Macrosopic Hemorrhagic Infarction Following Selective Coronary Thrombolysis
In Acute Myocardial Infarction

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Macrosopic hemorrhagic infarction was studied in 14 autopsied hearts with selective coronary thrombolysis (SCT) after acute myocardial infarction (AMI). In all patients urokinase, 240,000–720,000 units, had been selectively injected into ischemia-related coronary artery at 2–7 hours after the onset of AMI. The degree of stenosis after SCT was 90–99% in 13 patients and 100% in one patient.

According to the duration of illness at death, the 14 patients were classified into 3 stages; stage I: 4–9 hours; stage II: 15 hours to 11 days; stage III: 19 days to 12 months. Three hearts in stage I had no macrosopic hemorrhage. In stage II, marked and diffuse hemorrhage in the infarct area was macroscopically evident in 6 of 7 hearts. In a stage II patient, extravasation of contrast medium into the myocardium was found at 3 hours after the onset of AMI. In stage III, 4 hearts had massive fibrosis or granulation in the left ventricular wall without macroscopic hemorrhage.

Cardiac rupture was seen in 4 of 10 patients from stages I and II.

It is concluded that macroscopic bleeding appears in most patients with AMI treated with coronary thrombolysis. In the majority of cases, the hemorrhage increases gradually after SCT and becomes macroscopically definite approximately 15 hours after the onset of AMI. Rarely, massive bleeding appears earlier. Hemorrhagic infarction is replaced by massive fibrosis after approximately 2 weeks.

UNTIL now, infarction has been classified into anemic and hemorrhagic infarctions. Acute myocardial infarction (AMI) belongs to the anemic type, and macrosopic hemorrhage is rare in AMI. However, myocardial hemorrhage induced by reperfusion of the acute ischemic myocardium is well-known in animal models. With the new therapy of selective coronary thrombolysis in patients with AMI, reperfusion is induced during severe myocardial ischemia. Therefore, the purpose of the present paper is to define clinicopathologically whether or not macroscopic hemorrhagic infarction appears in such patients.

SUBJECTS AND METHODS
The subjects were 14 autopsied patients with selective coronary thrombolysis therapy (SCT) for acute myocardial infarction (AMI). There were 10 males and 4 females ranging in age from 59 to 83 years. All patients had urokinase injection of 240,000–720,000 units into the is-

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TABLE I  MACROSCOPIC CARDIAC HEMORRHAGE AND DURATION OF ILLNESS AT DEATH IN PATIENTS WITH MYOCARDIAL INFARCTION AND SELECTIVE CORONARY THROMBOLYSIS, USING UROKINASE

<table>
<thead>
<tr>
<th>Duration of illness at death</th>
<th>Number of cases</th>
<th>Diffuse &amp; marked hemorrhage</th>
<th>Focal &amp; marked hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I 4 – 9 hours</td>
<td>3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stage II 15 hours – 11 days</td>
<td>7</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Stage III 19 days – 12 months</td>
<td>4</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>6</td>
<td>1</td>
</tr>
</tbody>
</table>

All macroscopic bleeding was seen in the infarct areas. Diffuse and marked hemorrhage indicates that marked bleeding is noted approximately in the whole infarct areas. Focal hemorrhage indicates marked bleeding is focally localized in the infarct area.

chemia-related artery at 2–7 hours (mean, 4 hours) after the onset of AMI. Duration of the illness from the onset of AMI until death was 4 hours to 12 months.

After fixation of hearts in 10% formalin, each coronary artery was serially and transversely cut from ostium to periphery at 2–3 mm intervals. The degree of luminal narrowing was recorded as a percentage. The hearts were serially and transversely sliced at 1 cm intervals from apex to base.

Fig.1. Macroscopic findings of marked and diffuse hemorrhagic infarction (black) after selective coronary thrombolysis in acute myocardial infarction. A = anterior, P = posterior

Fig.2. Microscopic findings of hemorrhagic infarction obtained from infarct area of the heart in Fig.1. Note coagulation necrosis of myocytes and severe interstitial bleeding.

and were macroscopically observed. Myocardial tissues were embedded in paraffin, sectioned at 4 μm thickness, and stained with hematoxylin and eosin, Masson trichrome and Heidenhain iron hematoxylin.

RESULTS

According to the duration of illness at death, 14 patients were classified into 3 groups (Table I). In stage I, the patients died at 4–9 hours after the onset of acute myocardial infarction (AMI), and at 2–4 hours after selective coronary thrombolysis (SCT). Stage II had duration of illness until death from 15 hours to 11 days after the onset of AMI and of over 10 hours after SCT. In stage III, the duration of illness until death was from 19 days to 12 months.

Times from the onset of AMI to SCT were 3.8 ± 1.0 hours in stage I, 3.5 ± 1.0 hours in stage II, and 3.5 ± 1.0 hours in stage III. The quantity of urokinase injected was 360,000 ± 100,000 units in stage I, 460,000 ± 150,000 units in stage II and 400,000 ± 150,000 units in stage III. Times from the onset of AMI to SCT and the quantities of urokinase injected were similar in the above 3 stages. Before SCT, complete occlusion of the ischemia-related coronary artery was found in 2 of 3 in stage I, in 4 of 7 in stage II, and in 3 of 4 in stage III. After SCT, only one of 14 patients still had complete occlusion, and the degree of stenosis in the ischemia-related coronary artery was from 99 to 90% in the other 13 patients. Clinically and pathologically, 13 of 14 hearts had large infarction, and the other one, belonging to stage II, had a small subendocardial infarction. In 13 hearts with large infarcts, 12 hearts had transmural infarction and the other one had a subendocardial infarction and belonged to stage II.

All 3 hearts in stage I had no macroscopic hemorrhage (Table I). In stage II, marked and diffuse hemorrhage in the infarct area, where coagulation necrosis was microscopically detected, was macroscopically evident in 6 of 7 hearts (Table I, Figs. 1 and 2). In stage III, 4 hearts had massive fibrosis and/or granulation in the left ventricular wall and had macroscopically no definite hemorrhage.

CAUSE OF DEATH

Three patients in stage I died of cardiogenic shock, probably due to pump failure and/or arrhythmia following AMI. Of 7 patients in stage II, 4 died of cardiac tamponade due to cardiac rupture in the center of the AMI, 2 died of ventricular fibrillation or pump failure after AMI and the last died of a noncardiac disease, ileus. In stage III, 4 patients died of pump failure and/or arrhythmia following reinfarction.

DISCUSSION

The present study revealed that, in hearts with acute myocardial infarction (AMI) and selective coronary thrombolysis (SCT) using urokinase, diffuse and marked macroscopic hemorrhage in the infarct area was seen in 6 of 7 patients in stage II, but was not noted in those in stage I and III. Previously we reported a patient with the findings of extravasation of contrast medium into the myocardium within 3 hours of the onset of AMI9 In that case it was postulated that massive bleeding had already occurred within 3 hours of the onset of AMI (stage I). This indicates that, in most cases, bleeding in the infarct area increases gradually after SCT. It becomes macroscopically definite approximately 10 hours after SCT and sometimes 15 hours after the onset of AMI. Rarely, massive bleeding appears earlier. The hemorrhage is absorbed within a few weeks and is replaced by fibrosis. As most hearts in stage II had marked and diffuse hemorrhage, it is suggested that some of clinical cases with AMI have similar hemorrhage after SCT.

It has been reported that marked and diffuse hemorrhagic infarction is rare in patients with AMI without SCT. In experimental studies, bleeding in the infarct area was induced by reperfusion after coronary occlusion. Urokinase has a thrombolytic effect, and the injection induces a bleeding tendency in the tissue. Therefore, hemorrhagic infarction in human AMI with SCT is due to the combined effects of reperfusion and the injection of urokinase.

In animal models, myocardial cells in the left ventricular wall have transmurally irreversible cellular damage during ischemia. This occurs within 2 hours of the occlusion of a coronary artery in pigs without collateral circulation and within 6 hours of the occlusion of a coronary artery in dogs with rich collateral circulation. Bleeding in the infarct area after SCT increases gradually and becomes macroscopically definite approximately 15 hours after the onset of AMI. Such bleeding may not contribute to extending cell necrosis due to ischemia. However, we cannot deny the toxic effect of extravascular blood on living myocardial cells.
It is concluded that marked and diffuse hemorrhagic infarction appears frequently after SCT in patients with AMI. The combined effects of reperfusion after ischemia and injections of large doses of urokinase are important in its pathogenesis.

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