HEMORRHAGIC MYOCARDIAL INFARCTION AFTER REPERFUSION DETECTED BY X-RAY CT

—Experimental and Clinical Study—

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The purpose of this study was to determine whether computed tomography (CT) can detect hemorrhagic infarction occurring after intracoronary thrombolytic therapy (ICT) for acute myocardial infarction (AMI).

In an experimental study, 12 dogs underwent 2–4 h of left anterior descending artery (LAD) occlusion, followed by reperfusion, and infusion of contrast material into the LAD. After CT examination, the heart was cut into transverse sections. A good correlation was obtained between the CT-enhanced area and the hemorrhagic area in the sliced heart section ($r=0.895$, $p<0.001$).

In a clinical study, we applied CT immediately after ICT in 25 patients with AMI. In 13 of 25 patients, the CT showed post-ICT myocardial enhancement areas. To evaluate the relationship of the enhancement areas shown by CT to the viability of the myocardium, we compared enhancement areas by CT with the corresponding perfusion defect areas of Thallium-201 imaging (SPECT) one month later. There was no significant correlation between the enhancement areas and perfusion defect areas ($r=0.38$, $p>0.1$). The SPECT defect areas were consistently smaller than the CT enhancement areas.

These results indicate that CT can detect hemorrhage into the myocardium after ICT, and that after ICT half the AMI patients showed hemorrhagic infarction. However, hemorrhage did not cause complete deterioration of the myocardium.

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THE reperfusion of acutely ischemic myocardium by intracoronary administration of a fibrinolytic agent (urokinase) is now widely used for the treatment of acute myocardial infarction. A potential adverse effect of intra-coronary thrombolysis therapy (ICT) is hemorrhagic infarction which, it is thought, may increase infarct size¹ and/or

delay healing in the necrotic myocardium?

In experimental studies, hemorrhagic infarction frequently occurs with coronary reperfusion for acutely ischemic myocardium^{1–7}. However clinically, only a few hemorrhagic infarctions have been reported after ICT for acute myocardial infarction as diagnosed by angiography^{8–10} or autopsy^{11–13}.

One case of acute myocardial infarction we studied by computed tomography (CT)

Key words:

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Fig. 1. Computed tomogram of the heart taken immediately after intra-coronary thrombolysis therapy. Anterolateral wall of the left ventricle and interventricular-septum is enhanced (→).

after ICT showed myocardial enhancement (Fig. 1), but there have been no reports regarding whether CT can detect hemorrhage in the myocardium, i.e. hemorrhagic infarction. In the present study, we conducted experimental research to determine whether CT can precisely detect hemorrhage in the myocardium. We also aimed to elucidate the frequency and determinants of hemorrhagic infarction detected by CT immediately after ICT in clinical cases.

METHODS

1. Experimental study

Twelve mongrel dogs each weighing 12–26 kg were anesthetized with pentobarbital-Na (25 mg/kg). The heart was exposed by a left lateral thoracotomy through the fourth intercostal space. The left anterior descending artery (LAD) was exposed just below the first diagonal branch and occluded with a small bull-dog clamp. The branches of the left circumflex artery and right coronary artery located close to the LAD were also blocked.

Two electrocardiograms were recorded with the bipolar standard lead I and a unipolar electrode attached to the apex of the left ventricle. The occurrence of myocardial infarction was detected by new ST segment elevation and abnormal Q waves. After 2–4 h of occlusion, the myocardium was reperfused by releasing the clamp. For ven-

tricular arrhythmias with coronary occlusion and reperfusion, lidocaine was administered at 1 mg/min after 50-mg bolus injection. The ischemic myocardium was reperfused for 10–15 min, then a canula was inserted directly into the LAD and 10–20 ml of contrast material (Iopamiron370® -Iopamidol, 370 mg of I/ml) was injected in 10 min. About 10–20 min later, the dog was sacrificed, and the heart was excised and suspended in a water-filled box for CT. After CT examination, the heart was fixed in formalin and cut into 1 cm thick transverse slices. In 2 cases, the CT-enhanced area was compared with the infarct size using the triphenyl-tetrazolium chloride (TTC) technique¹⁴.

Hemorrhage was detected macroscopically and microscopically in the sliced heart muscle. Myocardium clearly stained by contrast material, as judged by 3 examiners, was defined as myocardial enhancement. At the same time, the CT value of the enhancement area was measured. The area of the contrast enhancement (EHA) by CT and the macroscopically hemorrhagic area (HA) in sliced sections of the heart were planimetered, and the EHA and HA were compared.

2. Clinical study

The subjects were 25 patients with acute myocardial infarction caused by total occlusion (TIMI 0) or very severe stenosis (TIMI 1) of the left coronary artery. They were 20 men and 5 women ranging in age from 42 to 75 years (mean age, 59 years). Patients with TIMI 2 and 3 in the coronary angiogram before ICT, and cases of unsuccessful reperfusion by thrombolytic agents were excluded. (According to the TIMI study¹⁵ the TIMI grades were as follows. TIMI 0: no perfusion, TIMI 1: penetration without perfusion, TIMI 2: partial perfusion, TIMI 3: complete perfusion). In cases of successful reperfusion, the left coronary artery was angiographed using 60–70 ml of contrast material (Iopamiron370®). The heart CT was examined about 20–30 min after ICT in all patients. We defined myocardial enhancement as clearly stained myocardium by contrast material in the CT view. The CT values of the enhanced area, and the non-infarcted area (area perfused by non-occluded branch of the left coronary artery) were

Fig.2. The calculation of %EH in CT view and %D in SPECT view

%EH: x/y

x: circumference of the myocardial enhancement area

y: circumference of the entire left ventricular wall

%D: a/b

a: circumference of the complete defect area

b: circumference of the entire left ventricular wall

measured.

To evaluate the consequences of hemorrhagic infarction in the patients with myocardial enhancement detected by CT, the spect image (SPECT) and the planar image (PLANAR) of the resting $^{201}\text{Thallium}$ scan were performed one month after the CT. In the CT view, in which the widest myocardial enhancement area was present, the ratio of the circumference of the myocardial enhancement area to the circumference of the entire left ventricular wall was calculated (%EH). In the horizontal view of SPECT, approximately the same view as the CT, the

ratio of the circumference of the complete defect area to the circumference of the entire left ventricle was calculated (%D). The complete defect area was traced using the PLANAR view. The %EH and %D were compared (Fig. 2).

In both the experimental and clinical studies, the CT was examined with CTW1000[®] (Hitachi), at 120 KV, for 4.5 sec for each slice at intervals of 1 cm.

RESULTS

1. Experimental study

Fig.3. Myocardial enhancement area by CT and the macroscopic hemorrhagic area in the same dog

- A: CT view: Extravasation of the contrast material is seen (myocardial enhancement).
 B: Same slice of the heart with the CT view
 Black hemorrhagic area is spread from the anterior wall of the left ventricle to the interventricular-septum, especially in the endocardial side (→).

Eight of the 12 dogs had gross hemorrhages in the left ventricular anterior wall and interventricular septum, mainly on the endocardial side. In the CT view of the same slice as in the fixed heart, the area of myocardial enhancement resembled the macroscopic hemorrhagic area (Fig. 3). In the area of gross hemorrhage, interstitial hemorrhage was found microscopically (Fig. 4). Myocardial enhancement was present in three or 4 slices of the CT views for each case, and the CT values of the myocardial enhancement areas and non-infarcted areas were $91-220$ (156 ± 54), and $50-64$ (57 ± 8) respectively.

In all cases of gross hemorrhage in the sliced heart, there was always EHA in the CT view. The EHAs by CT and the HAs of the sliced heart were highly correlated ($r=0.895$, $p<0.001$). The EHA tended to be larger than the HA (Fig. 5).

In the 2 cases in which infarct size by the TTC technique was compared with the CT-enhancement area, the CT-enhancement area was smaller than the infarct area and the macroscopic hemorrhagic area was smaller than the CT-enhancement area. In these 2 cases, the CT values of the EHA and non-enhanced area in the infarcted area were $106-200$ and $60-66$, respectively. In 4

Fig.4. Microscopic interstitial hemorrhage
Erythrocytes are scattered in the intermyocardial space.

Fig.5. The relation of the enhancement area by CT (EHA) to the macroscopic hemorrhagic area in the sliced heart (EH)
Good correlation is found between EHA and EH. EHA tends to be larger than EH.

cases in which the CT showed no enhancement, the CT values of the infarcted areas were 50–58.

2. Clinical study

CT showed myocardial enhancement immediately after ICT in 13 cases (Group 1), but in the 12 other cases there was no

enhancement (Group 2) (Table I). Of the 13 cases in group 1, intramyocardial contrast material detected by angiogram appeared in only two. In group 1, the myocardial enhancement areas were present in three or more slices of CT, and the CT values of the enhancement areas and the non-infarcted areas were 104–231 (160 ± 43), and 46–60 (53 ± 6), respectively. In group 2, the CT values of the infarcted but non-enhanced areas were 67–87 (75 ± 6).

In group 2, there were two patients with early reperfusion (within 2 h after the onset of myocardial infarction), and three other patients with fair or good collaterals to the occluded vessels. Excluding these five cases in group 2, all of the 13 cases of group 1 and seven cases of group 2 had no or poor collaterals to the occluded vessels, and their occluded vessels were reperfused more slowly (more than 2 h after the onset of myocardial infarction). There was no difference between the 13 patients in group 1 and the seven patients in group 2 in the time from the onset of myocardial infarction to reperfusion, in the total units of urokinase, or in the amount of contrast material.

In the 13 patients in group 1, the correlation was not good between the %EH by CT

TABLE I CLINICAL FEATURES OF 25 CASES WITH ACUTE MYOCARDIAL INFARCTION

No.	Age	Sex	EH by CT	Contrast in LV	AMI related coronary artery	TIMI	Collaterals	Time for Recanalization	Total Units of UK	Max CK
	years							hours	×10,000 units	units
<i>Group 1</i>										
1	62	M	+	+	LAD 7	0	0	4	72	4195
2	74	M	+	—	LAD 6	0	0	3	48	5005
3	53	M	+	—	LAD 6	0	0	3.3	TPA	7720
4	63	M	+	—	LAD 6	0	0	3.5	120	5592
5	54	F	+	—	LAD 6	0	P	2.8	144	7775
6	67	M	+	—	LAD 6	1	P	3	72	5730
7	48	M	+	+	LAD 6	0	P	4.1	72	5010
8	57	M	+	—	LAD 6	1	P	4.5	48	3801
9	47	M	+	—	LAD 6	0	P	4.5	120	7855
10	60	M	+	—	LCX 11	0	0	4	96	4240
11	73	M	+	—	LAD 6	0	0	3.5	72	5822
12	62	F	+	—	LAD 7	0	0	4	72	1235
13	54	M	+	—	LCX 13	0	0	3	120	4686
<i>Group 2</i>										
14	57	M	—	—	LAD 6	0	0	3.5	96	8415
15	66	M	—	—	LAD 6	1	0	6	144	4415
16	65	F	—	—	LAD 6	0	0	5	48	2271
17	51	M	—	—	LAD 7	0	F	4.5	120	1182
18	59	F	—	—	LAD 7	0	P	5	120	4070
19	59	M	—	—	LAD 7	0	0	4.2	120	1321
20	42	M	—	—	LAD 6	1	F	2.0	60	1941
21	75	M	—	—	LAD 6	1	F	3.2	72	1368
22	68	M	—	—	LCX 11	1	0	5.5	96	8505
23	59	F	—	—	LAD 7	0	P	1.5	96	370
24	48	M	—	—	LCX 13	0	0	4.5	96	884
25	56	M	—	—	LAD 6	0	G	4	48	6345

EH: Enhancement of myocardium by CT

Contrast in LV: Persistent pooling of the left ventricle by angiography after ICT

LAD: Left anterior descending artery

LCX: Left circumflex artery

Collaterals: Collaterals to the occluded coronary artery

O: No collaterals, P: poor collaterals, F: fair collaterals, G: Good collaterals

UK: Urokinase (×10,000 units)

CK: Creatin phosphokinase (I.U.)

TIMI: Definition of perfusion of the infarct related artery in the TIMI trial¹⁵

0: no perfusion

1: penetration without perfusion

2: partial perfusion

3: complete perfusion

and the %D by SPECT ($r=0.38$, $p>0.1$), and the %D was no larger than the %EH in any case (Fig. 6).

DISCUSSION

In experimental studies, reperfusion of occluded coronary arteries frequently results

in hemorrhagic infarction, especially in cases of more than 2 h of coronary occlusion. However, in clinical cases, there have been few reports of hemorrhagic infarction after coronary thrombolysis, found only by autopsy^{11,12} or angiographic examination⁸⁻¹⁰. Angiographically, the persistent pooling of contrast material in the myocardium is

Fig.6. Relation of %EH by CT and %D by SPECT in 13 patients with hemorrhagic infarction

There is no good correlation between %EH and %D. %D is not larger than %EH in any case.

thought to indicate hemorrhage in the myocardium, and Yamamoto and associates reported that only 10 of 74 cases (14%) had angiographic hemorrhage immediately after coronary thrombolysis.⁹ In our study, persistent pooling of contrast material occurred in only 2 of 25 cases (8%). The very low frequency of clinical hemorrhagic infarction may be the consequence of inappropriate methods for detection of myocardial hemorrhage.

X-ray CT has been validated as a useful method for diagnosing myocardial infarction. Masuda and associates examined CT in 103 patients with myocardial infarction, and found an initial filling defect and late enhancement of the infarcted myocardium using intravenous injection of contrast material!⁶ They speculated regarding the mechanism of late enhancement that micro-

Fig.7. Case. Intracoronary thrombolysis therapy for acute myocardial infarction

- A: Coronary angiogram of right anterior oblique (RAO) view immediately after admission: Left anterior descending artery (LAD) is totally occluded in the proximal portion (→).
- B: Coronary angiogram of RAO view after intra-coronary administration of 720,000 units of urokinase: the LAD is patent with a high degree of stenosis where the vessel was totally occluded in Fig. A.
- C: RAO view and D: LAO view of the heart: Contrast material is seen in the anterolateral wall of the left ventricle (C), and the interventricular-septum (D).

vascular damage in the infarcted area may allow the extravasation of contrast material. However, this late enhancement by CT was not examined immediately after thrombolytic therapy. Moreover, there has been no report of CT immediately after reperfusion by thrombolytic therapy.

A case with acute myocardial infarction alerted us to examine CT immediately after coronary thrombolysis in 1987. A 62-year-old man was admitted with chest pain of 2 h duration. An immediate coronary angiogram demonstrated complete occlusion of the mid-portion of the left anterior descending artery (LAD #7, Fig. 7A). With intracoronary administration of 720,000 units of urokinase, the LAD became patent with a high degree of stenosis (Fig. 7B). However, after a while, the ST segment in the precordial leads re-elevated. An angiogram demonstrated a still patent LAD, but contrast material appeared in the myocardium of the anterolateral wall of the left ventricle and inter-ventricular septum (Fig. 7C, D). This view of extravasation of contrast material in the myocardium has been thought to indicate hemorrhagic infarction.^{7,9,10} CT of the chest immediately after ICT showed enhancement of the myocardium in the same portion as the extravasation (Fig. 1).

This outcome showed that X-ray CT could be used to detect hemorrhagic infarction after ICT. Therefore, we tried to detect hemorrhage in the myocardium by CT.

We first investigated whether CT could detect hemorrhage in the myocardium in mongrel dogs. As reported, with 2–4 h occlusion of the LAD followed by reperfusion, hemorrhage in the myocardium occurred in various degrees in 8 of the 12 dogs. Fishbein and associates¹⁷ found that 5.5 h of coronary occlusion caused vascular injury within the myocardial necrotic area, and that reperfusion caused hemorrhage in 50–60% of the area of preexisting vascular injury. In our study of 2 experimental cases with the TTC technique, the myocardial hemorrhagic area was smaller than the CT-enhancement area, and the CT-enhancement area was smaller than the infarct area detected by TTC. The area of the gross hemorrhage of sliced heart, which appeared dark, was well correlated with the area of myocardial enhancement shown by CT ($r=0.895$). The re-

gression equation of the relation between the area of the gross hemorrhage and the enhancement area by CT was $y=0.76x$ (x : enhancement area by CT, y : hemorrhagic area).

In the 8 cases of myocardial gross hemorrhage of sliced heart, CT always showed myocardial enhancement whose CT values were over 91. And, in 4 other dogs that had no gross hemorrhage in the sliced heart, CT showed no enhancement of the myocardium whose CT values were under 66. In the 2 experimental cases with the TTC technique, the CT values of the enhancement areas were over 100, whereas those of non-enhanced areas within the infarcted areas were 60–66. This result suggested that CT-enhancement cannot occur in the infarcted area without vascular injury and myocardial hemorrhage. It also showed that CT can differentiate hemorrhagic infarction from non-hemorrhagic infarction.

Our study shows that myocardial enhancement by CT does not indicate hemorrhage itself but indicates the area of injured vessels caused by ischemia and extravasation of contrast material (molecular weight 777). According to the regression equation, the hemorrhagic area in the slice is about 3/4 as large as the enhancement area by CT. This does not contradict Fishbein's report. Thus, the enhancement of the myocardium by CT is an indirect sign of the presence of myocardial hemorrhage.

Our clinical study was not conducted under the same conditions as the experimental study. However, considering the volume of contrast material, injection speed, and the same CT values of the enhancement area, we need not be concerned about an artificial effect in the result.

In our clinical studies, CT enhancement was detected in 13 patients, and there was no enhancement in 12 patients, including 2 with early reperfusion within 2 h of onset of myocardial infarction and 3 patients with good or fair collaterals to the occluded vessels. In the 13 patients with enhancement, the occluded vessels had poor or no collaterals and were reperfused more than 2 h after the onset. As reported in the previous experimental study, myocardial hemorrhage was associated with severe myocardial necrosis and vascular injury, and it seldom occur-

red in cases with early reperfusion or when the occluded vessels had good collaterals? In our clinical study, in 7 patients with late reperfusion and poor or no collaterals to occluded vessels, no enhancement was detected by CT. Comparing these 7 cases without enhancement to the 13 cases with enhancement, there was no difference in the time from the onset to the reperfusion, total amount of contrast material, or in the total units of urokinase. Other determinants may contribute to the occurrence of hemorrhage, so further investigation is needed.

The frequency of hemorrhagic infarction detected by CT in this clinical study was lower than previously reported. Three patients in group 2 had CT values of the infarcted areas over 80, but clear staining of the myocardium was not detected by CT. In these 3 cases, the possibility of the extravasation of a small amount of the contrast material to the myocardium cannot be excluded.

In previous extension studies some investigators found that hemorrhage caused extension of the infarction, but others reported that hemorrhage with reperfusion occurred only within necrotic tissue where there had already been severe vascular injury and irreversible myocardial injury before reperfusion^{2,17,18}. To investigate whether the gross hemorrhagic area shown by CT would become completely necrotic, a ²⁰¹Tl myocardial scintigram (SPECT) was made one month later.

There was no correlation between the complete defect area seen in the horizontal view of SPECT and myocardial enhancement area shown by CT. The completely necrotic area tended to be narrower than the myocardial enhancement area. So the area of vascular injury and hemorrhage will not necessarily become completely necrotic from the endocardial to the epicardial side.

In a previous experimental study, Fishbein reported that 52% of the necrotic area contained injured vasculature, and the hemorrhagic area constituted 50–60% of the region with injured vessels¹⁷. Kloner also found that hemorrhage constituted approximately 40% of the mid ventricular infarct area¹⁸. According to these reports, the necrotic region may spread to 2 or 3 times the area of vascular injury and hemorrhage

detected by CT. However, we have found that the necrotic area is not as large as these experimental studies showed. Maybe there were “islands” or “peninsulas” of ischemic but viable myocardium adjacent to the necrotic myocardium especially on the epicardial side.

In conclusion, CT can detect hemorrhage with vascular injury after coronary thrombolysis; and clinically, hemorrhagic infarction occurs more frequently than previously reported. Acute myocardial infarction with early reperfusion and occluded vessels with good collaterals do not incur hemorrhage. The hemorrhagic area detected by CT does not necessarily become completely necrotic later. Moreover, the hemorrhage detected by CT may indicate an indirect feature of clinical reperfusion injury. Further investigation is required.

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