The Pathophysiology of Myocardial Stunning: Reversibility, Accumulation and Continuity of the Ischemic Myocardial Damage after Reperfusion

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In order to understand the pathophysiology of myocardial stunning, reversibility, accumulation and continuity of ischemic myocardial damage after reperfusion should be studied. Then, to analyze these three factors, myocardial function, metabolism and morphology under ischemia and reperfusion were studied in anesthetized, open-chest dogs.

When myocardial ischemia was induced by occlusion of the left anterior descending coronary artery, percentage regional systolic shortening (%SS) of ischemic myocardium sharply decreased and became stable 10 min after occlusion. After reperfusion, ischemic myocardium showed active shortening after within 30-min occlusion, but did not after more than 60-min occlusion. During 90-min of ischemia, extracellular K+ concentration (Ke) steeply increased for first 10 min and was almost stable for next 10 min. Then, Ke straightly increased till 90 min. Metabolic rates, calculated from myocardial tissue CO2 and pH, steeply increased for first 20 min and sharply decreased for next 10 min. After 30 min, these two variables were almost stable, near zero. By electron-microscopy with cytochemistry, distribution of Na/K ATPase to myocardial cell membrane was observed to be almost after 15-min occlusion but distinctly sparse with destruction of cell membrane after 30-min occlusion. Therefore, irreversible myocardial damage appears after about 20-min ischemia and is almost complete after 60 min. Reversibility of damage to ischemic myocardium after reperfusion may mainly occur within 60-min ischemia. Although stunned myocardium in a narrow sense is may appear after reperfusion within less than 20-min of ischemia, stunned myocardium in a broad sense may appear within less than 60-min ischemia.

When reversible myocardial ischemia (4- or 15-min occlusion) was repeated after short time intervals (20-min reperfusion), %SS of ischemic myocardium was gradually decreased with each ischemic episode. Active shortening of ischemic myocardium disappeared after more than two episodes of 15-min occlusion. Fluctuation of PCO2, pH and Ke of ischemic myocardium was gradually depressed with each occlusion. Metabolic viability of ischemic myocardium was cumulatively depressed by repeated brief occlusion. Naturally, myocardial damage was more severe after repeated 15-min occlusion than after 4-min occlusion. Accumulation of ischemic myocardial damage may arise as brief ischemia, which only induces reversible damage, is repeated.

Key words:
Myocardial stunning
Ischemic myocardial damage
Reperfusion
Metabolic viability
Latent myocardial damage

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At last, continuity of ischemic myocardial damage was studied. The effect of 5-min occlusion to %SS of ischemic myocardium was apparently reversed after 90-min reperfusion. Early contractile failure was advanced even after very short duration of ischemia. Thus, myocardial function will be latently damaged. Fluctuation of PCO2, pH and Ke was still depressed, thus, metabolic viability of ischemic myocardium will be latently depressed. This phenomenon, continuity of latent myocardial damage, is very important condition preceding myocardial stunning.

MYOCARDIUM reperfused after ischemia exhibits prolonged but reversible depression of contractile function, so-called myocardial stunning!

The severity and the time course of myocardial dysfunction after reperfusion depend on the duration of myocardial ischemia. This phenomenon is very important for the indication of coronary revascularization therapy and the prognosis of patients with coronary heart disease.

In order to know the pathophysiology of myocardial stunning, reversibility, accumulation and continuity of the ischemic myocardial damage after reperfusion should be studied.

In this paper, myocardial function, metabolism and morphology under ischemia and reperfusion will be experimentally studied to analyze these three factors.

METHODS

Mongrel dogs of either sex weighing from 14 to 27 Kgs were anesthetized with intravenous sodium pentobarbital (25 mg/kg) and artificial respiration with room air was instituted with a Harvard respirator. After thoracotomy, the left anterior descending (LAD) coronary artery was dissected between the first and second diagonal branches and fitted with a pneumatic occluder to produce the ischemic and reperfused myocardium. In order to study the regional myocardial function, a pair of sonocrystals was implanted in the middle layer of the left ventricle and oriented parallel to the minor axis. The segmental length at end-diastole (EDL), at end-systole (ESL) and at the beginning of ejection (SLej) was measured with a pulse transit sonomicrometer. The regional myocardial contractility was manifested as % systolic shortening (%SS: [EDL-ESL]/EDL) (x 100), % shortening of ejection phase (%EJ: [SLej-ESL]/EDL) (x 100) and % shortening of isometric contraction phase (%IS: [EDL-SLej]/EDL) (x 100). To measure the regional myocardial blood flow (MBF), thermocouples were implanted in the middle layer of the left ventricle. In the same region, myocardial tissue PCO2 and pH were measured by sensors of PCO2 and pH. Metabolic rate (MR) was calculated as follows: MR (PCO2) = PCO2(t) – PCO2(t-10) (mmHg), MR (H concentration) = 10 – pH(t) – 10 – pH(t-10) (nmol/L), X; value of X at t times after occlusion.

Extracellular K+ concentration (Ke) was also measured in the same region. Ke equilibrium potential (Ek) was calculated as follows: Ek = 61.5 mV × log (Ko/Ki – 0.33 × delta Ko), 61.5 mV; Nernst slope (37°C), Ko; extracellular K+, Ki; intracellular K+ (100 mmol).

Aortic and left ventricular pressures were measured by catheter-tip manometers. In several dog hearts, Na/K ATPase distributed in myocardial cell membranes was stained for cytochemistry by Ernst method.

PROTOCOL

Group 1: In 45 dogs, LAD was occluded for 4 min (n=9), 15 min (n=9), 30 min (n=9), 60 min (n=9) or 90 min (n=9), and reperfused 20 min. Regional myocardial function, EDL, ESL, %SS, %EJ and %IS were studied in these situations.

Group 2: In 10 dogs, we studied about myocardial metabolism, i.e. PCO2 and pH, and Ke during 90-min LAD occlusion. Na/K ATPase distributed in myocardial cell membrane was measured.

Group 3: In 20 dogs, 4- or 15-min occlusion and 20-min reperfusion were repeated three times. In these situations, %SS, %EJ, %IS, PCO2, pH and Ke were measured.

Group 4: In order to reveal the influence of brief ischemia, i.e. 5-min occlusion in this experiment, 2-min occlusion was used as a
tool of analyzing latent myocardial damage after reperfusion. At first, LAD was occluded for 2 min and reperfused 15 min. This 2-min occlusion was called trial 1. 20 dogs were divided into two groups. In control group (n=10), subsequent 95-min reperfusion was continued. In 5-min occlusion group (5-min group; n=10), LAD was occluded 5 min and reperfused 90 min. Then, LAD was occluded for 2 min as a trial 2 in both groups. Two trials were compared in each group and between two groups to evaluate latent myocardial damage caused by 5-min occlusion. %SS, %JE, %IS, PCO2 and pH, and Ke were measured in these situations.

STATISTICAL ANALYSIS

Data were presented as mean ± SEM. Student's t test was used and differences were considered significant when p<0.05.

RESULTS

Group 1: After LAD occlusion, %SS immediately decreased and was almost stable within first 10 min (Fig.1). The later the reperfusion, the more severe the myocardial dys function. When reperfusion was allowed after more than 60-min occlusion, active shortening did not recover. %JE was mainly concerned in the disappearance of active shortening.

Group 2: Effects of acute myocardial ischemia on myocardial metabolism were shown in Fig.2. When occlusion started, PCO2 was sharply increased and reached maximal level after about 20 min. Then, it fell rapidly. pH varied conversely with PCO2. MR calculated from PCO2 and pH were positive for first 20 min and negative after that. Ke was 3.33±0.19 mEq/L before occlusion. During the first 10-min occlusion, Ke straightly increased to 6.26±0.57 mEq/L (first Ke increase) and was almost stable for the next 10 min (6.79±0.83 mEq/L). After 20-min occlusion, Ke straightly increased again till 90 min (14.36±1.91 mEq/L, second Ke increase). MBF was immediately reduced to about 10% of pre-occluded level just after occlusion and was stable for 90 min.

As shown in Fig.3, Na/K ATPase distribution in myocardial cell membranes, (stained black granules), 15 min after LAD occlusion, was similar to distribution in nonischemic cell membranes. Cell membranes and mitochondria were not clearly injured. 30 min after occlusion, cell membranes were gradually injured and Na/K ATPase was roughly distributed. 60 min after, cell membranes were completely destroyed.

Group 3: When LAD occlusion was repe-
Fig. 2. Tissue PCO₂, tissue pH and these metabolic rates of the ischemic myocardium during 90-min LAD occlusion.

ated, %SS was decreased during reperfusion after both 4- and 15-min occlusions (Fig. 4). When 15-min occlusion and 20-min reperfusion were repeated more than twice, active shortening of ischemic myocardium disappeared. %EJ was mainly concerned in the disappearance of active shortening.

Proportionally as 4- or 15-min occlusion was repeated, the rate of increase of PCO₂, the rate of decrease of pH and the rate of increase of Ke were all decreased (Fig. 5). Naturally, damage was more severe after repeated 15-min occlusion than after repeated 4-min occlusion.

Group 4: Effects of 5-min occlusion to the myocardial function, PCO₂, pH and Ke were studied in comparison between trial 1 and 2. In control group, no significant differences were noticed between the two trials. In 5-min group, the earlier deterioration of myocardial function after trial 2 was clearly demonstrated, and transient post-ischemic hyperactivity immediately after reperfusion disappeared in trial 2 (Fig. 6). Myocardial function after 5-min occlusion completely recovered after 90-min reperfusion, but subse-
Fig. 3. Na/K ATPase distributed in myocardial cell membranes under myocardial ischemia: 15-min LAD occlusion (left panel); Na/K ATPase staining black granules was not so different to it in non-ischemic cell membranes. Cell membranes and mitochondria were not clearly injured. 30-min LAD occlusion (right panel); Cell membranes were gradually injured and Na/K ATPase was roughly distributed.

Fig. 4. Regional myocardial function (%SS, %EJ and %IS) during 3-time repeated 4- or 15-min LAD occlusion.
Fig. 5. Regional myocardial tissue PCO₂, pH and extracellular K⁺ concentration under 3-time repeated 4- or 15-min LAD occlusion.

Subsequently new ischemic challenge (trial 2) caused the earlier progression of myocardial dysfunction comparable to that in trial 1.

Shown in Table I, maximal PCO₂, pH and Ke showed no significant differences between two trials in control group. In 5-min group, maximal PCO₂ and Ke were significantly decreased and pH was significantly increased in trial 2 compared to trial 1. MR of PCO₂ and pH in both trials showed no significant differences in control group, but marked depression of MR in trial 2 was shown in 5-min group after 90-min reperfusion.

**DISCUSSION**

Myocardial ischemia has been viewed as an all-or-none process that causes myocardial necrosis when prolonged and severe, but whose effects are transient when it is brief or mild. In 1982, Braunwald proposed the new idea of "myocardial stunning". In order to understand the pathophysiology of myocardial stunning, reversibility, accumulation and continuity of ischemic myocardial damage under reperfusion, metabolism and morphology after reperfusion were experimentally studied to analyze these three factors.

At first, we studied the reversibility of re-
perfused myocardium. When LAD was occluded, %SS was immediately decreased and almost stable within first 10 min. The latter the reperfusion was, the more severe the myocardial dys function was. When reperfusion was begun after more than 60-min occlusion, active shortening did not recover. We have already reported that active shortening was considerably recovered after 30-min occlusion but was not after 60-min occlusion followed by 120-min reperfusion. In 30- or 60-min occlusion, LAD flow, MBF and coronary vascular resistance in the ischemic myocardium were almost recovered to the pre-occluded level after 60-min reperfusion. The myocardial tissue PCO₂ and pH also recovered to the pre-occluded level after 60-min reperfusion. Ischemic myocardial damage appeared to be almost all recovered within 60-min of reperfusion. We studied ischemic myocardial metabolism for 90-min LAD occlusion. When occlusion was started, PCO₂ sharply increased and reached maximal level after about 20 min. Then, it
TABLE 1 MYOCARDIAL TISSUE PCO₂, pH AND EXTRACELLULAR K⁺ CONCENTRATION DURING TRIAL 1 AND 2 IN CONTROL AND 5-MIN LAD OCCLUSION GROUPS (trial 1 and 2; 2-min occlusion, mean ± SEM)

<table>
<thead>
<tr>
<th></th>
<th>Control Group</th>
<th>5-min Occlusion Group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Trial-1</td>
<td>Trial-2</td>
</tr>
<tr>
<td>extracellular K⁺</td>
<td>46.1±0.11</td>
<td>4.67±0.10</td>
</tr>
<tr>
<td>concentration (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tissue pCO₂ (mmHg)</td>
<td>60.9±3.6</td>
<td>59.3±3.7</td>
</tr>
<tr>
<td>CO₂ metabolic rate</td>
<td>11.9±3.9</td>
<td>12.0±4.1</td>
</tr>
<tr>
<td>(mmHg/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tissue pH (pH unit)</td>
<td>7.12±0.03</td>
<td>7.12±0.03</td>
</tr>
<tr>
<td>proton metabolic rate</td>
<td>17.4±6.6</td>
<td>16.8±3.7</td>
</tr>
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*p < 0.05  **p < 0.01 (compared to Trial-1: intragroup comparison)

steeply decreased. This late fall looks like "paradoxical improvement phenomenon". On the other hand, the time course of pH was opposite to PCO₂. MR calculated from PCO₂ and pH were positive for first 20 min and negative after that. Therefore, terminal products of myocardial metabolism, CO₂ and H-ion, were steeply increased during first 20 min, decreased for about 40 min, and was almost stable after 60 min. The depression of metabolic viability of ischemic myocardium may start at about 20 min after ischemia and reach the terminal stage within about 60 min.

After coronary occlusion, Ke steeply increased for first 10 min (first increase) and was almost stable for next 10 min. Then, Ke straightly increased again till 90 min (second increase). How different over the mechanisms causing the first and second Ke increase?

Na/K ATPase distributed in myocardial cell membrane plays a very important role in the intusus and efflux of K⁺ in myocardial cells. 15 min after occlusion, the distribution of Na/K ATPase was different from the non-ischemic cells. 30 min after, cell membrane was gradually damaged and Na/K ATPase was roughly distributed. 60 min after, cell membrane was completely destroyed. These data suggest that irreversible myocardial damage will appear after about 20-min ischemia and be almost complete within 60 min. As we² already reported, oxidative phosphorylation, especially State 3, Ca and Mg contents of mitochondria did not significantly change in 30-min occlusion and 120-min reperfusion. After 60-min occlusion and 120-reperfusion, these variables were very different. State 3 was depressed, Ca content increased and Mg content decreased. These data suggest reperfusion injury. We have already reported that 60-min occlusion and 120-min reperfusion showed contraction band in myofibrils and amorphous dense matrix in mitochondria. These findings show so called reperfusion injury. Therefore, the reversibility of acute ischemic myocardium after reperfusion may mainly remain within 60-min of ischemia. Although stunned myocardium in a narrow sense may appear after reperfusion within less than 20 min of ischemia, stunned myocardium in a broad sense may appear within less than 60 min of ischemia. Clinically, the concept of stunned myocardium is liable to be recognized in a broad sense because of PTCR, CABG and some other myocardial protection therapy. Although scar contraction is induced by irreversible myocardial damage, wall movement and left ventricular function are improved to some extent in ischemic damage? Therefore, it is incorrect to say that the improvement of myocardial function is a function of the recovery of ischemic myocardium. This is the point of disagreement of the concept, especially among clinicians.

Secondly we studied the accumulation of

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ischemic myocardial damage when brief reversible myocardial ischemia was repeated over short time intervals. We selected 4 and 15 min coronary occlusions. The former is a brief duration of coronary occlusion similar to an anginal attack and the latter is the maximum duration of reversible ischemic damage. When 4- or 15-min occlusion and 20-min reperfusion was repeated three times, %SS was decreased during reperfusion after both 4- and 15-min occlusion. When 15-min occlusion was repeated more than twice, active shortening of ischemic myocardium disappeared. %EJ was mainly concerned in the disappearance of active shortening. In proportion to brief ischemia, in which only induced reversible damage was repeated, the rate of increase of PCO₂, the rate of decrease of pH and the rate of increase of Ke were all decreased. Naturally, myocardial damage was more severe after repeated 15-min occlusion than after repeated 4-min occlusion. Then, metabolic viability of ischemic myocardium was gradually decreased, and myocardial damage was cumulatively advanced. Also, these data suggest that the heterogeneity of ischemic damage in reperfused myocardium.

Therefore, duration of coronary occlusion (duration of anginal attack), repeated times (frequency of anginal attack) and duration of reperfusion (interval of anginal attack) decide the degree of stunned myocardium. When reversible myocardial ischemia is repeated, myocardial function and metabolism are cumulatively damaged.

Finally, we studied the continuity of ischemic myocardial damage. There are already many reports about the continuity of ischemic myocardial damage. In one report, the effect of 5-min coronary occlusion on the contractile function of reperfused myocardium continued for only 30 min. However, in second report, it continued for more than 3 h.

How long will the myocardial damage induced by brief coronary occlusion persist?

We studied the effect of 5-min LAD occlusion to myocardial function, PCO₂ and pH, and Ke for 90-min reperfusion. In control group, no significant differences were noticed between the two trials. In 5-min group, the earlier deterioration of myocardial function after trial 2 was clearly demonstrated and transient post-ischemic hyperactivity immediately after reperfusion disappeared in trial 2. Namely, myocardial function after 5-min occlusion was apparently recovered with 90-min reperfusion, but a subsequently new ischemic challenge (trial 2) caused the earlier progression of myocardial function compared to that in trial 1. This phenomenon indicates that there remains latent abnormality in post-ischemic myocardium.

Maximal PCO₂ and pH showed no significant differences between two trials in control group. In 5-min group, PCO₂ was significantly decreased and pH was significantly increased in trial 2 compared to trial 1. MR of PCO₂ and pH in both trials showed no significant differences in control group. On the other hand, marked depression in trial 2 was shown in 5-min group in spite of 90-min reperfusion. Furthermore, Ke did not significantly change in two trials in control group, but significantly decreased in trial 2 compared to trial 1 in 5-min group. The mechanism for Ke elevation in the hyperacute phase is supposed to be enhanced permeability of cell membrane. So, the reduction of CO₂ and proton production may partly explain the diminished K loss from the ischemic myocardium. Depressed myocardial viability seems to cause this altered response of myocardium to the new ischemia.

Therefore, the pre-stage of manifest myocardial stunning or latent myocardial stunning is characterized by the following findings. Namely, earlier deterioration of myocardial contractile function will appear when brief myocardial ischemia is newly challenged. The cause of this phenomenon is supposed to be depression of the metabolic viability of the ischemic myocardium.

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