Role of Coronary Artery Spasm in Progression of Organic Coronary Stenosis and Acute Myocardial Infarction in a Swine Model

Importance of Mode of Onset and Duration of Coronary Artery Spasm

Takeshi Kuga, MD; Hitonobu Tomoike, MD; Wataru Mitsuoka, MD; Shogo Egashira, MD; Yu-Ichi Ohara, MD; Akira Takeshita, MD; and Motoomi Nakamura, MD

Background. Coronary spasm may play an important role in progression of organic coronary stenosis and myocardial infarction, but the mechanisms responsible for these complications are not known. This study aimed to examine whether the mode of onset and the duration of coronary spasm influenced progression of organic coronary stenosis and acute myocardial infarction in a swine model of coronary spasm.

Methods and Results. Göttingen miniature pigs were subjected to cholesterol feeding, balloon-induced coronary arterial denudation, and x-ray irradiation. Five months later, coronary spasm was induced by intracoronary injection of serotonin. In 10 pigs, coronary spasm was provoked abruptly and maintained for 25 minutes by five repeated intracoronary injections of serotonin (10 µg/kg) every 5 minutes (group A, abrupt onset and short duration). In group B, coronary spasm was provoked gradually by intracoronary injections of serotonin at graded doses of 0.1, 0.3, and 0.6 µg/kg every 5 minutes and was then maintained for 25 minutes in four pigs (group B1, gradual onset and short duration) and for 120 minutes in six pigs (group B2, gradual onset and long duration) by repeated intracoronary injections of serotonin (10 µg/kg) every 5 minutes. Intramural hemorrhage was noted histologically at the spastic site more frequently in group A with abrupt onset (nine of 10 pigs) than in group B with gradual onset (two of 10 pigs) \( p < 0.01 \). Progression of organic coronary stenosis due to intramural hemorrhage was noted in seven pigs (six pigs in group A and one pig in group B), including three cases of total coronary occlusion. Evidence for the evolution of acute myocardial infarction (serial ECG findings, left ventriculograms, and histological findings) was noted in one pig (7%) of group A or B1 with short duration and in five of six pigs (83%) in group B2 with long duration \( p < 0.01 \) versus group A and B1.

Conclusions. These results indicate that 1) intramural hemorrhage was frequently induced by coronary spasm of abrupt but not of gradual onset, 2) intramural hemorrhage resulted in acute progression of coronary stenosis and sometimes resulted in persistent total coronary occlusion leading to acute myocardial infarction, and 3) prolonged coronary spasm resulted in acute myocardial infarction without progression of organic coronary stenosis. (Circulation 1993; 87: 573–582)

KEY WORDS • coronary spasm • hemorrhage, intramural • stenoses • myocardial infarction

Coronary artery spasm plays an important role in the pathogenesis of a wide variety of ischemic heart disease, not only in variant angina but also in unstable angina, myocardial infarction, ventricular arrhythmia, and sudden death.1–12 Coronary spasm also plays an important role in acute coronary occlusion and restenosis after percutaneous transluminal coronary angioplasty.13,14 Although recent clinicopathological studies noted plaque rupture and subsequent coronary thrombosis as a cause of progression of coronary stenosis and myocardial infarction,15–18 the cause of plaque rupture remained to be elucidated. One of the most credible causes of plaque rupture is coronary spasm.5–8 The cause-and-effect relations between coronary spasm and these acute ischemic syndromes have not been rigorously examined, however, partly because of the lack of an appropriate animal model. We have established a swine model of coronary spasm with a grant from the Research Foundation for Cancer and Cardiovascular Diseases.

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coronary atherosclerosis. In this animal model, coronary spasm similar to that in variant angina can be repeatedly provoked by intracoronary injections of serotonin. We also have shown that severe coronary spasm induces intramural hemorrhage resulting from tearing of the dense capillary network in the atheroma. Since it is easy to control the severity and the duration of coronary spasm by changing the dose and the frequency of administration of the monoamine, our animal model appears to be suited to examining whether the mode of onset and the duration of coronary spasm affect the progression of organic coronary stenosis and the development of acute myocardial infarction.

The present study was designed to examine 1) whether coronary spasm augments organic coronary stenosis, 2) whether coronary spasm induces myocardial infarction, and 3) if so, whether the mode of onset and the duration of coronary spasm affect the progression of organic coronary stenosis and the development of acute myocardial infarction.

**Methods**

**Animal Preparation**

Twenty male Göttingen miniature pigs were housed individually at controlled room temperature and were fed a semisynthetic diet. The composition of the semisynthetic diet was peanut oil 2.3%, corn oil 0.7%, whole milk powder 53.7%, casein 5.7%, sucrose 21.3%, cholesterol 2%, sodium cholate 1.1%, salt mixture 1.4%, vitamin mixture 3.5%, and cellulose 8.9%. After 4 weeks on the diet, pigs were lightly anesthetized with ketamine hydrochloride (12.5 mg/kg i.m.) followed by sodium pentobarbital (20 mg/kg i.v.); they were then intubated and ventilated with room air and supplemental oxygen (Shinano, Inc., Tokyo). The carotid artery was aseptically exposed, and a green Kifa catheter (Kifa, Stockholm) was inserted into the orifice of the left coronary artery. The intima of the left anterior descending (n=15) or the left circumflex coronary artery (n=5) was denuded with a balloon catheter (2F embolomcyte catheter, Edwards Laboratory, Santa Ana, Calif.) under the guidance of fluoroscopy as described. One week later, the balloon denudation of the previously denuded site was repeated under anesthesia. The denuded site was selectively irradiated with x-rays (1,500 rad) twice, at 2 and 3 months after initiation of the cholesterol diet. Total plasma cholesterol was measured enzymatically after 5 months of cholesterol feeding.

**Coronary Angiography, Left Ventriculography, and Hemodynamic Measurements**

Selective coronary angiography was performed as described previously. The extent of coronary constriction evoked with serotonin was assessed as percent reduction of the luminal diameter in comparison with that after nitroglycerin (20 µg/kg i.v.). Coronary spasm was defined as percent luminal reduction >75%. Contrast left ventriculography was performed in a left anterior oblique projection. A contrast dye was injected through a pigtail catheter inserted into the left ventricle with a mechanical injector (Mark II, Medrad, Pittsburgh, Pa.). The posture of the animal and the distance between the animal and the image intensifier were kept constant during the experiment. Standard 12-lead ECGs were monitored on a multichannel pen recorder (Polygraph System, NEC-Sanei, Japan) and stored on a tape with an FM data recorder (DFR 3915, Sony, Japan) before and after induction of coronary spasm. ECGs in leads I, II, III, V₁, and V₆ were continuously recorded during the experiment. Arterial pressure was continuously monitored with a strain gauge manometer.

**Experimental Protocols**

After 5 months of cholesterol feeding, pigs were anesthetized, intubated, and ventilated with room air and supplemental oxygen. First, coronary angiography was performed 5 minutes after administration of nitroglycerin (20 µg/kg i.v.). Then, contrast left ventriculography was performed. Pigs were randomly allotted to the following three groups, and they were subjected to the procedures for provocation of coronary spasm at 60 minutes after administration of nitroglycerin (Figure 1). In 10 pigs (group A), coronary spasm was provoked...
TABLE 1. Baseline Data

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Body weight (kg)</th>
<th>AoP (mm Hg)</th>
<th>Heart rate (bpm)</th>
<th>Serum cholesterol (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>10</td>
<td>33.2±1.5</td>
<td>126±7/99±7</td>
<td>136±13</td>
<td>428±28</td>
</tr>
<tr>
<td>B</td>
<td>10</td>
<td>29.7±2.3</td>
<td>119±6/91±6</td>
<td>127±10</td>
<td>414±37</td>
</tr>
</tbody>
</table>

AoP, aortic pressure (systolic/diastolic); bpm, beats per minute. Values are mean±SEM. AoP and heart rate are those at the experiment for provocation of coronary spasm. Values are not different between group A and group B.

abruptly by an intracoronary (i.c.) injection of serotonin (10 µg/kg) and maintained for 25 minutes by repeated injections of serotonin (10 µg/kg i.c.) every 5 minutes. In another 10 pigs (group B), coronary spasm was provoked gradually over 10 minutes by injections of serotonin at graded doses (0.1, 0.3, and 0.6 µg/kg i.c.) every 5 minutes. Coronary spasm was maintained for 25 minutes in four pigs (group B1) and 120 minutes in six pigs (group B2) by five or 24 repeated injections of serotonin (10 µg/kg i.c.) every 5 minutes, respectively.

To assess the extent of coronary constriction, coronary angiography was performed at 3, 13, and 23 minutes after the first injection of serotonin in group A (Figure 1). Coronary angiography was performed at 3, 8, 13, 18, 28, and 38 minutes after the first administration of serotonin in group B1 and after that, every 15 minutes in group B2 (Figure 1). To prevent ventricular fibrillation, lidocaine (1 mg/kg i.v.) was administered before provocation of coronary spasm in all pigs, followed by infusion of 1 mg/min i.v. throughout the experiment. Heparin (5,000 units i.v.) was administered before the angiographic study and was added every 5 hours in all pigs. In group B2, to minimize intracoronary thrombosis, urokinase (30×10⁴ units i.v.) was administered by bolus just before provocation of spasm, followed by drip infusion of urokinase (30×10⁴ units) for 120 minutes.

In pigs that did not die during the provocation of spasm, coronary angiography was performed 1 hour after provocation of coronary spasm to evaluate sudden progression of organic coronary stenosis. Coronary angiography was performed 5 minutes after administration of nitroglycerin (20 µg/kg i.v.). Contrast left ventriculography was not performed at this time. After awakening, pigs were returned to their rooms.

Twenty-four hours and 7 days after provocation of spasm, pigs were again anesthetized and intubated. Coronary angiography was performed 5 minutes after administration of nitroglycerin (20 µg/kg i.v.) to assess late progression of organic coronary stenosis. Contrast left ventrilocography was also taken at that time.

Because seven of 20 pigs died of ventricular fibrillation during provocation of coronary spasm, angiographic progression of organic stenosis and evolution of acute myocardial infarction could not be evaluated. In these seven pigs, we evaluated intramural hemorrhage and progression of coronary stenosis histologically.

Quantitative Analysis of Coronary Angiography

Cinefilm was projected on a viewing screen (ELMO-35B, Nishimoto Sangyo, Osaka, Japan). The end-diastolic frame was selected by ECG waves recorded on cinefilm, and photographs (13×18 cm) were made for measurements of the diameter of the coronary artery. The diameter of the coronary artery was measured with a caliper by at least two observers in a blinded manner. With this technique, we confirmed excellent correlation between the repeated measurements (r=0.99, p<0.001) and between different observers (r=0.96, p<0.001).

An angiographic progression of organic coronary stenosis was defined as the decrease of the absolute value of diameter >25% of the original absolute value.

Histological Study

After the pig died of ventricular fibrillation or after the angiographic studies, thoracotomy was performed with

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TABLE 2. Results of Provocation of Coronary Artery Spasm

<table>
<thead>
<tr>
<th>Number of pigs</th>
<th>Group A</th>
<th>Group B1</th>
<th>Group B2</th>
<th>Two-tailed p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of spasm</td>
<td>Sudden</td>
<td>Gradual</td>
<td>Gradual</td>
<td></td>
</tr>
<tr>
<td>Duration of spasm</td>
<td>25 minutes</td>
<td>25 minutes</td>
<td>120 minutes</td>
<td></td>
</tr>
<tr>
<td>Sudden death due to VF</td>
<td>6/10 (60%)</td>
<td>1/10 (10%)</td>
<td></td>
<td>0.0572</td>
</tr>
<tr>
<td>Intramural hemorrhage</td>
<td>9/10 (90%)</td>
<td>2/10 (20%)</td>
<td></td>
<td>0.0054</td>
</tr>
<tr>
<td>Progression of organic stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiographic</td>
<td>2/4*(50%)</td>
<td>0/9*(0%)</td>
<td></td>
<td>0.154</td>
</tr>
<tr>
<td>Histological</td>
<td>4/10 (40%)</td>
<td>1/10 (10%)</td>
<td></td>
<td>0.3034</td>
</tr>
<tr>
<td>Angiographic or histological</td>
<td>6/10 (60%)</td>
<td>1/10 (10%)</td>
<td></td>
<td>0.0572</td>
</tr>
<tr>
<td>AMI</td>
<td>With total occlusion of coronary artery</td>
<td>1/10 (10%)</td>
<td>0/10 (0%)</td>
<td>1.0</td>
</tr>
<tr>
<td>Without progression of organic stenosis</td>
<td>0/14 (0%)</td>
<td>5/6 (83%)</td>
<td></td>
<td>0.0004</td>
</tr>
</tbody>
</table>

VF, ventricular fibrillation; AMI, acute myocardial infarction. The two-tailed p values were calculated by Fisher's method.

*Angiographic progression of organic coronary stenosis was evaluated in four of 10 pigs in group A and in nine of 10 pigs in group B because the rest of the pigs died of ventricular fibrillation before the angiographic study.
positive-pressure respiration, and a polyethylene cannula was inserted into the ascending aorta from a subclavian artery. After exsanguination and ligation of the descending aorta, the coronary artery was perfused via a constant-pressure perfusion system with oxygenated saline (1,000 ml) containing nitroglycerin (2 mg/l) under physiological perfusion pressure for about 20 minutes, then perfusion of half-strength Karnovsky fixative was begun. The left coronary artery and its branches were dissected and cut transversely into segments at 2-mm intervals along their main trunk. These segments were dehydrated with alcohol, cleaned with xylene, embedded in paraffin, sectioned 3 μm thick, and stained with hematoxylin and eosin or with the Weigert–van Gieson procedure. In pigs that died during provocation of coronary spasm, the coronary artery was perfused with half-strength Karnovsky fixative under physiological perfusion pressure and then subjected to the same procedures.

After removal of the coronary arteries, the heart was immersed in half-strength Karnovsky fixative for >1 week and was then sliced serially and latitudinally at 1.5-cm intervals. Each slice was embedded in paraffin, cut into 4-μm-thick sections, and stained with hematoxylin and eosin.

**Data Analysis**

All results are expressed as mean±SEM. The differences in body weight, aortic pressure, heart rate, and serum cholesterol level between groups were evaluated by Student’s t test. To compare the frequency of ventricular fibrillation, intramural hemorrhage, progression of organic coronary stenosis, and acute myocardial infarction between groups, we calculated p values by the Fisher method and used a two-sided test because of the small number of data. A probability of less than 5% was considered statistically significant.

**Results**

**Baseline Data**

Body weight, blood pressure, heart rate, and serum cholesterol level were not significantly different between group A and group B (Table 1).

**Mode of Onset and Duration of Coronary Spasm**

Figure 1 shows changes in percent luminal narrowing at the previously denuded site after the intracoronary administration of serotonin. In group A, coronary spasm was induced abruptly and was maintained for at least 25 minutes. ST segment elevation (>1 mm) was
noted at 2 minutes after the intracoronary administration of serotonin and continued for about 25 minutes. In group B, coronary constriction gradually progressed by intracoronary injections of graded doses of serotonin to the level of percent luminal narrowing >75%. Percent luminal narrowing >75% associated with ECG ST elevation was maintained for 25 minutes in group B1 and for 120 minutes in group B2.

**Abrupt Versus Gradual Onset of Coronary Spasm and the Occurrence of Ventricular Fibrillation**

Ventricular fibrillation was noted in six pigs of group A, in one pig of group B1, and none of group B2 during provocation of coronary spasm, but the incidence of ventricular fibrillation was not statistically significant between group A and group B (Table 2). All seven pigs that developed ventricular fibrillation died during provocation of spasm.

**Abrupt Versus Gradual Onset of Coronary Spasm and the Occurrence of Intramural Hemorrhage**

Intramural hemorrhage was noted at the spastic sites in nine pigs of group A (90%), one pig of group B1 (25%), and one pig of group B2 (17%). The incidence of intramural hemorrhage was significantly higher in group A than in group B ($p<0.01$) (Table 2). Intramural hemorrhage was noted at the spastic site, where foam cells but no fibrous tissue were present. In one pig of group A in which intramural hemorrhage was not noted, the spastic site showed rigid fibrous tissue without foam cells, whereas in the other 19 pigs, spastic sites had foam cells in variable proportions.

**Progression of Organic Coronary Stenosis Caused by Intramural Hemorrhage**

Of 11 pigs that had intramural hemorrhage, five pigs (all in group A) died of ventricular fibrillation during
provocation of coronary spasm. In the remaining six pigs (four in group A and two in group B), coronary angiography under treatment with nitroglycerin could be performed after provocation of spasm. Angiographic progression of organic stenosis at the spastic site caused by intramural hemorrhage was noted only in two of six pigs (both in group A; Table 2). Figure 2 shows a case in which progression of organic coronary stenosis was documented angiographically after provocation of coronary spasm. The second marginal branch, in which percent luminal narrowing was 44% before provocation of spasm, was totally occluded during coronary spasm. Administration of nitroglycerin by intravenous bolus did not relieve total occlusion (Figure 2C), which remained at 1 and 7 days after provocation of coronary spasm (data not shown). Histological examination of the site of spasm-induced occlusion showed subtotal obstruction resulting from massive intramural hemorrhage. In this pig, acute myocardial infarction was histologically evident at the area perfused by the occluded branch (Table 2).

Progression of organic coronary stenosis caused by intramural hemorrhage was suspected histologically but not documented angiographically in five pigs (four in group A and one in group B; Table 2). In two of these five pigs (both in group A), total coronary occlusion caused by massive intramural hemorrhage was histologically documented at the spastic site, which had been patent before provocation of coronary spasm (Figure 3). In these two pigs showing total occlusion, angiographic progression of coronary stenosis and evolution of acute myocardial infarction was not documented because of sudden death during provocation of coronary spasm. In the other three pigs, progression of organic coronary stenosis was caused by massive hemorrhage in the space between the internal lamina elastica and the endothelium, which protruded into the lumen. Intramural hemorrhage was seen not only in the thickened intima, in which capillaries (vasa vasorum) were present as described previously, but also in the mild atheroma, in
which capillaries were not noted (Figure 4). Serial sections revealed the continuation of massive hemorrhage at the deeper site of the severely thickened intima to the hematoma-like lesion protruding into the lumen. Plaque rupture and coronary thrombosis were not noted in the coronary segments evaluated histologically.

**Myocardial Infarction Provoked by Prolonged Coronary Spasm**

Evolution of acute myocardial infarction was diagnosed by serial ECG findings, left ventriculograms, and histological findings. In groups A and B1, only one pig developed acute myocardial infarction, whereas in group B2, acute myocardial infarction ensued in five of six pigs (Table 2). Figure 5 shows the left ventriculograms before and 1 and 7 days after provocation of coronary spasm in the left anterior descending coronary artery in a pig of group B2. In this pig, akinesis of the area perfused by the spastic artery was noted at 24 hours as well as 7 days after provocation of coronary spasm. The vessel responsible for akinesis was patent at 1 hour, 24 hours, and 7 days after provocation of coronary spasm. Histological examination confirmed acute myocardial infarction at the akinetic lesion in this pig (Figure 6). The left descending coronary artery was patent, and neither intramural hemorrhage nor coronary thrombi were seen. Figure 7 shows the series of representative ECGs before, during, and 24 hours after provocation of coronary spasm at the left anterior descending coronary artery in another pig of group B2. ST segment elevation in V1 during coronary spasm progressed to abnormal Q waves in leads V1 through V4 at 24 hours after provocation of coronary spasm.

**Discussion**

The major observations in the present study are that 1) intramural hemorrhage was frequently induced by severe coronary spasm of abrupt but not of gradual onset, 2) intramural hemorrhage acutely augmented organic coronary stenosis and sometimes resulted in persistent total coronary occlusion leading to acute myocardial infarction, and 3) prolonged coronary spasm induced acute myocardial infarction without occlusion of the artery.

Our previous studies indicate that spastic sites show mild intimal thickening without intra-atheromatous capillaries in animal models of coronary spasm produced by coronary artery denudation with or without cholesterol feeding.19,20 In these animal models, neither intramural hemorrhage nor progression of organic stenosis was induced by coronary spasm. However, x-irradiation combined with denudation and cholesterol feed-

**FIGURE 5. Left ventriculograms demonstrating acute myocardial infarction in a pig of group B2.** Coronary spasm was provoked at the distal portion of the left anterior descending coronary artery and was maintained for 120 minutes. Shown are left ventriculograms before (panel A), 24 hours after (panel B), and 7 days after (panel C) provocation of coronary spasm. Anteroapical hypokinesis was evident in panels B and C.
ing induced thickened atheromatous lesions with intratheromatous capillaries. In this x-irradiated model, we previously demonstrated that coronary spasm induced intramural hemorrhage and obtained indirect evidence that coronary spasm caused progression of organic coronary stenosis. Thus, we used this x-irradiated animal model in the present study.

**Mode of Onset of Coronary Spasm and Intramural Hemorrhage**

We have recently demonstrated that coronary spasm may evoke intramural hemorrhage when coronary spasm is severe and persistent. In the present study, intramural hemorrhage was observed in nine of 10 pigs in group A (coronary spasm with abrupt onset) and in only two of 10 pigs in group B (coronary spasm with gradual onset). These results suggest that intramural hemorrhage was frequently induced by severe coronary spasm of abrupt onset but not by coronary spasm of gradual onset. Intramural hemorrhage was always noted in the soft lipid-rich tissue at the spastic site but not in the rigid fibrous tissue. We have previously shown that intramural hemorrhage results from torn capillaries around the soft atheromatous gruels and foam cells. Torn capillaries leading to intramural hemorrhage are also demonstrated in the atherosclerotic coronary artery in human, although intracoronary thrombosis is seen most frequently. These results suggest that drag generated by coronary spasm may mechanically tear the capillaries and that this effect may be stronger with coronary spasm of abrupt than gradual onset.

**FIGURE 6.** Histological evidence of acute myocardial infarction in a pig of group B2. Panel A: Macroscopic finding of acute myocardial infarction at 7 days after provocation of spasm. Coronary spasm was provoked at the left anterior descending coronary artery. Panel B: Microscopic finding of myocardial infarction at 7 days after provocation of spasm.
Progression of Organic Coronary Stenosis Caused by Coronary Spasm

Our results indicate that coronary spasm caused intramural hemorrhage in 11 pigs, of which seven pigs developed acute progression of organic stenosis, including complete obstruction in three pigs. These results suggest that spasm-induced intramural hemorrhage is an important factor responsible for acute progression of organic stenosis. Several reports have suggested that progression of organic coronary stenosis may result from intramural hemorrhage in patients with ischemic heart disease.8,25–28 Wartman25 studied serial sections of 41 occluded coronary arteries and demonstrated that occlusion in six arteries (15%) was caused by intramural hemorrhage without thrombus. The origin of intramural hemorrhage is under debate. Some investigators traced the origin of intramural hemorrhage to intimal dissection from the lumen,17,26 whereas others considered that intramural hemorrhage originated from capillaries within the atheromatous plaque.8,23,25,27 We have previously demonstrated that intramural hemorrhage derived from capillaries in the atheroma.21 We also found in this study that the surface of atheroma with intramural hemorrhage was covered with endothelium. These results suggest that intramural hemorrhage derived from ruptured capillaries in the atheroma in our animal model.

Several case reports have suggested the causative role of coronary spasm in progression of organic coronary stenosis.19 Nobuyoshi et al.25 have shown that the positive response to the ergonovine provocative test was a strong risk factor for progression of organic coronary stenosis in a large number of patients with angina pectoris (n=234). On the other hand, a recent study by Kaski et al.29 has failed to demonstrate the progression of organic stenosis at the spastic site in patients with variant angina. However, the number of patients in the study by Kaski et al was small (n=10). Because many factors, including the mode of onset (sudden versus gradual) of coronary spasm and the histological characteristics of the spastic site (soft lipid-rich versus rigid fibrous tissue), may influence the progression of organic stenosis, it is difficult to interpret the results obtained from small numbers of patients.

Coronary Spasm as a Cause of Myocardial Infarction

There are many reports suggesting the pathogenetic role of coronary spasm in evolution of myocardial infarction.1–7 Several mechanisms may be involved in spasm-induced myocardial infarction. First, prolonged coronary spasm per se without coronary thrombosis or progression of organic stenosis may result in myocardial infarction.2–4 This mechanism was responsible for myocardial infarction in five pigs of group B2, in which coronary spasm was sustained for 120 minutes. Second, intramural hemorrhage induced by spasm may result in total coronary occlusion leading to myocardial infarction. This mechanism was involved in myocardial infarction in one pig of group A, as shown in Figure 2. Total occlusion of a coronary artery caused by intramural hemorrhage is not an uncommon necropsy observation in patients who died of acute myocardial infarction,25–28,30 although angiographic and pathological studies suggested that most cases of acute myocardial infarction are accompanied by plaque rupture and thrombus formation.13,16 However, there was no direct evidence indicating that coronary spasm induced intramural hemorrhage leading to total occlusion of coronary artery. Our results indicate that this process might indeed occur during coronary spasm. Third, coronary spasm may produce coronary thrombosis, resulting in myocardial infarction.5–8 In this study, we tried to minimize the contribution of this mechanism by continuous infusion of urokinase.

In group B2, with a long duration of coronary spasm, we used urokinase to minimize the occurrence of coronary thromboembolism. Urokinase might have altered the results, however, because thrombolytic therapy is known to induce a procoagulant state.31 We consider this possibility less likely, for the following reasons. First, urokinase used in the present study exhibits much less prothrombotic activity than streptokinase.32 Second, angiographic findings deny the existence of intracoronary occlusive thrombi in the present study. Third, angiographic and histological findings suggest that pigs did not have a high-grade residual coronary stenosis with ruptured atheroma, which provides a continuing thrombogenic stimulus.33 Fourth, we also used a sufficient dose of heparin, which not only inhibits the increase in throm-
bogenic activity induced by urokinase but also enhances the thrombolytic effects of urokinase by preventing new fibrin formation and its incorporation.24

Clinical Implications

The coronary atherosclerosis in our animal model may be different from that in humans because the atherosclerosis in the animal model was induced rapidly by a combination of cholesterol feeding, coronary denudation, and X-irradiation. Thus, there are some limitations in extrapolating the results obtained from the animal model to clinical implications. Nonetheless, our results suggest that coronary spasm plays an important role in promoting organic coronary stenosis and evolution of acute myocardial infarction. Moreover, the results suggest that the mode of onset (sudden or gradual) and the duration of coronary spasm affect the incidence of these complications. It is generally considered that coronary thrombosis associated with plaque rupture is a predominant cause of acute myocardial infarction. However, the mechanisms responsible for plaque rupture are still unknown. Compressive forces of spasm may rupture the atheroma and extrude atheromatous material into the lumen.8 In fact, plaque rupture and coronary thrombosis are often found at the spastic site in patients with variant angina.3-7 In this experiment, neither plaque rupture nor coronary thrombosis was found. However, histological findings suggest the possibility that intraplaque pressure and volume might increase by means of intramural hemorrhage. Further studies are needed to determine whether intramural hemorrhage leads to plaque rupture and, if so, what factors influence the occurrence of rupture.

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