of ischemic area. These results do not necessarily indicate an absolute time limit until the beginning of reperfusion by emergency coronary bypass surgery, because the delayed recovery of myocardial contractility was observed in our short time studies and confirmed by our long term ones. Theroux et al. ligated the left circumflex coronary artery of dogs for 2 hours and observed late recovery of regional myocardial function after 4 weeks reperfusion. In our studies, restoration of myocardial contractility occurred when reperfusion began in dogs with 4 hours of coronary occlusion. When approximately 20 to 25% of left ventricular area is inactivated by any pathological process, the extent of fiber shortening required of the remaining functioning muscle begins to exceed its physiological limits. Therefore, reduction of infarct size and restoration of regional myocardial contractility are the most important factors to prevent power failure in acute myocardial infarction. From the result of our experiment, it can be expected that application of emergency coronary bypass surgery may take an important role in the treatment of acute myocardial infarction with power failure, when it is performed within restricted periods (4 hours) after the onset of the disease.

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