The Pathogenesis of an Impending Infarction and its Treatment

— An angioscopic analysis —

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To clarify the pathogenesis of an impending infarction and to investigate the difference between the pathogenesis of an acute myocardial infarction and an impending infarction, we have performed percutaneous transluminal coronary angiography in 13 patients with an impending infarction and in 13 patients with an acute myocardial infarction. As a result, coronary thrombi were observed in 12 of the 13 patients with an impending infarction, and a similar frequency of thrombi was observed in the patients with an acute myocardial infarction. Further, grayish white thrombi were observed in 9 of 12 patients with an impending infarction, but no such thrombi were noted in those with an acute myocardial infarction. Reddish thrombi, however, were observed in all patients with acute myocardial infarction, whereas such thrombi were observed in only 3 of 12 patients with an impending infarction. Informatively, occlusive thrombi occurred more frequently in patients with an acute myocardial infarction than in those with an impending infarction.

As a thrombus plays an important role in an impending infarction, we also evaluated the effect of anticoagulant and thrombolytic therapy for an impending infarction in 79 patients. The incidence of recurrent angina and a subsequent acute myocardial infarction were significantly higher in non-heparin-treated patients and in thrombolytic-treated patients than in heparin-treated patients.

In conclusion, a thrombus plays an important role in the pathogenesis of an impending infarction and in an acute myocardial infarction, though the characteristics of the thrombus differ in each instance. This difference may account for the differing results of thrombolytic therapy. Heparin was found an effective treatment for myocardial ischemia in an impending infarction.

(*Jpn Circ J* 1992; **56**: 1160–1165)

IN cases manifesting as acute coronary disorders, such as an unstable angina or an acute myocardial infarction, the morphologic changes in the coronary arteries are clinically evaluated by coronary arteriography for signs such as asymmetric stenosis in the form of a convex intraluminal obstruction with

overhanging edges¹ or an irregular and/or hazy border^{2,3} that would indicate a plaque rupture with a thrombus formation. Although a powerful diagnostic tool, arteriography displays only the shadow of any luminal changes. Thus, it provides little information about the nature and surface of atherosclerotic plaque and thrombus, and therefore is inadequate in investigating the pathogenesis of impending infarction. On the other hand, angiography discloses luminal changes in minute detail^{4,5}. Recently, we

Key words:

Angioscopy
Impending infarction
Acute myocardial infarction
Thrombus

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Fig.1. The frequency of coronary thrombi. Coronary thrombi were observed by angiography in all patients with acute myocardial infarction and in most patients with an impending infarction.

have developed a new percutaneous transluminal coronary angioscope⁶ that allows angiography to be performed during the actual acute phase of an acute myocardial infarction or an impending infarction during an emergency coronary arteriography. Using this new angioscope, we have undertaken this study to clarify the pathogenesis of an impending infarction, and to investigate the difference in the pathogenesis between an acute myocardial infarction and an impending infarction, and finally to evaluate the methods of treatment for an impending infarction.

PATIENTS AND METHODS

Pathogenesis of an impending infarction

Percutaneous transluminal coronary angiography was performed in 13 patients with an impending infarction and in 13 patients with acute myocardial infarction. An impending infarction was defined as a significant acceleration of a previously established stable angina that induced a pain that could

Fig.2. The characteristics of the coronary thrombi.

The frequency of white thrombi was higher in patients with an impending infarction. While some reddish thrombi were observed in impending infarction patients, all patients with an acute myocardial infarction had reddish thrombi.

not be relieved by conventional therapy while the patient was at rest. No patient examined had an elevation of creatine phosphokinase (CPK) greater than twice the normal level. Further, all patients with an acute myocardial infarction had a characteristic history of prolonged chest pain that was verified by diagnostic electrocardiographic changes, and by the presence of elevated serum cardiac enzymes (CPK-MB and a myocine light chain). Coronary arteriography and coronary angiography were performed within 28 h of the last chest pain in patients with an impending infarction and within 8 h of the onset of an acute myocardial infarction.

Coronary angiography was performed with an angioscope that incorporates a balloon at the distal tip and an angulation mechanism that was developed at our institute. Several factors were taken into consideration in determining the site for the coronary angiography. In cases of single vessel disease, the target vessel was considered to be an ischemia-related artery and the most severe stenotic lesion was observed. In patients with a multivessel disease, the ischemia-related artery was designated by an occluded or a significantly stenotic vessel that corresponded most closely to the ischemic area,

Fig.3. The frequency of occlusive thrombi. The frequency of occlusive thrombi was significantly higher in patients with an acute myocardial infarction than in those with an impending infarction.

Fig.4. The incidence of a recurrent angina in heparin-treated patients and in non-heparin-treated patients.

determined by ST-T segment changes during pain at rest.

Thrombi were defined as red and/or white masses adhering to the intima and protruding into the inner lumen. Coronary thrombi were readily distinguished by color: those that were grayish-white and those that were all red or mixed red and white. Prior to the start of our study, informed written consent, which was approved by our Institutional Review Board, was obtained from all patients. Coronary angiography was not performed in cases presenting with a left main or left main equivalent coronary artery disease, or if

Fig.5. The incidence of an acute myocardial infarction in heparin-treated patients and in non-heparin-treated patients.

Fig.6. A comparison of the incidence of a recurrent angina between patients with an impending infarction given thrombolytic therapy (urokinase) or anticoagulant therapy (heparin).

there was less than a 50% stenosis in the major coronary branches.

Treatment for an impending infarction

1. Anticoagulant therapy

Seventy-two patients with an unstable angina, including patients with an impending infarction were assigned to either the heparin-treated group or non-heparin-treated group. A drip infusion of heparin (500–1,000 U/h) was administered for 32 h from admission. Coronary arteriography was done within 4 days after admission. The endpoint of this study was a frequently recurrent chest pain and/or an acute myocardial infarction. Patients with a frequently re-

current angina or an acute myocardial infarction underwent coronary arteriography at the endpoint, and either percutaneous transluminal coronary angioplasty or coronary artery bypass surgery was performed. The incidence of a recurrent angina or an acute myocardial infarction was studied.

2. Thrombolytic therapy

On undergoing emergency coronary arteriography on admission, 7 patients were treated with 960,000 units of intracoronary urokinase. For those patients, no intravenous drip infusion of heparin was administered for 3 days. Further, the incidence of a recurrent angina was evaluated between those urokinase-treated patients and patients treated with heparin.

Statistic analysis

The chi-square test was used to evaluate all the obtained data and the effect of treatment.

RESULTS

Coronary thrombi were observed in 12 of 13 patients with an impending infarction and in all patients with an acute myocardial infarction (Fig. 1), although the type of thrombi in each group differed. Grayish-white thrombi were observed in 9 of 12 patients with an impending infarction but not in those with an acute myocardial infarction. In contrast, reddish thrombi were observed in only 3 patients (25%) with an impending infarction, whereas they were observed in all patients with an acute myocardial infarction (Fig. 2). Further, the frequency of a complete occlusion in the culprit lesions responsible for an impending infarction and an acute myocardial infarction at the time of the angiography was significantly higher in patients with an acute myocardial infarction than in those with an unstable angina (Fig. 3). Finally, the elapsed time from the onset of episodes of chest pain to coronary angiography was significantly higher in patients with an impending infarction than for those with an acute myocardial infarction.

With respect to other clinical and angiographic characteristics, there were no significant differences between the 2 groups.

Anticoagulant and thrombolytic therapy in patients with an impending infarction

Recurrent angina occurred in only 4 of 27 patients (15%) treated with a drip infusion of heparin, whereas a recurrent angina persisted in 21 of 45 patients (47%) who had received no heparin treatment. Further, there was a significant difference in the incidence of a recurrent angina between the heparin-treated group and the non-heparin-treated group (Fig. 4). The incidence of acute myocardial infarction was also significantly higher in the heparin-treated group than in the non-heparin-treated group (Fig. 5). There were no other significant differences between the 2 groups with respect to antiplatelet therapy or other conventional therapy, the number of diseased vessels, and a previous myocardial infarction.

A recurrent angina occurred in 5 of 7 patients (71%) who had been treated with urokinase but without a subsequent heparin drip infusion. The incidence of a recurrent angina was significantly higher in urokinase-treated patients who received no heparin than patients treated with heparin ($p < 0.05$) (Fig. 6).

DISCUSSION

Pathogenesis of impending infarction

Angiographic, angioscopic, pathologic, and biochemical data have implicated the presence of a thrombus in the pathogenesis of an unstable angina including an impending infarction, and an acute myocardial infarction^{4,5,7-11}. Our angioscopic study has demonstrated, however, that an impending infarction differs from an acute myocardial infarction with respect to the type of thrombus. Most patients with an unstable angina were found to have grayish-white thrombi, whereas reddish thrombi predominated in patients with an acute myocardial infarction.

Two mechanisms are speculated to explain the existence of grayish with thrombi in patients with an impending infarction. First, as a general rule, thrombi forming in rapidly flowing blood, e.g., as in a coronary artery, consist mainly of aggregated platelets with some fibrin. Thus, since only a few red cells are entrapped, the thrombi are pale, varying from grayish white to a pale red¹². It was reported that the extent of the platelet deposi-

tion was significantly high at high wall shear rates,¹³ which was characteristic of medium-sized stenotic arteries, e.g., a coronary artery stenosis. Therefore, as there was no complete occlusion in the ischemia-related arteries at the time of angiography but only tight stenoses, the effects of the blood rheology may have produced the grayish-white thrombi.

Second, in a previous angiographic study involving an experimental model of thrombosis and thrombolysis,¹⁴ gray or silver thrombi appeared after red thrombi were lysed by urokinase. Microscopic examination of these thrombi revealed a tight fibrin network and platelet aggregates with a coagulation of blood cells that was slight. These thrombi did not disappear, although the dose of urokinase was increased. Therefore, as the elapsed time from last rest pain to the angiography averaged 19 h in our study, it may be that an endogenous thrombolysis⁹ occurred by the time of the angiography, so that the appearance of these thrombi resembled those of this previous experimental study. Also, some parts of the thrombi that were seen might have resulted from fragmentation and embolization.

Vasoconstriction is said to be caused by a reduction in the production of both the endothelium-derived relaxing factor (EDRF) and prostacyclin (PGI₂) in dysfunctional endothelium,¹⁵⁻¹⁹ a condition which often exists in an unstable angina^{4,5,8} and it has been found that the release of endothelium-independent vasoconstrictor substances from platelets and thrombi^{15,19} causes a transient blood flow stasis and enhances thrombus formation and may produce reddish thrombi²⁰ even in an unstable angina. One previous study²¹ has reported that thrombolytic therapy was effective during an ongoing anginal attack in an unstable angina. Since the arteriography of that study showed a total or subtotal occlusion in most instances, thrombi during such an ongoing anginal attack may be similar to the thrombi of an acute myocardial infarction.

Thus, with the exception of some cases of an impending infarction that manifest a complete or subtotal occlusion during an ongoing anginal attack, thrombolytic therapy may not be found very efficacious for an impending infarction because the thrombolytic agents

appear to be less effective on grayish white thrombi which are platelet-rich²² or on platelet aggregatory thrombi with tight fibrin networks.²³

The effectiveness of heparin and the lack of efficacy of urokinase for the treatment of an impending infarction suggest that the acute effect of heparin is not attributable to its activity on intracoronary thrombotic growth but rather to the inhibition of thrombin formation. Pathologic and angiographic studies have shown that a refractory, unstable angina is often associated with plaque fissuring or ulceration^{4,5,8} which can easily trigger the local formation of thrombin, in an amount sufficient to cause vascular contraction in the absence of endothelium.^{19,24}

Clinically, a continuous infusion of heparin provides a prompt, effective, and safe therapy for myocardial ischemia, particularly in cases of an impending infarction refractory to conventional treatment. New and promising drugs that meet the desired profile, such as the specific thrombin inhibitor hirudin²⁵ or argatroban²⁶ may be even more effective for an impending infarction.

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