Intracoronary Thrombodynamics in the Early Phase of Acute Myocardial Infarction

HARUO TOMODA, M.D. AND ITSURO YOKOTA, M.S.*

Intracoronary thrombodynamics in the early phase of acute myocardial infarction were studied in an experimental canine model. Intracoronary thrombus was precipitated at the mock ruptured atheromatous plaque consisting of cholesterol and collagen.

1. Myocardial infarction occurred in 10 and sudden death in 2 secondary to intracoronary thrombotic occlusion in 15 control experiments.

2. Pretreatment with an antiplatelet drug, ticlopidine, significantly reduced the incidence of myocardial infarction and sudden death (7/18, 39% vs. 12/15, 80%, p < 0.05).

3. During the period when intracoronary thrombus was precipitated, a transient reduction in aortic pressure induced by nitroglycerin resulted in rapid progression of intracoronary thrombotic occlusion in 7 of 21 animals and in 5 of 17 animals treated with nitroprusside. The terminated coronary blood flow could be restored by raising coronary perfusion pressure with methoxamine in 5 of 10 cases with coronary thrombotic occlusion.

4. Cigarette smoking appeared to accelerate the completion of coronary thrombotic occlusion.

5. Sudden death occurred in 12 of 43 models without pharmacological intervention during coronary thrombotic occlusion associated with myocardial dysnergy.

Six sudden deaths occurred within 10 min and 9 within 30 min following coronary thrombotic occlusion. Postmortem complete autolysis of intracoronary thrombus was observed in 24% and partial thrombolysis in 28%.

It is practically impossible to observe instantaneous hemodynamic, biochemical or pathological changes at the onset of acute myocardial infarction in clinical cases.

Therefore, data obtained in experimental animals with coronary artery ligation have been the main source of pathophysiological understanding for this particular issue. On the other hand, detailed pathological studies have disclosed that intracoronary thrombus is encountered in more than 90% of patients who die within 24 hours of the onset of acute myocardial infarction, and the thrombus bearing portions of the vessel show rupture of atheromatous plaque in which the blood has direct contract with cholesterol, collagenous fiber and other atheromatous debris resulting in platelet aggregation, initiation of the coagulation mechanism, and thrombus formation1–3 Reports on coronary thrombolysis for evolving acute myocardial infarction have also indicated the importance of the intracoronary thrombus for initiation of myocardial infarction4,5

Thus, the present author has developed an
in a pericardial cradle. A polyvinylchloride tube with an external diameter of 1 mm was inserted via a small diagonal branch, and the tip of the tube was advanced and exposed to the lumen of the anterior descending coronary artery (LAD) at the beginning of each experiment. The tube was prefilled with a 1:1 mixture of collagen (bovine Achilles tendon, Sigma No C-9879) and cholesterol, which protruded from the tip of the tube (Fig. 1). An electromagnetic flowmeter was set around the LAD, 1 cm proximal to the tube. A specially designed constrictor was placed on the LAD where the tip of the tube was located. The aortic flow was measured with an electromagnetic flowmeter and left ventricular and aortic pressures were measured via large bore cannulas directly connected to pressure transducers. A length gauge and a silver electrode were sutured in the LAD area. The constriction of the LAD was adjusted so as to obtain a 10% decrease of LAD flow. Measurements of flows, pressures, myocardial contraction and ECG were obtained throughout the experiment. Occurrence of myocardial infarction was identified when the phasic LAD flow disappeared associated with asynergic myocardial contraction for more than an hour. The end point of the experiment was an hour after the occurrence of myocardial infarction or 7 hours after the initiation of the study when myocardial infarction did not occur. At the end of every experiment, the animal was sacrificed, and the LAD was clamped at 1 cm distal to the mock atheromatous plaque and incised to ascertain the presence of thrombus.

(1) Fifteen animals were studied as a control group.

(2) An antiplatelet agent, ticlopidine 100 mg/day was administered orally in 18 animals for a week preceding the experiment.

(3) Intravenous administration of nitroglycerin was attempted in 21 animals at a dosage of 10 μg/kg as a bolus intravenous injection, when spontaneous gradual reduction in coronary blood flow of 50% of the initial value due to the intracoronary thrombus formation was observed. Intravenous bolus administration of sodium nitroprusside was attempted in another 17 animals at a dosage of 10 μg/kg, when the spontaneous reduction of the coronary blood flow of 50% of the initial value was observed. Furthermore, the effects of raising coronary perfusion pressure on an occlusive intracoronary thrombus were studied in the animals that had myocardial infarction in

**MATERIALS AND METHODS**

Experiments were performed on 145 mongrel dogs, weighing 10 to 25 kg. Each animal was anesthetized with intravenous sodium pentobarbital and the chest was opened with the use of artificial ventilation. The heart was suspended

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Fig. 2a. Electrocardiographic and hemodynamic changes during evolving myocardial infarction due to intracoronary thrombus. Gradual reduction in coronary blood flow followed by paradoxical contraction and ST elevation is indicated. CF = coronary blood flow; Length = myocardial segmental length.

Fig. 2b. An example of sudden death. The reduction of coronary blood flow has resulted in myocardial dysenergy and ST elevation and then ventricular fibrillation. AoF = aortic flow; CF = coronary arterial blood flow; Length = myocardial segmental length; LVP = left ventricular pressure.

the preceding experiments by intravenous administration of 0.1 mg/kg of methoxamine 30 min after cessation of coronary blood flow.

(4) In 6 animals a cigarette which contained 2.1 mg of nicotine was smoked through the inlet of the respirator; one inhalation every three respiratory cycles over 2 min.

(5) Of 43 animals with intracoronary occlu-
Fig. 3a. Effects of nitroglycerin (NTG). There is a transient change in the coronary blood flow associated with a transient reduction in aortic pressure induced by NTG. Abbreviations are the same as in Fig. 2.

Fig. 3b. Effects of nitroglycerin (NTG). A transient reduction in aortic pressure induced by NTG followed by a continuous reduction in coronary blood flow, which has resulted in paradoxical contraction and ST elevation. An occlusive intracoronary thrombus originating from the mock atheromatous plaque was recovered at autopsy. Abbreviations are the same as in Fig. 2.
Table 1: Effects of Nitroglycerin

<table>
<thead>
<tr>
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<th>Group I</th>
<th>Group II</th>
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<tbody>
<tr>
<td><strong>Myocardial Infarction (-)</strong></td>
<td>17%</td>
<td>14%</td>
</tr>
<tr>
<td><strong>Heart rate (1/min)</strong></td>
<td>93 ± 5**</td>
<td>72 ± 4**</td>
</tr>
<tr>
<td><strong>Aortic diastolic pressure (mmHg)</strong></td>
<td>78 ± 4**</td>
<td>80 ± 3**</td>
</tr>
<tr>
<td><strong>Aortic blood flow (ml/min)</strong></td>
<td>100 ± 3</td>
<td>104 ± 4</td>
</tr>
<tr>
<td><strong>LAD coronary blood flow (ml/min)</strong></td>
<td>14 ± 1</td>
<td>14 ± 1</td>
</tr>
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Fig. 4. Effects of methoxamine. Augmentation in aortic pressure is accompanied by a sudden increase of coronary blood flow, which has resulted in restoration of myocardial contraction and an improvement in ST elevation. Abbreviations are the same as in Fig. 2.

Fig. 4. Effects of methoxamine. Augmentation in aortic pressure is accompanied by a sudden increase of coronary blood flow, which has resulted in restoration of myocardial contraction and an improvement in ST elevation. Abbreviations are the same as in Fig. 2.

Sepsis thrombus and without pharmacological intervention, 12 died within an hour of the coronary occlusion (sudden death group). The pathophysiological changes in the sudden death group were analyzed to study factors relevant to sudden death induced by coronary thrombosis.

(6) The possibility of postmortem coronary thrombolysis was studied in the experimental

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model. Twenty-five of the myocardial infarction or sudden death animals encountered in the present model were sacrificed an hour after the onset of myocardial infarction or immediately following sudden death. The coronary artery was clamped at the sites distal and proximal to the mock ruptured atheromatous plaque and the artery was incised at the level of the mock plaque under a microscope.

The intracoronary thrombus was observed, photographed and measured by a caliper.

The weight of the thrombus was calculated assuming the thrombus as an ellipsoid with the specific gravity of 1.0. The incised coronary arterial wall was closed by suturing with an 8–0 suture string, and thereafter the clamps were released.

Two hours later, the sutured coronary artery was again incised and the thrombus was photographed, measured and weighed.

**RESULTS**

*Control study* Intracoronary thrombus was precipitated by the mock atheromatous plaque in 13 of the 15 control animals. Myocardial infarction was induced in 10 and sudden death in 2. Coronary blood flow decreased gradually or cyclically to end in myocardial infarction or sudden death (Fig. 2).

*Ticlopidine study* In 18 animals pretreated with ticlopidine, there were 6 myocardial infarctions and 1 sudden death due to the intracoronary occlusive thrombi. The incidence (7/18, 39%) was significantly lower than that of the control group (80%, *p* < 0.05). There were 7 occlusive thrombi and 5 non-occlusive thrombi.

*Effects of coronary perfusion pressure* As indicated in Fig. 3 and Table I, aortic pressure as well as left ventricular pressure started to decrease associated with reduced diastolic myocardial length 11 ± 1 seconds following nitroglycerin administration.

Left anterior descending coronary artery blood flow indicated a transient increase in 8 of the 21 animals and a transient decrease in 6 of them (Fig. 3a).

On the other hand, in 7 of the 21 animals, LAD flow decreased continuously following the nitroglycerin administration until complete cessation of LAD flow occurred at 1–10 min (average: 3.6 ± 1.3 min) associated with paradoxical myocardial contraction and ST elevation, which continued for up to 30 min (Fig. 3b).
Effects of smoking

Fig. 5. Effects of smoking. Smoking appears to have enhanced catecholamine secretion and then completion of coronary thrombotic occlusion. Abbreviations are the same as in Fig. 2.

Fig. 6. An example of partial postmortem coronary thrombolysis. A: immediately after sudden death, B: two hours after sudden death. See text for further explanations. Thrombus is indicated by small arrows and the tube filled with cholesterol-collagen mixture is indicated by thick arrows.

As indicated in Table I, left ventricular as well as aortic pressure decreased and heart rate increased significantly in both groups with or without myocardial infarction and there was no significant difference in the values between the 2 groups.

There were no significant changes in aortic flow and significant reductions in left ventricular dp/dt in both groups. There was a transient reduction in LAD flow in 12 of the 17 animals that received sodium nitroprusside, and there was a continuous reduction in LAD flow to end in

myocardial infarction in 5 of them. As indicated in Fig. 4, there was a significant increase in left ventricular and aortic pressures and transient increase in diastolic myocardial length with a significant decrease in aortic flow by methoxa-
mine administration. In 5 of the 10 animals with thrombotic coronary artery occlusion, LAD flow was restored abruptly associated with improved myocardial contraction and ST changes in 31 ± 3 sec (Table II).

Effects of smoking Smoking during intra-

coronary thrombus precipitation induced the changes that are similar to those induced by catecholamine administration; there were marked increases in heart rate, systemic blood pressure, aortic flow, coronary blood flow and myocardial contraction. However, coronary blood flow decreased following the transient changes down to complete cessation and ended in myocardial infarction in 2 of them (Fig. 5).

Sudden death All of the sudden death group died of ventricular fibrillation associated with thrombus induced reduction and cessation of coronary blood flow and myocardial dysnergy. No sudden death occurred without dysnergy or during spontaneous recanalization. Six of the sudden deaths occurred within 10 min and 9 within 30 min following thrombotic coronary occlusion. There were no significant differences in the incidence of multifocal or couplet ventricular premature beats in either 2 sudden death or non-sudden death group. There was a marked increase in frequency of ventricular arrhythmias up to more than 20/min in 8 of the 12 sudden deaths within 1 min before death (Fig. 2b).

Postmortem thrombolysis 21 myocardial infarctions and four sudden deaths induced by the intracoronary thrombotic occlusion were studied. Sudden deaths occurred at 8 ± 2 min following cessation of the coronary blood flow, while those with myocardial infarction were sacrificed 60 min following cessation of the coronary blood flow. The calculated weights of the intracoronary thrombi were 6 ± 2 mg in myocardial infarction, 6 ± 3 mg in sudden death and all of them were occlusive.

Two hours after death, the thrombi were lysed completely in 4 of the 21 myocardial infarctions and in 2 of the 4 sudden deaths and decreased in size by more than 3 mg in 7 of the rest of myocardial infarction. There was a significant correlation between the calculated weight of the thrombus (y) and the actual weight (x); y = 0.674x + 0.584 (r = 0.923, p < 0.01) (Fig. 6).

DISCUSSION

In clinical cases, myocardial infarction might not occur in such a mode as encountered in the conventional experimental model with simple ligation of the coronary artery.

In the present model of acute myocardial infarction, coronary blood flow decreased gradually over 10–420 min associated with significant changes in ECG and myocardial contraction. Occasionally, reduced or disappeared coronary blood flow was restored due to positional changes or disruption of the intracoronary thrombi.

Thus, in the cases of acute myocardial infarction due to intracoronary thrombotic occlusion, coronary blood flow appears not to decrease instantly as seen in experimental coronary ligation. Moreover, there is no way of knowing exactly when chest pain occurs, since the identification of the onset of myocardial infarction by the onset of chest pain in clinical cases is not accurate and most probably earlier than the complete occlusion of the coronary arteries.

Effects of antiplatelet drug The antiplatelet effect of ticlopidine is attributed to the prevention of the combination of platelets with fibrino-
gen to induce a thrombasthenic state? Based on the data obtained in the present study, ticlopidine may be preferable to aspirin in a trial to prevent myocardial infarction in coronary heart disease because there is no such problem as aspirin dilemma.

Effects of coronary perfusion pressure Nitro-
glycerin was once considered contraindicated for acute myocardial infarction, as it was thought to induce hemodynamic deterioration. Recently, however, nitrates have been used in patients in the impending or acute phase of myocardial infarction for protection of the ischemic myocardium. The present study on an experimental model with mock atheromatous plaque and evolving intracoronary thrombus revealed the fact that nitroglycerin administration induced a rapid reduction in coronary artery blood flow resulting in acute myocardial infarction associated with occlusive intracoronary thrombus formation with an incidence of 33%. In all of the animals with myocardial infarction, occlusive intracor-

nary thrombi were confirmed as originating from the collagen-cholesterol mixture which imitates the contents of atheromatous plaque. On the other hand, similar effects to induce myocardial infarction were observed with nitroprusside, which has more potent effects on systemic arter-
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ies and has essentially different actions on coronary arteries compared with nitroglycerin; nitroprusside dilates coronary arterioles, i.e., resistance vessels, while nitroglycerin dilates larger coronary arteries, i.e., capacitance vessels. However, the most significant common change induced by the drugs was the reduction in aortic pressure. The reduction in coronary artery perfusion pressure appears to be an important factor in promoting the completion of occlusive intracoronary thrombus by attenuating the mechanical destruction of the precipitating thrombus. To further prove this assumption, methoxamine, which increases systemic and coronary arterial resistance was infused as a bolus injection in those with nitroglycerin or nitroprusside induced LAD thrombotic occlusion.

Coronary blood flow was restored in 5 of the 10 subjects following a significant increase in aortic pressure. Such an abrupt restoration of coronary blood flow in the experimental model is thought to be due to dislodgement or disintegration of platelet aggregates or thrombi by coronary blood flow under augmented coronary perfusion pressure.

**Effects of smoking** The effects of smoking in the present study might be different from those seen in clinical cases because of the differences in body size, mode of smoking and history of smoking, and the number of experiments was too limited to make a conclusion. However, apparently accelerated intracoronary thrombotic occlusion by smoking appears to be due to increased platelet aggregatory effects as well as adrenergically mediated coronary vasoconstriction.

**Sudden death and postmortem coronary thrombolysis** In the present study, sudden death induced by coronary occlusive thrombus was exclusively due to ventricular fibrillation and sudden death was not encountered as long as myocardial dysnergy was not apparent. Ventricular fibrillation did not occur when spontaneous coronary blood flow appeared associated with dislodgement or partial disintegration of the thrombus most probably due to the limited volume of increase in coronary blood flow in such a situation. In clinical settings, sudden death due to ischemic heart disease may occur when transient or persistent severe myocardial ischemia associated with myocardial dysfunction is present. Sudden death occurred most frequently within 30 min, especially within 10 min following complete cessation of coronary blood flow and the result was similar to that reported in myocardial ischemia induced by simple coronary ligation. However, the incidence of sudden death was less frequent in the present model most probably due to the gradual reduction in the coronary blood flow which may have offered opening of collateral circulation decreasing the possibility of developing reentrant circuit. The relatively low and variable frequencies of intracoronary occlusive thrombi in those who died suddenly due to coronary artery disease have brought discrepancies in the possible causative factors of sudden death. The importance of coronary spasm or microthrombi or platelet aggregates as peripheral coronary artery embolization has been raised as a possible cause of sudden death. As for the possibility of the postmortem lysis of recent intracoronary thrombi, however, there has been no systemic experimental or clinical study. In the present study, the fresh intracoronary thrombi obtained an hour after the onset of acute myocardial infarction or immediately after sudden death, lysed completely in 24% (6/25) and decreased in size significantly in 28% (7/25). In all of them, the sutured coronary arteries were apparently filled with serous fluid following the release of the clamps. The blood collected from the ascending aorta 2 hours following the death showed almost diminished fibrinogen (from 275 ± 34 mg/ml to less than 35 mg/dl) and moderately decreased plasminogen (from 54 ± 5% to 27 ± 4%). Therefore, it is possible that the intracoronary thrombi immersed in such fluid had been lysed completely during the postmortem period.

Cardiac massage or electrical cardioversion may accelerate the thrombolysis by increasing the mixing effects of the intracoronary thrombi with the fluid.

The possibility of the postmortem lysis of intracoronary thrombi may be one of the missing links in defining the causes of sudden death.

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