Quantitative analysis of infarct size, contraction band necrosis, and coagulation necrosis in human autopsied hearts with acute myocardial infarction after treatment with selective intracoronary thrombolysis

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ABSTRACT To assess the importance of contraction band necrosis (CBN) in patients with acute myocardial infarction (AMI) treated with selective intracoronary thrombolysis, CBN, coagulation necrosis, and infarct size (expressed as CBN + coagulation necrosis) were analyzed quantitatively in 16 autopsied hearts. Intracoronary thrombolysis was performed from 2 to 6 hr after the onset of AMI, and the time from the onset of AMI to death was 7 to 168 hr. Cineangiography revealed no evidence of good collateral circulation in any of the patients. The 16 patients were classified into three groups: six patients with successful thrombolysis (100% to 99% stenosis, group I), five patients with unsuccessful thrombolysis (100% to 100%, group II), and five patients with 99% stenosis before thrombolysis (group III). Among the three groups, there were no significant differences in the time from the onset of AMI to thrombolysis, the time from the onset of AMI to death, the cause of death, or the degree of collateral circulation. The percentage of the risk area involved by the infarct in group I (82 ± 6%) was similar to that in group II (80 ± 11%). Infarct size was not reduced in group I because collateral circulation was not good and because the degree of recanalization after thrombolysis was 1%. However, the percentage of the infarct area with CBN was significantly higher in group I (20 ± 9%) than in group II (3 ± 3%). This finding shows that diffuse CBN occurred after reperfusion in patients with AMI treated with thrombolysis. In group III, three hearts had a smaller infarct area than that in group I or II and a larger area of CBN than that in group II. In the other two hearts, the infarct area was similar to that in groups I and II and the CBN area was as small as in group II. We believe that in the former three cases, spontaneous recanalization occurred before thrombolysis and a considerable portion of the risk area was salvaged. In all three groups, the distribution of CBN was mainly in the peripheral zone of the infarct area. Most of the noninfarct tissue areas in the risk area were in the outer third of the left ventricular wall. These findings reflect the transmural gradient of ischemic cellular damage in human AMI. The degree of ischemia immediately before reperfusion is milder in the areas of CBN than in the areas of coagulation necrosis in human AMI. In conclusion, a method should be developed to protect the heart against CBN to reduce infarct size. 


SINCE Rentrop et al.1 first described selective intracoronary thrombolysis in patients with acute myocardial infarction (AMI) in 1979, the technique has been used more and more widely. An increased rate of recanalization in the infarct-related coronary artery and a lower death rate at the acute stage have been established. However, there are controversies about whether this procedure can salvage ischemic myocardium and reduce infarct size in human AMI.2–7 There is also rapidly increasing interest in reperfusion injury, such as contraction band necrosis (CBN) as an indicator of early reperfusion and hemorrhage as an indicator of late reperfusion.8–13 We recently reported the occurrence of hemorrhagic infarction in patients with AMI treated with thrombolysis.13 However, the relationship between thrombolysis and infarct size or CBN in patients.
with AMI has not yet been clarified. In a previous study, we analyzed quantitatively CBN in a preparation of ischemia and reperfusion in pig hearts without collateral circulation.\textsuperscript{10} However, CBN has not to our knowledge been studied quantitatively in human hearts.

Therefore this study was performed to examine quantitatively the relationship among infarct size, CBN, and coagulation necrosis in patients with AMI treated with thrombolysis.

**Patients and methods**

Nine hundred patients with clinical signs and symptoms of AMI were treated with intracoronary thrombolysis from 1982 to 1985 in 10 cooperating hospitals. There were 80 deaths and 35 autopsies. Five of the autopsied patients had thrombolysis performed over 6 hr from the onset of AMI and were omitted from the study. Eleven of the autopsied patients died earlier than 7 hr or later than 7 days after onset of AMI. In the former, it is difficult to detect histopathologically the acute infarct area, and in the latter the acute infarct area is replaced by granulation or fibrosis. Therefore these patients were also excluded. Three of the remaining 19 autopsied patients had old myocardial infarction in the risk area and were excluded from the study. As a result, the 16 patients without old myocardial infarction in the risk area, in whom thrombolysis was performed 2 to 6 hr after the onset of AMI and in whom the time between the onset of AMI and death was 7 hr to 7 days, were analyzed in this study. The clinical diagnosis of AMI was based on severe chest pain lasting more than 30 min, serial electrocardiographic findings of ST-T changes and/or the appearance of abnormal Q waves, and an increase in creatine kinase (CK), SGOT, and lactate dehydrogenase (LDH) levels. The clinicopathologic data are summarized in table I. In six patients, the infarct-related coronary artery was totally occluded before thrombolysis and was successfully recanalized (group I). Five patients had total occlusion before and after thrombolysis and at autopsy (group II). Five patients had subtotal occlusion of the infarct-related coronary artery before thrombolysis (group III). There were no significant differences among the three groups in age, time from the onset of AMI to thrombolysis, time from the onset to death, the cause of death, or the degree of collateral circulation (tables 1 and 2).

The protocol for thrombolysis was as follows. After informed consent was obtained, hemodynamic values were measured and then selective coronary angiography was performed in multiple views. The lesion of the infarct-related artery was identified and the severity of the stenosis was evaluated according to the criteria of the American Heart Association Committee Report.\textsuperscript{14} Collaterals were considered good if they were wide with normal density and normal washout time in the distal arterial segments.\textsuperscript{15} Collaterals were defined as poor if they were narrow with decreased density in the distal segments and intermediate if they were wide with normal density but delayed washout time or if they were narrow with normal density in the distal arterial segments.\textsuperscript{15} After the occlusion had been visualized, 0.5 mg of nitroglycerin was injected slowly into the occluded artery. If no change in the angiographic appearance of the vessel was noted, urokinase was infused continuously into the occluded vessel at

**TABLE I**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Degree of stenosis in infarct-related coronary artery (%)</th>
<th>Time from onset of AMI to SICT (hr)</th>
<th>Location of AMI/AMI to total LV wall area</th>
<th>% CBN to AMI area</th>
<th>Hemorrhage</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>IR 5 100 (\rightarrow 99) 99</td>
<td>3</td>
<td>ASL/84/83</td>
<td>37.5</td>
<td>S</td>
<td>CHF, VF</td>
</tr>
<tr>
<td>2</td>
<td>IR 5 100 (\rightarrow 99) 99</td>
<td>2.5 Poor</td>
<td>ASL/89/85</td>
<td>15.6</td>
<td>Ma</td>
<td>CHF</td>
</tr>
<tr>
<td>3</td>
<td>IR 6 100 (\rightarrow 99) 99</td>
<td>2</td>
<td>Absent</td>
<td>18.0</td>
<td>Ma</td>
<td>Rupture</td>
</tr>
<tr>
<td>4</td>
<td>IR 6 100 (\rightarrow 99) 99</td>
<td>6 Intermediate</td>
<td>AS/70/21</td>
<td>18.0</td>
<td>Mo</td>
<td>Rupture</td>
</tr>
<tr>
<td>5</td>
<td>IR 6 100 (\rightarrow 99) 99</td>
<td>6 Poor</td>
<td>AS/81/38</td>
<td>13.2</td>
<td>Ma</td>
<td>Rupture</td>
</tr>
<tr>
<td>6</td>
<td>IR 6 100 (\rightarrow 99) 99</td>
<td>6 Absent</td>
<td>AS/82/54</td>
<td>15.8</td>
<td>Mo</td>
<td>CHF</td>
</tr>
<tr>
<td>Group II</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>IR 6 100 (\rightarrow 100) 100</td>
<td>5 Intermediate</td>
<td>AS/93/41</td>
<td>3.7</td>
<td>Mo</td>
<td>Rupture</td>
</tr>
<tr>
<td>8</td>
<td>IR 6 100 (\rightarrow 100) 100</td>
<td>2 Intermediate</td>
<td>AS/71/50</td>
<td>0.0</td>
<td>Mo</td>
<td>Rupture</td>
</tr>
<tr>
<td>9</td>
<td>IR 11 100 (\rightarrow 100) 100</td>
<td>6 Absent</td>
<td>L/92/33</td>
<td>5.8</td>
<td>S</td>
<td>Rupture</td>
</tr>
<tr>
<td>10</td>
<td>IR 11 100 (\rightarrow 100) 100</td>
<td>5 Poor</td>
<td>L/73/40</td>
<td>1.4</td>
<td>Mo</td>
<td>CHF</td>
</tr>
<tr>
<td>11</td>
<td>IR 11 100 (\rightarrow 100) 100</td>
<td>6 Absent</td>
<td>L/71/12</td>
<td>5.8</td>
<td>Mo</td>
<td>Rupture</td>
</tr>
<tr>
<td>Group III</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>IR 1 99(\rightarrow 99) 99</td>
<td>3 Absent</td>
<td>I/86/41</td>
<td>0.0</td>
<td>Ma</td>
<td>CHF</td>
</tr>
<tr>
<td>13</td>
<td>IR 6 99(\rightarrow 99) 90</td>
<td>4 Poor</td>
<td>AS/77/49</td>
<td>2.0</td>
<td>Ma</td>
<td>CHF</td>
</tr>
<tr>
<td>14</td>
<td>IR 6 99(\rightarrow 99) 99</td>
<td>2 Poor</td>
<td>AS/66/29</td>
<td>6.4</td>
<td>Mo</td>
<td>Rupture</td>
</tr>
<tr>
<td>15</td>
<td>IR 6 99(\rightarrow 99) 99</td>
<td>4 Absent</td>
<td>AS/50/26</td>
<td>16.9</td>
<td>Mo</td>
<td>Rupture</td>
</tr>
<tr>
<td>16</td>
<td>IR 7 99(\rightarrow 99) 99</td>
<td>3 Absent</td>
<td>AS/62/22</td>
<td>12.9</td>
<td>Mo</td>
<td>Rupture</td>
</tr>
</tbody>
</table>

IR = infarct-related coronary artery, according to classification of coronary arteries by AHA; S = slight; Mo = moderate; Ma = marked; LV = left ventricular; AS = anteroseptal; L = lateral; I = inferior; VF = ventricular fibrillation; CHF = congestive heart failure.

See text for description of groups and degree of collateral circulation. See ref. 13 for description of degree of hemorrhage.

\textsuperscript{a}99\% stenosis with poor run-off.
PATHOPHYSIOLOGY AND NATURAL HISTORY—CORONARY THROMBOLYSIS

TABLE 2  
Clinical data of 16 autopsied cases of AMI treated with selective intracoronary thrombolysis

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Time from onset of AMI to CIT (hr)</th>
<th>UK dosage (× 10^4 U)</th>
<th>Time from onset of AMI to death (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>(n = 6)</td>
<td>4.3 ± 1.9</td>
<td>76 ± 45</td>
</tr>
<tr>
<td>Group II</td>
<td>(n = 5)</td>
<td>4.8 ± 1.6</td>
<td>103 ± 20</td>
</tr>
<tr>
<td>Group III</td>
<td>(n = 5)</td>
<td>3.2 ± 0.8</td>
<td>36 ± 29</td>
</tr>
</tbody>
</table>

UK = urokinase.  
See text for description of groups.

a rate of 24,000 U/min. Coronary angiography was repeated routinely at 10 min intervals during the infusion of urokinase until complete recanalization was achieved. If the occluded artery could not be recanalized after a large amount of urokinase (from 720,000 to 1,200,000 U) had been given, the procedure was terminated.

After thrombolysis, the patients received aspirin (300 mg/day) and a low dose of heparin (5000 U every 8 to 12 hr). Some patients received a vasodilator and nitrates. In the patients with congestive heart failure, a vasoconstrictor and/or inotropic counterpulsation was used.

Postmortem coronary angiography was done by the methods of Lee et al. and Koyanagi et al. Briefly, the left and right coronary arteries were cannulated with No. 6F polyethylene tubes, and postmortem coronary angiography was performed to determine the risk area of the infarct-related coronary artery with a barium-gelatin mixture at a pressure of 100 mm Hg. Antero-posterior and lateral roentgenograms were taken. Then the hearts were fixed in 10% formalin. Each coronary artery was cut serially and transversely from the ostium to the periphery at 2 to 3 mm intervals. The percentage of luminal narrowing was determined. The critical lesion of the infarct-related coronary artery was determined as the most severely stenotic point of the involved vessel and was compared with coronary angiographic findings at thrombolysis. The risk area was defined as all myocardium in the anatomic distribution of the involved vessel distal to this critical lesion.

The hearts were sliced serially and latitudinally at about 1 cm intervals from the apex to the base and roentgenograms of all slices were taken. Sections 3 to 4 mm thick were then cut just above or below the irradiated surface and roentgenograms of these sections were taken again. The risk area was determined by carefully following the course of each vessel by means of stereoscopic views of the transverse slices and whole heart arteriograms. Four whole transverse thin slices from the upper, middle, lower middle, and lowest portions were divided into six to eight sections each, which were embedded in paraffin, cut into 4 μm thick slices, and stained with hematoxylin-eosin, Masson’s trichrome, and Heidenhein iron hematoxylin. The degree of intramyocardial hemorrhage was classified as none, slight, moderate, or marked as described by Fujiwara et al.

Microscopically, the infarct area was classified as coagulation necrosis or CBN (figure 1). Coagulation necrosis, dark red myocytes contained multiple granulations in the cytoplasm in hematoxylin-eosin and Masson’s trichrome stains. Myofibrils stained with Masson’s trichrome showed relaxation and no supercontraction bands. In CBN, myocytes contained irregular and multiple supercontraction bands and frequently disrupted myofibrils. This was clearly observed in preparations stained with Masson’s trichrome. In addition, a dark red color and multiple granulations were evident.

Quantitative analysis of infarct area. CBN, and coagulation necrosis. The infarct area was identified microscopically at a magnification of ×100 or ×200 with an inverted microscope (Nikon TMS) and was traced by the method of Fujiwara et al. Briefly, a transparent overlay 0.10 mm thick was placed over the coverglass on a stained tissue section of a slide glass. Under an inverted microscope, the outlines of the infarct area and the area of CBN were traced carefully at a magnification of ×100 or ×200 on the transparent film with a stainless-steel needle with a tip width of 10 μm (figure 1). Then the tissue preparation with the traced transparent overlay was enlarged at a magnification of ×10 with a photographic enlarger (Fuji 639) on white paper (figure 1), and the risk area was added to the white paper.

The whole transverse left ventricular area, risk area, infarct area, areas of coagulation necrosis and CBN, and the noninfarct tissue area in the risk area on the white paper were analyzed quantitatively with an image analyzer (Olympus VIP).

The infarct area was expressed as a percentage of the total left ventricular area or of the risk area, and the area of CBN was expressed as a percentage of the infarct area. All data were expressed as the mean ± SD.

Statistical analysis. The percentage of the global acute infarct area and global CBN among the three groups was compared by one-way analysis of variance with multiple comparisons using a Bonferroni correction of the acceptable p level. The percentage of the noninfarct tissue areas in the outer, middle, and inner thirds of the left ventricular wall in the risk area for each group was compared by one-way analysis of variance with multiple comparisons using a Bonferroni correction of the acceptable p level. The percentage of the CBN in the peripheral and central zones of infarct area in each group was compared by a paired t test. The percentage of the total left ventricular wall involved by the acute infarction was compared by Student’s t test between the patients who died of congestive heart failure and rupture. Differences were considered significant at p < .01 for multiple comparisons with a Bonferroni procedure and at p < .05 for others.

Results

Infarct area and infarct-related coronary artery. The data are summarized in table 1 and figures 2 and 3. All 16 patients had acute transmural infarction. Two hearts had anterolateral-septal infarction, and the infarct-related coronary artery was the left main coronary artery. Ten hearts showed anteroseptal infarction, and the infarct-related vessel was the left anterior descending coronary artery. Lateral infarction was noted in three hearts, and the left circumflex coronary artery was the infarct-related artery. Posterior infarction was found in one patient, and the infarct-related artery was the right coronary artery. In all cases, the infarct area was localized within the coronary vascular beds distal to the lesion of the infarct-related coronary artery (risk area). No hearts had good collaterals.

The percentage of the total left ventricular wall involved by AMI was 56 ± 25% in group I, 36 ± 17%
in group II, and 33 ± 11% in group III. There were no statistical differences among the three groups. Six patients died of congestive heart failure, and the other 10 patients died of rupture of the left ventricular free wall. The infarct area was 59 ± 20% (41% to 85%) of the total left ventricular wall in the former and 33 ± 13% (12% to 54%) in the latter, a significant difference.

The AMI area was 82 ± 6% of the risk area in group I, 80 ± 11% in group II, and 68 ± 14% in group III. There were no statistical differences among the three groups (figures 2 and 3). The noninfarct tissue area in the outer, middle, and inner thirds of the left ventricular wall was 70 ± 11%, 17 ± 8%, and 14 ± 6% of the total noninfarct tissue areas in the risk area in group I, 57 ± 11%, 30 ± 11%, and 12 ± 6% in group II, and 66 ± 6%, 20 ± 4%, and 15 ± 8% in group III, respectively. The noninfarct tissue area in the risk area was for the most part in the outer third of the left ventricular wall (figure 4).

CBN, coagulation necrosis, and hemorrhage. The area of CBN was 20 ± 9% (13.2% to 37.5%) of the AMI area (CBN plus coagulation necrosis) in group I, 3 ± 3% (0 to 5.8%) in group II, and 8 ± 7% (0 to 16.9%) in group III (figure 5). This figure was significantly higher in group I than in group II (figure 5).

The infarct area was divided into peripheral and central zones. The peripheral zone was defined as the exterior and lateral thirds of the infarct area and the central zone as the remaining core zone of the infarct area. The peripheral zone is situated externally and laterally to the central zone. The areas of the peripheral and central zones are almost equal in each heart. CBN extended through 31 ± 11% of the peripheral zone in group I, 5 ± 4% in group II, and 11 ± 10% in group III. It involved 2 ± 4% of the central zone in group I, 1 ± 1% in group II, and 2 ± 2% in group III (figure 6). The CBN in the peripheral zone was 97 ± 5% of the total CBN in group I, 95 ± 9% in group II, and
89 ± 6% in group III (figure 6). In group II, CBN was seen only in the very narrow border zone between the infarct and noninfarct tissue areas (figure 2).

The tissue areas with hemorrhage were located mainly within the boundaries of the infarct in all 16 hearts (table 1). The center of the bleeding was the core of the infarct, in which coagulation necrosis was always seen. The tissue areas with CBN showed little or no hemorrhage.

Discussion

In this postmortem study of 16 patients with AMI treated with intracoronary thrombolysis, the infarct area involved 77 ± 12% of the risk area. More of the left ventricular wall was infarcted in patients who died of congestive heart failure than in those who died of cardiac rupture. These findings are similar to those reported in patients without coronary thrombolysis who died of AMI.16, 20, 21

The present data revealed that (1) there was no significant difference in the infarct size/risk area ratio between groups I and II, (2) CBN was diffusely present in group I but almost absent in group II, (3) the infarct size/risk area ratio and the percentage of the infarct containing CBN varied considerably in group III.

In patients with AMI surviving after treatment with thrombolysis, both the global and the regional ejection fractions have been reported to have improved, and quantitative thallium-201 perfusion imaging showed that the infarct size was reduced only when the infarct-related artery was successfully recanalized.22-25 These clinical data suggest that the infarct area/risk area ratio is smaller in patients with successful recanalization than in those with permanent occlusion. However, the present autopsy findings indicate that the infarct size was not reduced despite successful recanalization. None of these cases showed good collateral circulation before thrombolysis and the infarct-related coronary artery showed 99% stenosis after thrombolysis. In patients surviving after successful recanalization, 45% showed a degree of stenosis of 90% or less in the infarct-related coronary artery after thrombolysis26 and 29% had good collateral circulation.27 In animal preparations, the duration of occlusion after which reperfusion can salvage the myocardium in the risk area is within 60 to 120 min in the pig heart without collateral circulation10, 28 and within 6 hr in the dog heart with rich collaterals.29 Our group I exhibited recanalization 2 to 6 hr after the onset of AMI without good collaterals. Therefore the discrepancy between patients who survived and those who died may be explained by the degree of collateral circulation and the degree of recanalization. Virtually any population of autopsy patients represents a select subset, and in this case the degree
FIGURE 3. Percentage of risk area involved in AMI. GI indicates the group in which reperfusion was induced by thrombolysis, GII the group in which recanalization was unsuccessful, and GIII the group with subtotal occlusion of the infarct-related vessel before thrombolysis. Bars indicate mean ± SD. There is no statistically significant difference among the three groups.

of recanalization with successful thrombolysis was minimal and a very high percentage of the patients died of ventricular rupture. Hence, the results may be most applicable to this subgroup of patients.

CBN is considered to be caused by (1) reperfusion after ischemia or anoxia,10-12 (2) metabolic cell injury, e.g., from catecholamine or corticoid intoxication, Mg,K deficiency, or calcium paradox,30-32 (3) mechanical cell injury, e.g., from internal electric shock, cutting, or endomyocardial biopsy,33-35 or (4) acute transient hemorrhagic shock.36 None of our 16 patients had serum electrolyte imbalance, corticoid intoxication, internal electric shock, endomyocardial biopsy or acute transient hemorrhagic shock. However, most of the patients received catecholamines or external electric shock or exhibited clinical shock before their death. CBN caused by metabolic cell injury such as by catecholamines is known to occur diffusely throughout the left ventricular wall.30 According to the data on hemorrhagic shock, which is one of the various clinical shocks, the distribution of CBN is also diffuse in the ventricular wall.36 Although precise data on the relationship between CBN and external electric shock are not available, CBN caused by internal electric shock is localized in the outer third beneath the wall where the electric paddles were placed.34 However, in our 16 patients, CBN was always seen within the risk area. The specific localization of CBN indicates that, in this study, it is independent of metabolic cell injury, electric shock, or clinical shock.

The characteristic feature of AMI in group I with recanalization was the presence of diffuse CBN in the infarct area, mainly in the peripheral zone. The histologic findings were similar to those seen with reperfusion after 60 min of occlusion in pig hearts without collateral circulation10 and after occlusion of more than 3 hr in dog hearts with rich collaterals.29,37-40 In the experimental studies, reperfusion in the early stage of ischemia resulted in the development of CBN.10-12 Thus the diffuse CBN in the infarct area in group I is probably reperfusion injury. The hearts of patients surviving after recanalization may also have diffuse CBN.

In group II without recanalization, CBN was found focally and its location was limited to the very narrow border zone between the infarct and normal tissue. In pig hearts with permanent occlusion, CBN involved 2 ± 2% of the total AMI area, and the location of CBN was similar to that in our group II. Therefore, CBN in group II may be caused by mechanical cell injury in the border zone between ischemic and nonischmic myo-

FIGURE 4. Noninfarct tissue areas of the inner, middle, and outer thirds of the left ventricular wall as a percentage of the total noninfarct tissue areas in the risk area. Note that the noninfarct tissue areas were mainly in the outer third of the left ventricular wall. Groups identified as in figure 2. I = inner one-third of the left ventricular wall; M = middle one-third of the left ventricular wall; O = outer one-third of the left ventricular wall. Bars indicate mean ± SD.
cardium. However, we cannot deny the possibility of reperfusion injury at a level of microcirculation.

In group III, the percentage of the AMI area containing CBN and the infarct area/risk area ratio varied considerably. In three hearts (cases 14 to 16 of table 1), the percentage of the AMI area containing CBN was high compared with that in group I with recanalization and the infarct area/risk area ratio was lower than that in group I or II. In those patients, spontaneous recanalization probably occurred before thrombolysis, and a considerable portion of the risk area was salvaged. In the other two hearts (cases 12 and 13 of table 1), CBN was rarely seen, as in group II without recanalization. The infarct area/risk area ratio, the time from the onset of AMI to thrombolysis and the degree of collateral circulation were similar to those in groups I and II. However, in these two patients, the infarct-related artery showed 99% stenosis with poor run-off before and after thrombolysis. This suggests that 99% stenosis with poor run-off is nearly complete occlusion.

It has been reported that transmural gradients of the ischemic cellular damage occur from the inner third to the outer third in both pig and dog hearts after occlusion of a coronary artery. In the present study, the distribution of the noninfarct tissue areas in the risk area was for the most part in the outer third of the left ventricular wall, and the distribution of CBN was mostly in the peripheral zone of the infarct area in all groups. In experimental studies, reperfusion leads to CBN in the early stage of ischemia and hemorrhage and coagulation necrosis in the late stage. We reported previously that moderate or marked hemorrhage was seen in the center of the infarct area in patients treated with thrombolysis. In the present study, tissue areas with moderate or marked hemorrhage showed coagulation necrosis and tissue areas with CBN had little or no hemorrhage. These findings reflect the transmural gradient of ischemic cellular damage in human hearts.

The degree of ischemia immediately before reperfusion is milder in the areas of CBN than in the areas of coagulation necrosis and/or hemorrhage in human AMI, although it is generally considered that the myocytes with CBN are damaged irreversibly immediately before reperfusion. However, recent studies have revealed that when reperfusion is controlled as with the use of a low calcium solution, the infarct area can be reduced. This suggests that tissue areas that can be salvaged by controlled reperfusion after AMI may be areas with CBN.
Therefore it is necessary to develop methods to protect against CBN to reduce infarct size in human AMI.

The autopsies were performed in the following hospitals: Shizuoka City Hospital, Hamamatsu Rosai Hospital, Shimada City Hospital, Ogaki City Hospital, Takeda Hospital, Otowa Hospital, Kurashiki Central Hospital, Ohtsu Red Cross Hospital, Hiroshima City Hospital, and our Kyoto University Hospital. We are grateful to Drs. A. Takizawa, T. Takahashi, M. Yasuno, M. Kondo, Y. Sone, S. Tamaki, H. Nonogi, K. Mitsudo, K. Hirose, and H. Sato for clinical details of cases. Thanks are due to D. Mrozek for criticism of the manuscript and M. Jinnai and S. Tomita for secretarial assistance.

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