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Histopathological Study of Cardiac Rupture Following Myocardial Infarction With and Without Thrombolytic Therapy

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Abstract

The characteristics of cardiac rupture associated with thrombolytic therapy for acute myocardial infarction (MI) were studied in the hearts of 10 autopsy patients, 7 men and 3 women aged 41–80 years (mean 59.9±13.2 years), who died of rupture of the free wall of the left ventricle following acute MI. The site of rupture was examined histologically and the percentage areas of living myocytes, the processes of organization, necrosis and degeneration, and hemorrhage were compared in four patients who received thrombolytic therapy (group R) and six patients without thrombolytic therapy (group N). There were four pathological findings at the site of rupture : necrosis, neutrophil infiltration, hemorrhage, and evidence of the process of absorption. Group R consisted of two patients with hemorrhage, one with absorption, and one with unsuccessful reperfusion and neutrophilic infiltration. Group N included three patients with necrosis, two with neutrophilic infiltration, and one with hemorrhage. The percentage area involved by necrosis and degeneration was significantly lower in group R than in group N. Therefore, local stress produced by more surviving myocardium around the smaller necrosis area and the weakness of myocardium due to hemorrhage and absorption may provoke cardiac rupture in acute MI patients receiving thrombolytic agent.

Key Words

cardiac rupture, thrombolysis, acute myocardial infarction, reperfusion injury, myocardial hemorrhage

INTRODUCTION

The major causes of death in patients with acute myocardial infarction (MI) are heart failure, arrhythmias, and cardiac rupture. Many patients with acute MI currently receive thrombolytic therapy which is widely reported to be effective in improving the outcome[1–7]. Improved survival rate

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Table 1 Clinical profiles of acute myocardial infarction patients

Patient No.	Age (yrs)	Sex	MI location	No. of CAD	Ruptured days after MI	Mode of rupture	Status at rupture	Old MI
N1	68	M	Anteroseptal	1	<1	B	Irritable state	+
N2	44	M	Anterolateral	1	<1	B	Rest	−
N3	80	M	Anteroseptal	1	4	O	Chatting	−
N4	58	M	Anteroseptal	3	<1	B	Urination	−
N5	41	F	Anterolateral	2	2	O	Rest	−
N6	49	M	Anterior	2	5	B	Rest	+
R1	61	M	Posterolateral	2	4	B	Defecation	+
R2	69	F	Anterolateral	1	6	B	Rest	−
R3	75	M	Posterior	1	3	B	Hypertension	−
R4	53	F	Anterolateral	1	7	O	Defecation	−

N=patients without thrombolytic therapy; R=patients with thrombolytic therapy; M=male; F=female; CAD=coronary artery disease; B=blowout type; O=oozing type; MI=myocardial infarction

following reperfusion therapy is achieved, but whether the risk of cardiac rupture is increased or decreased is controversial[8–14]. Hemorrhage seems to be the major side effect of thrombolytic therapy, and there may be an association between thrombolytic therapy and cardiac rupture[12,16]. We investigated the relationship between cardiac rupture and thrombolytic therapy in a retrospective autopsy study of hearts from patients with acute MI who died of cardiac rupture and from patients who had been treated with or without thrombolytic therapy.

MATERIALS AND METHODS

This study reviewed 138 autopsy patients with MI seen between 1976 and 1991 at the Juntendo University Hospital. Thirteen of the 138 cases (9.4%) showed cardiac rupture following MI. Thrombolytic therapy has been given since 1987. Before 1987, eight of the 99 autopsy cases (8.1%) had cardiac rupture. After 1987, five of 39 cases (12.8%) had cardiac rupture.

This study included 10 autopsy cases with extensive examinations in seven men and three women aged 41 to 80 years (mean 59.9±13.2 years). All suffered rupture of the free wall in the center of the acute MI area. **Table 1** shows the clinical profiles of the patients. The MI was located in the anteroseptal (3), anterolateral (4), anterior (1), posterolateral (1), and posterior (1) areas. Six patients had single-vessel disease, three had double-vessel disease, and one had triple-vessel disease. Three of the 10 patients had a medical history of old MI and angina pectoris, while the others had no previous symptoms signs of ischemic heart disease. Four patients were treated with urokinase, a thrombolytic agent (group R), and six were not (group N). The total dose of urokinase ranged from 72 to 120×10^4 IU. The method of injection and combined therapy used is shown in **Table 2.**

The hearts obtained at autopsy were fixed with 10% buffered formalin. The site of rupture was identified, then transverse sections were made of the ventricle including the sites of rupture. Tissue blocks were embedded in paraffin and cut in 5 μm-thick slices. After staining by hematoxylin and eosin (H-E), azan, and pentachrome, the sections were examined under the microscope.

The site of myocardial rupture was assessed by estimating the percentage of the infarction area (5 mm from the rupture canal in both sides) which demonstrated coagulation and contraction necrosis, degeneration, the process of organization, living myocytes, and hemorrhage, using an automatic image analyzer, Zeiss, IBAS-2000 system. These parameters were compared in groups R and N.

Statistical analysis was performed using Student's *t*-test, and the chi-square test. A p level less than 0.05 was accepted as statistically significant.

RESULTS

The incidence of cardiac rupture following MI did not differ significantly in the patient groups R and N.

Cardiac rupture occurred within 7 days of MI onset in all 10 patients, apparently earlier in group N than in group R. Recanalization was unsuccessful in

Table 2 Therapeutic methods and result of thrombolysis

Patient No.	Duration of injection	Methods	Dose ($\times 10^4$IU)	PTCA	Recanalization	Patency (at autopsy)
R1	2 hrs	IC	72	−	+	+
R2	4 days	IC	96	−	−	−
R3	10 hrs	IV	96	−	+	+
R4	2 hrs	IC+IV	96+24	+	+	+

IC=intracoronary; IV=intravenous; PTCA=percutaneous transluminal coronary angioplasty. Other abbreviation as in Table 1.

one of the four patients in group R.

Various histopathologic changes occurred in the MI area including coagulation necrosis and/or contraction band necrosis, colliquative myocytolysis, hemorrhage, cell infiltration, and evidence of organization including absorption and fibrosis. These findings did not differ qualitatively between the two groups. However, the quantity and distribution of these findings differed in groups R and N. For example, the process of organization involved the entire MI area in group R, but had begun in the periphery of the MI area in group N.

Major pathologic findings at the sites of rupture were categorized into four types according to the predominant finding : necrosis (**Fig. 1**), neutrophil infiltration (**Fig. 2**), hemorrhage (**Figs. 3, 4**), and absorption (**Fig. 5**). Group N consisted of three cases of necrosis, two cases of neutrophil infiltration, and one case of hemorrhage. Group R consisted of hemorrhage in two cases, neutrophil infiltration in one case of unsuccessful recanalization, and absorption in one case. Hemorrhage occurred in more cases in group R than in group N, but the difference was not significant (**Table 3**). However, the hemorrhage in group R was more massive, stratified and widespread than that in group N (**Table 4, Fig. 4**).

Table 4 shows the percentage area of the site of rupture involved in each type of pathological finding. The percentage area demonstrating necrosis and degeneration was significantly smaller in group R than in group N (R : 68.6±15.5% vs N : 88.6±8.3%, $p<0.05$). The area showing living myocytes was significantly larger in group R than in group N (R : 14±8.5% vs N : 3.0±3.8%, $p<0.05$). The area of contraction band necrosis was higher in group R than in group N (R : 1.06±1.06% vs N : 0.15±0.23%), but the difference was not significant. The area of hemorrhage was larger in group R than in group N (R : 13.9±12.6% vs N : 8.4±8.6%), but the difference was not significant.

DISCUSSION

Reperfusion therapy can accelerate the heating of an MI[16-18], because of the early release from myocyte anoxia, reperfusion injury, hemorrhage, *etc.* The beneficial effect of reperfusion on the healing of MI in humans is generally accepted despite the lack of definite evidence. However, a study of coronary reperfusion in animals has revealed the acceleration of necrosis[19], the proliferation of granulation tissue into the MI area[20], the wave front phenomenon[21,22], less prominent cellular infiltration into the reperfused infarcts[23], increased contraction band necrosis of myocytes[21,24,25], and widespread hemorrhage[26-29].

Cowan *et al.*[30] recently studied the postmortem histologic changes in patients with acute MI treated with reperfusion therapy and found that early therapeutic coronary reperfusion altered the pattern of myocardial injury and the cellular response to evolving MI, so that the classical criteria for MI healing could not be applied.

Our study showed that the histological features of the ruptured site differed between group N (natural course) and group R (with reperfusion therapy). Most cases in group N showed neutrophil infiltration or necrosis in the myocardium affected by the infarct. All but one case without recanalization showed hemorrhage or the absorption process in group R. Therefore, the mode of cardiac rupture occurring after successful reperfusion may differ from that occurring during the natural course of MI or in the absence of successful reperfusion.

We found a smaller area of necrosis and degeneration at the site of rupture in group R than in group N. Living myocytes, hemorrhagic lesion and absorption lesion were more prominent in group R than in group N.

The occurrence of a hemorrhagic MI following

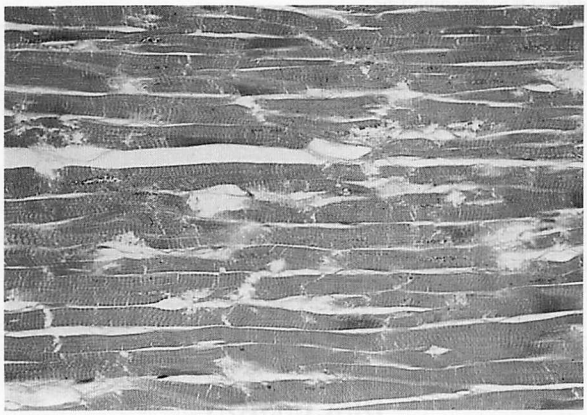

Fig. 1 Coagulation necrosis (patient N6)

Myocyte nuclei have disappeared and the myocytes are eosinophilic. Stain of H-E (×200).

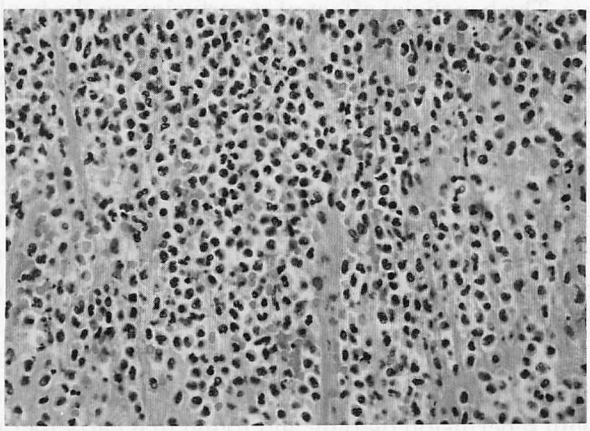

Fig. 2 Neutrophil infiltration (patient N5)

Numerous cell infiltrations in the MI area. Stain of H-E (×200).

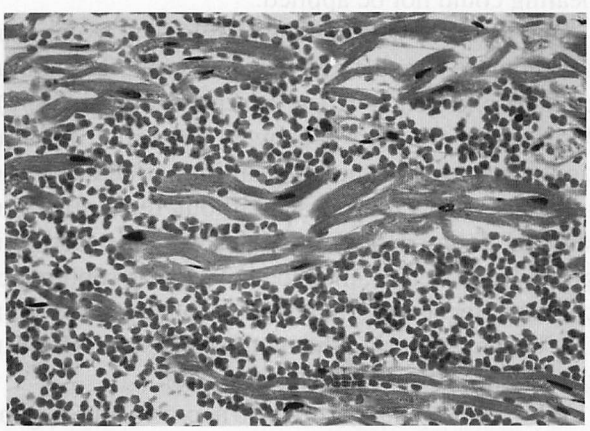

Fig. 3 Hemorrhagic infarction (patient N1)

Hemorrhage is seen in the infarct area. Stain of H-E (×200).

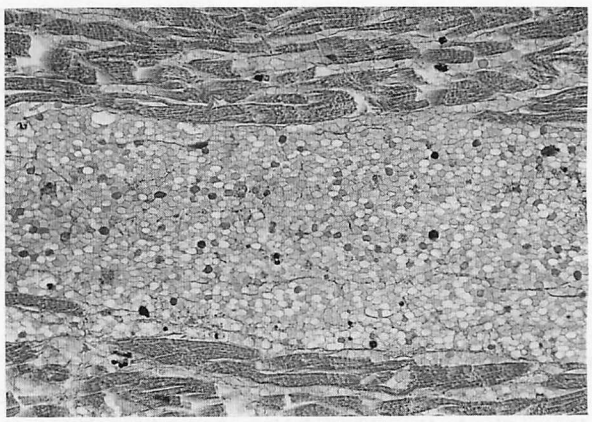

Fig. 4 Reperfusion hemorrhage (patient R4)

Massive hemorrhage was separated the myocyte bundle. Stain of H-E (×200).

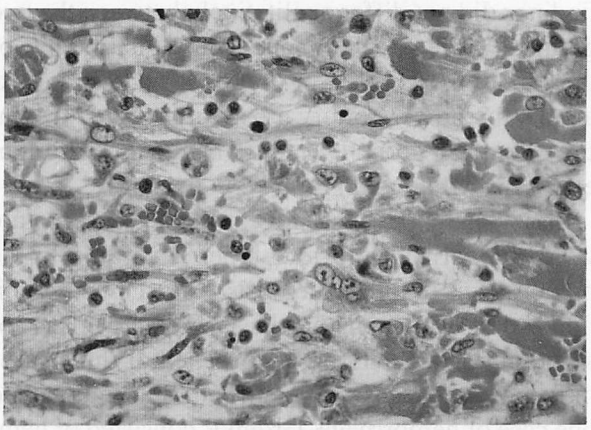

Fig. 5 Absorption process after MI in patient R1

Macrophages form scattered vacant areas in the MI area. Stain of H-E (×200).

Table 3 Histological features at rupture site

Patient No.	HW (g)	Major histology at rupture site
N1	400	Hemorrhage
N2	360	Necrosis
N3	390	Neutrophil infiltration
N4	490	Necrosis
N5	360	Neutrophil infiltration
N6	500	Necrosis
R1	350	Absorption process
R2	420	Neutrophil infiltration
R3	400	Hemorrhage
R4	410	Hemorrhage

HW = heart weight. Other abbreviations as in Table 1.

Table 4 Percentage area of pathologic lesions at the rupture site

Patient No.	Necrosis and degeneration*	Contraction band necrosis	Organization process	Hemorrhage	Living myocytes*
N1	74.18	0	0	25.8	0.02
N2	95.7	0.45	0	4.2	0
N3	87.6	0	0	3.6	8.8
N4	85.4	0.45	0	8.0	6.6
N5	96.4	0	0	3.6	0
N6	92.1	0	0	5.2	2.7
Average	88.6±8.3%	0.15±0.23%	0%	8.4±8.6%	3.0±3.8%
R1	73.3	2.3	0	1.4	25.3
R2	88.5	0.25	0	5.1	6.4
R3	56.3	1.6	0	27.2	16.5
R4	56.1	0.1	14.8	22.2	6.9
Average	68.6±15.5%	1.06±1.06%	3.7±7.4%	14.0±12.6%	13.8±8.5%

*$p<0.05$

reperfusion has been primarily considered as a special feature[27,31-35], and a positive relationship between hemorrhagic MI and cardiac rupture has been reported[12,15]. Two mechanisms have been proposed, cardiac rupture is caused by the dissemination of blood through regions of transmural necrosis[11], or hemorrhage delays healing of infarction[36]. We observed both mechanisms in group R. Dissemination of blood was seen in patients receiving late thrombolytic therapy, while delayed healing due to hemorrhage was present in those with early reperfusion and myocardial rupture. Therefore, even in early reperfusion, cardiac rupture due to hemorrhage may develop in the late phase.

More living myocytes around the MI area may cause more powerful traction on the area of cell necrosis and increase the risk of rupture in patients receiving reperfusion therapy.

We found absorption of dead tissue at the site of rupture in one patient in the R group. This pathologic finding has not been reported previously in cardiac rupture. The lesion was apparently produced by the simultaneous reperfusion and acceleration of the healing process in the infarcted area. This process might weaken the myocardium and result in predisposition toward rupture.

Reperfusion injury following administration of thrombolytic agent is another possible disadvantage of this therapy[37]. One form of reperfusion injury is contraction band necrosis. We found no clear relationship between contraction band necrosis and cardiac rupture in group R since contraction band necrosis occupied a smaller area of the ruptured site than other pathologic lesions.

Recent studies suggest that coronary angioplasty without thrombolytic therapy reduces the potentially harmful effects of myocardial hemorrhage[38]. Such therapy may in turn reduce the incidence of cardiac rupture[39].

Our study found cardiac rupture occurred earlier following MI in group N than in group R. Therefore, we believe that intensive therapy initially administered in the coronary care unit was effective against myocardial infarction, and that early rupture, probably due to necrosis and degeneration, may be prevented by administering thrombolytic therapy. However, late rupture may occur earlier when recanalization accelerates the healing of the infarction.

Our results suggest that reperfusion following thrombolytic therapy reduced the area of necrosis and degeneration and altered the pathologic features of the natural course of MI with cardiac rupture. The incidence of cardiac rupture in MI was not reduced by reperfusion therapy. Therefore, factors other than necrosis and degeneration, for example massive hemorrhage, tissue weakness due to the accelerated absorption of dead tissue, and different traction between necrotic and living myocyte areas, are involved in cardiac rupture in MI patients receiving thrombolytic therapy.

Study of a larger number of cases is needed to determine the causes of cardiac rupture in MI with successful reperfusion.

要　約

梗塞後心破裂剖検例の組織学的検討：血栓溶解療法の影響について

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急性心筋梗塞後の心破裂に対する血栓溶解療法の影響を明らかにするために，心筋梗塞後に左室自由壁破裂をきたした10剖検心(男7例，女3例，年齢41–80歳，平均年齢59.9±13.2歳)について検討した．破裂部位を組織学的に調べた後，残存心筋，器質化過程，壊死および変性心筋の占める面積率を算出し，血栓溶解療法を施行した群(R群)と，施行しなかった群(N群)で比較した．心破裂の主要な組織学的所見は，壊死優位型，好中球浸潤優位型，出血優位型，吸収機転型の4つに分類できた．R群では，出血優位型2例，吸収機転型1例と，再疎通不成功例の好中球浸潤優位型1例であり，N群では，壊死優位型3例と，好中球浸潤優位型2例，出血優位型1例であった．また壊死および変性心筋の占める面積率がN群よりR群で有意に低かった．以上より，心筋梗塞で血栓溶解療法を施行した症例では，梗塞巣の残存心筋により生じる局所ストレスや，出血，吸収機転による組織の脆弱性が心破裂を誘発するものと推測された．

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