A clinicopathologic study of patients with hemorrhagic myocardial infarction treated with selective coronary thrombolysis with urokinase

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ABSTRACT Hemorrhagic acute myocardial infarction (AMI) was studied after selective intracoronary thrombolysis (SICT) in 30 patients undergoing autopsy. Urokinase, 240,000 to 1,200,000 U, was selectively injected into the infarct-related coronary artery at 2 to 9 hr (4 ± 2 hr) after the onset of AMI. The infarct-related coronary artery showed complete occlusion in 21, 99% stenosis in eight, and 90% stenosis in one patient before SICT. After SICT, complete occlusion was seen in only five, 99% stenosis in 22, and 90% stenosis in three patients. Twenty-eight patients had transmural infarction and the other two had subendocardial infarction. Macroscopically and microscopically, the degree of hemorrhage was classified as no, slight, moderate, or marked bleeding and the hemorrhagic infarction was defined as moderate or marked diffuse bleeding in the infarct area. According to the interval from SICT to death, patients were also classified into stage I (early acute stage, 1 to 4 hr after SICT and 4 to 13 hr after the onset of AMI; n = 7), stage II (late acute stage, 9 hr to 11 days after SICT and 15 hr to 11 days after the onset of AMI; n = 18), or stage III (old infarction stage, over 17 days after AMI and SICT; n = 5). There were no significant differences with respect to the frequency of recanalization, the time from the onset of AMI to SICT, the dose of urokinase, or other clinical parameters among patients at the three stages. Only the hearts of patients in stage II showed hemorrhagic infarction, and it was found in 15 of 18 of these hearts. Marked diffuse hemorrhage was noted in six hearts, all of which showed recanalization after SICT. However, even in three patients in stage II without recanalization after SICT, moderate diffuse bleeding was evident. In all hearts, the hemorrhagic area was mostly localized within the infarct area. Thus, in most of the patients with AMI treated with SICT, hemorrhage increases gradually after SICT, becomes moderately or markedly diffuse after 4 hr, and is replaced by fibrosis after 3 to 4 weeks. The hemorrhagic infarction is due to the combined effects of reperfusion and large doses of urokinase. The time delay of bleeding seems to depend on the low perfusion pressure in the portion distal to the stenosed, infarct-related coronary artery. It is unlikely that hemorrhage expands the infarct area.

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INFARCTION has been classified into anemic and hemorrhagic types.¹ In humans, acute myocardial infarction (AMI) is generally of the anemic type and hemorrhagic infarction rarely occurs.¹ However, myocardial hemorrhage can be induced by reperfusion after acute ischemia in animal preparations.²⁻⁴ In man, hemorrhagic infarction after reperfusion has also been described after long periods of intraoperative myocardial ischemia.¹⁰,¹¹ Selective intracoronary thrombolysis (SICT) with streptokinase or urokinase is being administered more and more frequently to patients with AMI,¹²⁻¹⁷ and several cases of hemorrhagic AMI after SICT have been reported.¹⁸⁻²² At present, the potential benefits of SICT have not been established, either clinically or pathologically.

Therefore, we performed clinicopathologic studies of patients with hemorrhagic infarction after SICT with urokinase. The severity of hemorrhage was classified and its relationship to the duration of illness, the
degree of stenosis of the infarct-related coronary artery, the infarct area, and various clinical parameters was examined.

**Subjects and methods**

The subjects were 30 Japanese patients undergoing autopsy who had been diagnosed with myocardial infarction by clinical signs and symptoms. SICT had been performed in all patients. The clinical diagnosis of AMI was based on severe chest pain, a serial electrocardiographic change comprising ST-T changes (elevation or depression) and/or the appearance of abnormal Q waves, and an increase in levels of the enzymes creatine kinase (CK), SGOT, and lactate dehydrogenase (LDH). There were 17 men and 13 women ranging in age from 45 to 83 years old. In each case, 240,000 to 1,200,000 U urokinase was injected into the ischemia-related coronary artery at 2 to 9 hr after the onset of AMI. Duration of illness from the onset of AMI (chest pain) until death was 4 hr to 12 months, and is summarized according to the interval after SICT in table 1.

Patients in this study were those undergoing autopsy at the 11 hospitals with departments of cardiology and coronary care units listed in the acknowledgments. The autopsies were done from 1982 to 1984. Each hospital had staff qualified to perform SICT with urokinase. The total number of patients treated with SICT was 850; there were 75 deaths. The mortality rates at the hospitals ranged from 7% to 12%. Autopsy was permitted in the 30 patients studied only.

The protocol for SICT was as follows. After hemodynamic values were measured, selective coronary angiography was performed in multiple views to identify the infarct-related vessel. After visualizing the occlusion, 0.5 mg of nitroglycerin was injected. The follow-up duration for the 30 patients was 7 months, except in the case of death. The 18 patients who survived were treated with aspirin, beta blockers, and digoxin. The 12 patients who died were autopsied and the cause of death was identified from the clinical data and the conditions at the time of death.

**TABLE 1**

Summary of data from 30 patients ordered according to the interval from SICT to death

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Sex</th>
<th>Time from SICT to death</th>
<th>Time from the onset of AMI to SICT (hr)</th>
<th>Degree of stenosis in the infarct-related coronary artery (%)</th>
<th>Dose of urokinase (x 10^6 U)</th>
<th>Cardiogenic shock</th>
<th>Pathologic findings</th>
<th>Degree and extent of hemorrhage</th>
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<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>M</td>
<td>1 hr</td>
<td>3</td>
<td>4 hr</td>
<td>98</td>
<td>+</td>
<td>AL/T</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>F</td>
<td>1 hr</td>
<td>4</td>
<td>6 hr</td>
<td>100</td>
<td>-</td>
<td>S/T</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>M</td>
<td>1 hr</td>
<td>4</td>
<td>6 hr</td>
<td>100</td>
<td>-</td>
<td>AS/T</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>M</td>
<td>1 hr</td>
<td>6</td>
<td>7 hr</td>
<td>100</td>
<td>-</td>
<td>LT</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>M</td>
<td>3 hr</td>
<td>3</td>
<td>6 hr</td>
<td>99</td>
<td>-</td>
<td>P/T</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>F</td>
<td>3 hr</td>
<td>9</td>
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<td>99</td>
<td>-</td>
<td>AS/T</td>
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<tr>
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<td>15</td>
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<td>100</td>
<td>-</td>
<td>ALS/T</td>
</tr>
<tr>
<td>9</td>
<td>83</td>
<td>M</td>
<td>12 hr</td>
<td>3</td>
<td>15 hr</td>
<td>99</td>
<td>-</td>
<td>AL/T</td>
</tr>
<tr>
<td>10</td>
<td>71</td>
<td>F</td>
<td>12 hr</td>
<td>4</td>
<td>16 hr</td>
<td>99</td>
<td>-</td>
<td>AS/T</td>
</tr>
<tr>
<td>11</td>
<td>45</td>
<td>M</td>
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<td>3</td>
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<td>100</td>
<td>-</td>
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</tr>
<tr>
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<td>-</td>
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<td>5</td>
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<td>-</td>
<td>L/P/T</td>
</tr>
<tr>
<td>14</td>
<td>48</td>
<td>M</td>
<td>2 days</td>
<td>6</td>
<td>2 days</td>
<td>100</td>
<td>-</td>
<td>ALS/T</td>
</tr>
<tr>
<td>15</td>
<td>72</td>
<td>M</td>
<td>2 days</td>
<td>2</td>
<td>2 days</td>
<td>100</td>
<td>+</td>
<td>ALS/T</td>
</tr>
<tr>
<td>16</td>
<td>73</td>
<td>F</td>
<td>2 days</td>
<td>2</td>
<td>2 days</td>
<td>100</td>
<td>+</td>
<td>ALS/T</td>
</tr>
<tr>
<td>17</td>
<td>74</td>
<td>F</td>
<td>2 days</td>
<td>2</td>
<td>2 days</td>
<td>100</td>
<td>+</td>
<td>ALS/T</td>
</tr>
<tr>
<td>18</td>
<td>76</td>
<td>F</td>
<td>2 days</td>
<td>2</td>
<td>2 days</td>
<td>100</td>
<td>+</td>
<td>P/T</td>
</tr>
<tr>
<td>19</td>
<td>62</td>
<td>F</td>
<td>2 days</td>
<td>2</td>
<td>2 days</td>
<td>100</td>
<td>+</td>
<td>ALS/T</td>
</tr>
<tr>
<td>20</td>
<td>73</td>
<td>F</td>
<td>5 days</td>
<td>2</td>
<td>5 days</td>
<td>100</td>
<td>+</td>
<td>ALS/T</td>
</tr>
<tr>
<td>21</td>
<td>74</td>
<td>M</td>
<td>5 days</td>
<td>2</td>
<td>5 days</td>
<td>100</td>
<td>+</td>
<td>ALS/T</td>
</tr>
<tr>
<td>22</td>
<td>68</td>
<td>M</td>
<td>5 days</td>
<td>5</td>
<td>5 days</td>
<td>100</td>
<td>+</td>
<td>ALS/T</td>
</tr>
<tr>
<td>23</td>
<td>75</td>
<td>M</td>
<td>7 days</td>
<td>4</td>
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<td>99</td>
<td>+</td>
<td>AS/T</td>
</tr>
<tr>
<td>24</td>
<td>75</td>
<td>M</td>
<td>9 days</td>
<td>3</td>
<td>9 days</td>
<td>100</td>
<td>+</td>
<td>AS/T</td>
</tr>
<tr>
<td>25</td>
<td>71</td>
<td>F</td>
<td>11 days</td>
<td>7</td>
<td>11 days</td>
<td>90</td>
<td>+</td>
<td>AS/T</td>
</tr>
<tr>
<td>26</td>
<td>70</td>
<td>M</td>
<td>19 days</td>
<td>4</td>
<td>19 days</td>
<td>90</td>
<td>+</td>
<td>AS/T</td>
</tr>
<tr>
<td>27</td>
<td>53</td>
<td>M</td>
<td>40 days</td>
<td>5</td>
<td>40 days</td>
<td>99</td>
<td>+</td>
<td>AS/T</td>
</tr>
<tr>
<td>28</td>
<td>73</td>
<td>F</td>
<td>60 days</td>
<td>5</td>
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<td>100</td>
<td>+</td>
<td>P/T</td>
</tr>
<tr>
<td>29</td>
<td>59</td>
<td>M</td>
<td>12 mo</td>
<td>3</td>
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<td>100</td>
<td>+</td>
<td>P/T</td>
</tr>
<tr>
<td>30</td>
<td>71</td>
<td>F</td>
<td>24 mo</td>
<td>3</td>
<td>24 mo</td>
<td>100</td>
<td>+</td>
<td>AS/T</td>
</tr>
</tbody>
</table>

OMI = old myocardial infarction; IR = infarct-related coronary artery, according to the classification of coronary artery by AHA; A = anterior; L = lateral; S = septal; P = posterior; T = transmural; sub = subendocardial; N = no hemorrhage; D = diffuse; F = focal; S = slight; Mo = moderate; Ma = marked.

The definition of degree of stenosis in the infarct-related coronary artery and cardiogenic shock was based on the AHA Committee Report.27

At least 10 hr after SICT.
slowly injected into the occluded artery. If no change in the angiographic appearance of the vessel was noted, urokinase was continuously infused, selectively, into the occluded vessel at a rate of 24,000 U/min. Coronary angiography was repeated routinely at 10 min intervals during the infusion of urokinase until complete reperfusion was achieved. If the occluded artery could not be recanalized after a large amount of urokinase (from 720,000 to 1,200,00 U) had been given, the attempt was terminated.

After SICT, the patients in whom recanalization was successful received aspirin (300 mg/day) and a low dose of heparin (5,000 units every 8 to 12 hr). Some patients received a vasodilator and nitrates. In the patients with cardiogenic shock, vasoconstrictors and/or intra-aortic counterpulsation were used. Blood pressure, heart rate, the electrocardiogram, pulmonary capillary wedge pressure by Swan-Ganz catheter, and levels of various enzymes (LDH, CK, SGOT, etc.) were serially measured approximately 5 days after the onset of AMI.

After fixation in 10% formalin at autopsy, each heart was sliced serially and latitudinally at about 1 cm intervals from the apex to the base, observed macroscopically, and photographed in color. Each of two large transverse slices obtained from a half and the lower third of the heart was divided into six to eight sections, and all were used for histologic examination. These were embedded in paraffin, cut into 4 μm thick slices, and stained with hematoxylin-eosin, Masson’s trichrome, Heidenheim iron hematoxylin, and hematoxylin basic fuchsin picric acid. Infarct areas were examined macroscopically and microscopically. Each coronary artery was serially and transversely cut from the ostium to the periphery at 2 to 3 mm intervals. The degree of luminal narrowing was recorded as a percentage.

Microscopically, myocardial infarction was considered to be in the early acute stage (4 to 13 hr after the onset of AMI in this study) when the myocytes were more deeply stained with eosin, stained a brilliant red with hematoxylin basic fuchsin picric acid, and had a granular, banded cytoplasm, with nuclei.32 The areas with contraction band necrosis were counted. Myocardial infarction in the late acute stage (15 hr to 11 days after the onset of AMI in this study) was that represented by coagulation or contraction band necrosis of myocytes, with the disappearance of nuclei, inflammatory cell infiltration, the necrosis, and/or granululation. Features of the “old” stage (over 17 days after the onset of AMI) were massive scarring and/or granulation. Necrosis or fibrosis involving more than the inner half of the myocardial wall was considered “transmural” and only that involving the inner half of the myocardial wall was considered “subendocardial.”24

**Statistical analysis.** Data are expressed as mean ± SD. Comparison of the data among groups was performed by one-way analysis of variance with multiple comparison and χ² analysis with Yate’s correction.25 Statistical significance was determined at the level of p < .05.

**Results**

**Infarct area and the related coronary artery.** All data are summarized in table 1. In all of the 30 hearts, the histologic findings in the infarct areas reflected the interval from the onset of AMI to death. Transmural infarction was detected in 28 hearts and subendocardial infarction was seen in the other two. Anterolateral-septal infarction was noted in eight hearts and antero-septal infarction was found in 13. Five hearts showed posterior (clinically inferior) infarction and two hearts contained a posterolateral infarction. In the other two hearts, the infarct area was localized in the lateral wall.

The infarct-related coronary artery showed complete occlusion in 21, 99% stenosis in eight, and 90% stenosis in one patient before SICT. After SICT, there was complete occlusion in only five, 99% stenosis in 22, and 90% stenosis in three patients.

**Relationship between infarct areas and areas with hemorrhage.** Microscopically, the tissue areas with hemorrhage (figures 1 and 2) were basically localized within the boundaries of the infarct in all of the 30 hearts (figure 3). The center of diffuse bleeding was the core of the infarct. Tissue layers of infarct without bleeding were almost always found outside of the infarcted tissues that showed definite bleeding (figure 3). However, definite focal bleeding was seen in the tissue areas without infarction throughout the perimysium, where red blood cells from the bleeding infarct area had continuously invaded the area of tissue without infarct (figure 4).

**Macroscopic and microscopic classification of hemorrhage and the definition of hemorrhagic infarction.** Microscopically, the degree of intramyocardial hemorrhage was divided into groups of no, slight, moderate, or marked bleeding, as shown in figure 1. Even in tissues with no macroscopical evidence of hemorrhage, microscopically focal red blood cells were noted in the infarct. In tissues with macroscopically slight hemorrhage, microscopically many focal red blood cells were found in intermyocytes (interstitial space among myocytes) and the perimysium (figure 2, A1 and 2). In cases of a macroscopically moderate hemorrhage, many diffuse red blood cells were seen in the intermyocyte and perimysium (figure 2, B). Marked hemorrhage showed numerous diffuse red blood cells in intermyocytes, where the myocytes were markedly dissociated by the compact invasion of red blood cells, and in the perimysium (figure 2, C). Microscopic observation revealed that the bleeding in the intermyocyte originated from the capillaries and in the perimysium was derived mainly from the venules and sinusoids and sometimes arterioles (figure 5). Marked dilatation of venules and sinusoids due to congestion of red blood cells and compact concentration of red blood cells in the capillary were frequently seen (figure 5). Hemorrhage covering an area greater than 50% of the total infarct area on microscopic observation was referred to as diffuse and that covering less than 50% as focal. Hemorrhagic infarction was defined as moderate or marked diffuse bleeding in the infarct area.

**Relationship between hemorrhagic infarction and the interval from SICT to death.** The patients were considered to have died at one of three stages (table 2) according to
the interval from SICT to death. Patients in stage I (early acute stage) died 1 to 4 hr after SICT and at 4 to 13 hr after the onset of AMI, those in stage II (late acute stage) died from 9 hr to 11 days after SICT and from 15 hr to 11 days after the onset of AMI, and those in stage III (old stage) died more than 17 days after the onset of AMI and SICT.

There was no evidence of hemorrhagic infarction in the hearts of the seven patients in stage I. Macroscopically three hearts had no hemorrhage and one showed slight focal hemorrhage. The other three hearts had slight diffuse hemorrhage with or without moderate focal hemorrhage. Hearts of 15 of the 18 patients in stage II showed hemorrhagic infarction. Six had marked diffuse hemorrhage, and in nine it was moderate and diffuse. Five of the nine hearts with moderate diffuse bleeding had marked focal bleeding. Three hearts had slight diffuse bleeding. Hemorrhagic infarction was not seen in any of the five hearts of patients in stage III. Macroscopically two hearts had no bleeding, two hearts showed slight focal hemorrhage, and the other one had slight diffuse hemorrhage.

Relationship between hemorrhagic infarction and other various clinical parameters. A comparison of clinical parameter values for patients in stages I to III is shown in table 3. There was no evidence of significant differences in the various clinical parameters (age, sex, interval from the onset of AMI to SICT, dose of urokinase, degree of stenosis after SICT, blood pressure, and frequencies of shock) among the three groups, except for the interval from SICT to death.

For the 18 patients in stage II, the relationship between the degree of hemorrhage and the various clinical parameters was examined (table 4). Between the six patients with marked diffuse hemorrhage and the 12 with moderate or slight diffuse hemorrhage, there were no significant differences with respect to the dose of urokinase, interval from the onset of AMI to SICT, or the degree of stenosis in the infarct-related coronary artery before or after SICT. Five of the six patients with marked diffuse bleeding had had a good control of blood pressure and showed no evidence of shock at least 10 hr after SICT. In only one patient did shock occur immediately after SICT. Six of the seven patients who developed cardiogenic shock after SICT showed no marked diffuse hemorrhage. Of the 11 without shock, five showed marked diffuse hemorrhage, five moderate diffuse hemorrhage, and one slight diffuse hemorrhage. The hearts of three patients (Nos. 13, 18, and 19) in whom the infarct-related coronary arteries showed no recanalization after SICT and who died in stage II had moderate diffuse hemorrhage.

Discussion

Clinicopathologic observations of patients with AMI receiving SICT with urokinase revealed that in
the early acute stage (stage I), diffusely moderate or marked hemorrhage was not present in the areas with AMI. Diffuse and marked or moderate hemorrhage appeared in the late acute stage (stage II) and hemorrhage disappeared in the chronic stage (stage III). There were no significant differences among patients in the three stages with respect to the interval from the onset of AMI to SICT, frequency or degree of recanalization, the dose of urokinase, frequency of cardiogenic shock after SICT, or macroscopic infarct area. Therefore, it appears that diffuse bleeding in the infarct area increases gradually after SICT and becomes macroscopically definite over 4 hr after SICT. This diffuse hemorrhage is absorbed after approximately 3 to 4 weeks and is replaced by fibrosis. However, several cases in which coronary cineangiography showed focal pooling of the contrast medium in the early acute stage have been reported. We found moderate focal bleeding in two of the seven hearts of patients in stage I. Therefore, definite focal bleeding may appear in those in stage I.

Generally, hemorrhagic myocardial infarction has been considered rare in human AMI and the definition has not yet been established. Of the 60 patients with AMI without SICT on which we have recently performed autopsy, including 40 who died from 15 hr to 11 days after the onset of AMI (stage II in this study), moderate diffuse hemorrhage was noted only in two at stage II and there was no evidence of marked diffuse hemorrhage (figure 6). Slight diffuse hemorrhage was noted in one of the 14 patients in stage I and in nine of the 40 patients in stage II. Moderate or marked focal hemorrhage was found in eight and three hearts from those in stage II, respectively. Of the pa-
patients receiving SICT, moderate and marked diffuse hemorrhage was found in nine and six of the 18 hearts of those in stage 11, respectively (figure 6). Thus, it is reasonable that hemorrhagic myocardial infarction be defined as moderate or marked diffuse bleeding in the infarct area. There is little doubt that recanalization and/or large doses of urokinase produced the hemorrhagic infarction observed.

Myocardial hemorrhage is observed after experimental reperfusion following ligation of the coronary artery\(^2\text{-}^9\) and occasionally after coronary artery bypass in patients with AMI\(^10\text{-}^11\). It is generally considered that hemorrhage after SICT in human and experimental AMI may not be the result of streptokinase per se, but rather the consequence of early myocardial reperfusion after SICT\(^9,^10\) In the present study, most of patients who underwent SICT showed diffuse hemorrhage in the infarct area. However, 43% of patients had the same anatomic characteristics before and after SICT. In the five patients with complete occlusion before and after SICT, autopsy showed diffuse hemorrhage and complete occlusion of the infarct-related coronary artery. It is therefore difficult to explain diffuse hemorrhage as being the result of reperfusion alone in case of patients with AMI receiving SICT. In patients without complete occlusion after SICT, urokinase reached the infarct tissues after both successful and unsuccessful SICT. In patients with complete occlusion before and after SICT, a large amount of urokinase (over 720,000 U) was injected. Three patients (Nos. 13, 18, and 19) had cineangiographically visible collaterals. In these patients, urokinase probably reached the infarcted tissues through the collateral flow and caused diffuse hemorrhage. However, in two other patients (Nos. 4 and 7), cineangiography revealed no collaterals. Although the precise mechanism of the diffuse hemorrhage in these two patients remains to be determined, it may well be that natural recanalization that appeared transiently and/or collateral flow that was not detected cineangiographically led to the hemorrhage when a large amount of urokinase was given. Thus, in addition to reperfusion, a large dose of urokinase is also an important factor in the pathogenesis of hemorrhagic infarction in human AMI.

In animal preparations of complete reperfusion after coronary ligation, diffuse and definite hemorrhage appears within 3 hr after reperfusion (in stage I of the present study)\(^3,^5,^9\) In human AMI, the recanalized artery is usually markedly stenotic (90% to 99%), so that there is a definite difference between effects of

![FIGURE 3](image_url). Relationship between infarcted and hemorrhagic areas. Infarct area at the microscopic level (light dots) and macroscopic hemorrhagic area (dark dots) were traced. Note hemorrhage is seen within the boundaries of the infarct. A = anterior; P = posterior.

![FIGURE 4](image_url). Bleeding in tissue areas without infarction. Throughout the perimysium, red blood cells invaded continuously from the bleeding infarct area into noninfarcted tissue.
SICT in humans and those in animal preparations without stenosis in the recanalized artery. The present study revealed that in patients with shock after SICT, marked diffuse hemorrhage was rare, but in those without shock the degree of hemorrhage was variable. Therefore, low perfusion pressure in the distal portion of the infarct-related coronary artery due to the stenosis after SICT and shock appears to be an important determinant of the severity of bleeding and would explain the time delay of bleeding in human AMI compared with that in an animal preparation.

Hemorrhagic infarction appeared in most patients with or without recanalization, in the late acute stage of AMI (stage II) when SICT was administered from 2 to 7 hr after the onset of AMI. The number of patients with cardiogenic shock before administration of urokinase was 11 of 30 patients, a number greater than that in any reported series of patients receiving SICT. The fact that all the subjects underwent autopsy has to be considered, but diffuse hemorrhage was noted in most patients with or without shock before SICT. Marked diffuse hemorrhage appeared mostly in the patients in whom thrombolysis was successful but who did not develop shock immediately after SICT. Angiographically, our 30 patients did not differ significantly from other patients undergoing SICT. This suggests that a hemorrhagic infarct similar to that seen in our

### FIGURE 5
Vessels and bleeding in hemorrhagic infarction. *Top,* Hemorrhage from capillaries into the intermyocytes. Arrow heads indicate capillaries. *Bottom,* Hemorrhage from sinusoid (arrow head) and venule (arrow) in the perimysium. (Hematoxylin-eosin stain, original magnification ×400.)

### TABLE 2
Macroscopic findings of hemorrhagic myocardial infarction according to interval from SICT to death

<table>
<thead>
<tr>
<th></th>
<th>Stage I</th>
<th>Stage II</th>
<th>Stage III</th>
<th>Total</th>
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</thead>
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<tr>
<td>No diffuse hemorrhage</td>
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<td>0</td>
<td>4 (2\textsuperscript{a})</td>
<td>8</td>
</tr>
<tr>
<td>Slight diffuse hemorrhage</td>
<td>3 (2\textsuperscript{b})</td>
<td>3 (1\textsuperscript{b})</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Moderate diffuse hemorrhage</td>
<td>0</td>
<td>9 (5\textsuperscript{c})</td>
<td>0</td>
<td>9</td>
</tr>
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<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Total number of patients</td>
<td>7</td>
<td>18</td>
<td>5</td>
<td>30</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Number of patients with slight focal hemorrhage.
\textsuperscript{b}Number of patients with moderate focal hemorrhage.
\textsuperscript{c}Number of patients with marked focal hemorrhage.
patients is present in many of those surviving AMI and SICT, with or without recanalization and with or without shock.

Hemorrhage after SICT occurred mostly within the boundaries of the infarct. However, microscopic observation sometimes showed focal extension of bleeding into areas without infarct, although the extension was limited to within 3 mm of the margin of the infarct. In cases of ischemia, the microvascular cellular damage slowly followed damage to the myocytes. Hemorrhage became definite in the late acute stage of human AMI, when myocytes showed already irreversible cellular damage. This indicates that hemorrhage occurs in tissues already markedly damaged and that it rarely expands beyond the borders of the infarct zone. However, we cannot deny the possibility that the adjacent islands of viable myocardium may be jeopardized because of increased interstitial pressure induced by severe intramyocardial hemorrhage and subsequently diminished coronary perfusion. Hemorrhage may aggravate the ischemia within the area of damaged tissue. This speculation has been confirmed in animal preparations of reperfusion after ischemia.

Our data revealed that most of the patients undergoing autopsy after receiving SICT had transmural myocardial infarction. In three patients (Nos. 15, 20, and 21), fatal transmural AMI occurred despite recanalization 2 hr after the onset of AMI. Subendocardial infarction was evident in only two of 30 patients (Nos. 24 and 25). In one, the infarct-related coronary artery showed 90% stenosis before SICT. This suggests the limitations of SICT treatment for AMI when it is administered over 2 hr after the onset of AMI.

It is concluded that the incidence of hemorrhagic infarction after SICT in man is directly related to the amount of time from SICT when SICT is done between 2 and 9 hr after the onset of symptoms. It appears in most cases over 4 hr after SICT, regardless of recanalization, and is replaced by fibrosis after 3 to 4 weeks. The time delay is probably the result of low perfusion pressure in the portion distal to the severely stenosed coronary artery after SICT. With the advent of increased use of SICT for treatment of AMI, further investigation is warranted.

![FIGURE 6. Comparison of the frequency of hemorrhagic infarction in patients who did and did not undergo SICT. C = 60 patients with myocardial infarction who did not undergo SICT. All had a large transmural myocardial infarction and were from the same institutions as the group with SICT. Coronary cineangiography was not done in any of them in the early acute stage of AMI.](http://circ.ahajournals.org/doi/fig/10.1161/01.CIR.63.2.756)
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References
A clinicopathologic study of patients with hemorrhagic myocardial infarction treated with selective coronary thrombolysis with urokinase.
H Fujiwara, T Onodera, M Tanaka, T Fujiwara, D J Wu, C Kawai and Y Hamashima

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