MYOCARDIAL INFARCTION INDUCED BY CORONARY VENOUS THROMBOSIS
—— An Experimental Study ——

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In a previous study, we proved experimentally that transmural infarction was produced in the area of the left anterior descending artery (LAD) by coronary sinus occlusion attributable to thrombus formation. In an attempt to produce infarction due to thrombus formation and to investigate the influence of thrombosis, the anterior interventricular vein (AIV) was occluded in this study.

In each of 6 adult mongrel dogs, a balloon-tipped catheter was wedged in the AIV via the jugular vein. After the occlusion of blood flow by inflation of the balloon, thrombin (30-50 IU) was injected into the AIV to produce thrombosis and the balloon was removed 60 min later.

As a result, ischemic changes of ST and T in an ECG were clearly observed in all 6 dogs, and serum levels of myocardial enzymes supported the development of myocardial necrosis. Coronary arteriography performed 48 hours after the occlusion of the AIV showed normal findings in all 6 dogs, and residual thrombosis in the AIV were observed in 5 dogs by coronary venography. In these 5 dogs, very local contraction band necrosis (CBN) was noted in the epicardium surrounding the AIV. These experimental findings indicate the following: 1) CBN can also be induced by coronary venous occlusion, 2) once the occlusive mechanism acts on the coronary venous system, the changes which are clinically similar to myocardial infarction can be induced regardless of its causes, 3) ischemic changes in myocardium can be localized in the epicardium irrespective of its causes.

Therefore, these findings are considered to be important in the investigation of the clinical onset mechanism of myocardial infarction.

MYOCARDIAL infarction is induced by abrupt cessation of coronary arterial blood flow. However, in spite of the presence of apparent findings of myocardial infarction, we have sometimes encountered myocardial infarction in which neither clear abnormality in the coronary arteries nor coronary spasm is found. In these cases, it is usually thought that thrombi formed in the coronary arteries have dissolved with time. Can this dissolution of thrombus explain all myocardial infarction cases in which coronary arterial thrombi cannot be detected?

In a previous study, we proved that occlusion of the coronary venous system by thrombus formation induced clear myocar-
Fig. 1. Serial changes of ECG pattern after the AIV obstruction. (Dogs No. 1 and 4). In both cases, the ST elevation is observed immediately after the formation of thrombus. This is clearly seen by the precordial leads in dog No.1, and the precordial leads including I and aV_L in dog No.4. In dog No.1, the ST elevation recovered to the baseline level with time and coronary T appeared as well. In dog No.4, the ST elevation persisted for 48 hours.
AIV: anterior interventricular vein.

dial infarction in dogs, suggesting that coronary venous thrombosis might be considered as one of onset mechanism of myocardial infarction, and moreover demonstrating that the coronary arteriograms were normal in such cases? These results, however, were obtained experimentally by the occlusion of the coronary sinus (CS), and it is rare in a clinical situation that CS obstruction triggers the onset of myocardial infarction. Thus, we have investigated if myocardial infarction can be induced by the occlusion of coronary venous blood flow in a small area, and if the mode of onset and the area of the induced myocardial infarction are different from those of the myocardial infarction induced by the complete occlusion of the CS. The purpose of this study was to investigate the

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influence of the occlusion of the anterior interventricular vein (AIV) parallel to the left anterior descending artery (LAD) and to discuss the clinical significance of findings obtained in this study.

MATERIALS AND METHODS

Nine adult mongrel dogs weighing 9 to 16 kg (mean = 12.0 ± 3.2 kg) were used in this study. The animal was anesthetized with pentobarbital (25 mg/kg), intubated, and connected to a Harvard respirator under the controlled respiration with room air, and maintained by the 48 hours. An 8F guiding catheter for right coronary angioplasty was inserted into the right atrium via the jugular vein and placed at the CS ostium. Through this catheter, a balloon catheter for coronary angioplasty (2-2.5 mm in diameter, Simpson-Robert) was inserted into the AIV using a high torque floppy guide wire. The insertion of the balloon catheter into the AIV failed in three out of 9 dogs. These 3 dogs were not used in this study.

In 6 dogs, the balloon was inflated to obstruct completely the blood flow which was confirmed by the injection of contrast medium from the catheter tip. Thrombin (30-50 IU) was injected from the catheter tip into the AIV. One hour later, the retained balloon was removed gently after the detection of experimental thrombosis by coronary venography. Angiograms were performed for the confirmation of coronary arterial and venous obstruction. The coronary venography was carried out as reported previously. Blood was sampled serially to measure the serum levels of myocardial enzymes for 48 hours. ECG according to the method by Dettweiler et al. was also recorded during the experiment. After the experiment, the dogs were sacrificed and each heart was removed for gross and microscopic studies. The hearts were cut and the parts of them were used for triphenyl-tetrazolium-chloride (TTC) staining. The remaining parts were promptly fixed in 10% of formalin buffer and hematoxylin-eosin staining was used for histological observation.

The paired t-test was used for statistical analysis, and p less than 0.05 was defined to...
Fig. 3. Angiographic findings of the coronary artery and vein before and after thrombus formation in the AIV of dog No.4 (RAO 30°).
The coronary artery showed no change 48 hours after the occlusion of the AIV, while AIVs in 5 dogs (not including dog No.3) showed defects or occlusive findings attributable to thrombosis. The arrow indicates the defect due to thrombosis.
LAD: left anterior descending artery. LCx: left circumflex artery
CS: coronary sinus. GCV: great cardiac vein.

indicate a significant difference. The values were expressed as mean ± standard error (SE).

RESULTS

ECG changes: All 6 dogs showed some degree of changes in ECG findings after AIV occlusion. That is, the ST elevation was observed by the precordial leads in the dogs No. 1, 3, 5 and 6 and by the precordial leads including I and aV1 in the dogs No. 2 and 4. In the dog No. 3, the ST elevation was very short-lived and mild, and no coronary T appeared. In the remaining 5 dogs, the coronary T appeared after some time lapse. ECG changes in the dog No. 1 and 4 are depicted in Fig. 1.

Serum enzymes: In dog No. 3, no significant changes of serum enzymes were recognized by AIV occlusion. However, the serum levels of GOT and CPK were significantly increased after coronary venous occlusion in the other 5 dogs, and their peak values were observed after 6 to 9 hours. The serum levels of LDH and HBD also showed similar patterns as those of GOT and CPK with no statistical significance. Serial changes in the serum levels of myocardial enzymes in all 6 dogs are shown in Fig. 2.

Angiographic findings: No occlusive change was observed in the coronary arteries of all 6 dogs.
dogs, but the residual thrombosis were clearly visualized in the AIV area of 5 dogs by coronary venography. No clear thrombus formation was found in the coronary vein of the dog No. 3, and the thrombus was thought to have been dissolved. Fig. 3 is the coronary arterial and venous angiograms of the dog No. 4, in which the defect due to thrombi is observed in the AIV, but no abnormality is noted in the coronary arteries.

**Histological findings:** Macroscopic observation of cross section of the heart at the level of the AIV with thrombus formation showed the presence of hemorrhage localized in the epicardium surrounding the AIV of the dog No. 1, 2, 4 and 6 (Fig. 4). No significant changes were macroscopically observed in the dogs No. 3 and 5. In AIV, apparent thrombosis were recognized in No. 1, 2, 4, 6 dogs, and residual thrombosis was detected in No. 5 dog, but not in No. 3. TTC staining showed positive findings in the dogs No 1, 2, 4, 5 and 6, such as hemorrhagic changes in the epicardium (Fig. 5). Microscopic changes are listed in Table 1. In all cases except for No. 3, focal or spotty swelling of the myocardial cells and contraction band necrosis (CBN) were observed. These changes were localized in the epicardium in agreement with the site of macroscopically observed hemorrhage (Fig. 6). No ischemic myocardial changes were found on the endocardial side of the same regions.

**DISCUSSION**

The role of the coronary vein in the coronary circulatory system has been systematically discussed from a pathogenetic point of view only by a few investigators. This minor interest in the role of the coronary vein may be thought to reflect the general concept that the coronary venous system serves only as a blood pathway to circulate coronary arterial blood flow, and also that the cause of ischemic heart disease is not due to the disturbance of blood flow in the coronary venous system but only due to coronary arterial disorders. However, since there is no method to prove clinically and accurately the presence of circulatory disorder in the coronary venous system, it seems difficult to confirm that no circulatory disorders occur in the coronary venous system and ischemic heart disease cannot be induced by circulatory disorder in the coronary venous system.

In a previous study, we demonstrated that myocardial infarction could be induced by CS occlusion, attributable to thrombus
### TABLE 1 HISTOLOGICAL FINDINGS

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>Hemorrhage</th>
<th>Congestion</th>
<th>Swelling of myocyte</th>
<th>Contraction band</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>epicardium of ant. left vent.</td>
<td>+</td>
<td>focally, outer layer of ant. left vent.</td>
<td>spotty, outer layer of ant. left vent.</td>
</tr>
<tr>
<td>2.</td>
<td>outer layer of ant. left and right vent.</td>
<td>+</td>
<td>focally, outer layer of ant. left and right vent.</td>
<td>spotty, outer layer of ant. left and right vent.</td>
</tr>
<tr>
<td>3.</td>
<td>none</td>
<td>+</td>
<td>spotty, middle layer of ant. left vent.</td>
<td>none</td>
</tr>
<tr>
<td>4.</td>
<td>outer layer of antero-lateral left vent.</td>
<td>+</td>
<td>focally, outer layer of antero-lateral left vent.</td>
<td>spotty, outer layer of antero-lateral left vent.</td>
</tr>
<tr>
<td>5.</td>
<td>none</td>
<td>+</td>
<td>spotty, outer layer of antero-lateral left vent.</td>
<td>spotty, outer layer of antero-lateral left vent.</td>
</tr>
<tr>
<td>6.</td>
<td>outer layer of ant. left and right vent.</td>
<td>+</td>
<td>focally, outer layer of antero-lateral left and right vent.</td>
<td>spotty, outer layer of antero-lateral left and right vent.</td>
</tr>
</tbody>
</table>

ant. = anterior; vent. = ventricle; + = present

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Fig. 6. Histological findings. (Dog No. 4, Hematoxylin-eosin stain).
Original magnification: a;×10, b;×25, c;×50, d;×100.
Diffuse hemorrhage and the swelling of the myocardial cells are observed in the epicardium surrounding the AIV, and spotty CBs are also observed in these cells.
AIV: anterior interventricular vein. CB: contraction band.

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formation, and also that in spite of the development of myocardial infarction, occlusive changes due to thrombosis are not always observed in coronary arteries. That is, myocardium showed signs of myocardial infarction which were located in nearly transmural, and more apparently in the epicardium. Moreover, in these cases, we have clarified that the coronary arterial blood flow is not completely obstructed by the presence of Thesbian vessels and approximately 60% of the blood flow can be recirculated into the cardiac cavity. These finding suggest a possible pathogenesis in some clinical cases in which angiograms of the coronary arteries are normal but an apparent myocardial infarction is present. However, the disorder in which CS is completely blocked at its ostium is very hard to suppose practically. Therefore, in this study, we produced thrombi in the AIV corresponding to the circulating area of LAD, and studied whether or not myocardial infarction could be induced by a similar manner as in the case of CS occlusion. Furthermore, if myocardial infarction were induced, we also examined whether or not there are any differences in the area and mode of myocardial infarction development.

As a result, ECG showed remarkable changes which indicated the development of acute myocardial infarction in the region corresponding to the AIV circulating area. Moreover, the serum levels of myocardial enzymes pointed to the presence of myocardial necrosis. Histologically, on the other hand, spotty but clear ischemic changes and hemorrhage were observed limitedly in the epicardium of the anterior left ventricular wall. The most characteristic changes were the appearance of the contraction band (CB), which clearly opposed the prediction of coagulation necrosis as mentioned in our previous study.

Contraction band is generally observed when the myocardium, which has undergone ischemic damages, is reperfused, and its presence indicates that the myocardium has suffered from irreversible injury leading to necrosis. In the examination of ischemic changes induced by 60 minutes-ligation of the LAD in dogs, Sashida and his colleagues observed the appearance of calcium-containing inclusion bodies in the mitochondria of ischemic myocardial cells. Jennings and his co-workers advocated that the presence of inclusion bodies was suggestive of reperfusion which caused a large influx of calcium into the ischemic myocardium, leading to the production of CB due to overcontraction of the myocardium. Meanwhile, Kaneko and his colleagues proposed a hypothesis, the myocardial self-destruction theory, which stated that acute myocardial infarction was initiated by instantaneous overcontraction of myocardial fibers, resulting in death of the kinetic cells. Thus, they concluded that CB was the characteristic finding of kinetic cell death. Kaneko's hypothesis, however, has been rejected by some investigators, and is still controversial at present. It is also hard to suppose that
the results of our study are due to "myocardial overcontraction". 

The coronary venogram 48 hours after AIV occlusion demonstrated the presence of thrombi in the AIV of 5 dogs with CB; This finding is not suggestive of the occurrence of reperfusion. However, Matsuda and his co-workers reported that CBN could be observed in the dog having collateral circulation, even if reperfusion was not performed after ischemia, because reperfusion occurred via this collateral circulation. This phenomenon may be one of causative factors for CB formation which was observed in the present study. As we previously reported, the thrombosis by CS occlusion which spread to a wide area of myocardium suggested the impairment of the intra-myocardial capillary network, transmurally. Therefore, the ischemic region could not receive sufficient blood supply from peri-ischemic area, and resulting in coagulation necrosis. In AIV occlusion, on the other hand, the ischemic region was so narrow and thrombi were not massive compared with CS occlusion. Then, it is possible that thrombi in the coronary vein were partially dissolved leading to commencement of the blood flow, or that blood was supplied from peri-ischemic regions and the coronary arterial blood flow was maintained to some degree. These conditions may allow for possible reperfusion mechanism. 

When the myocardium shows local ischemic changes, they are restricted to the endocardium, and are generally known as sub-endocardial infarction. However, the possibility that ischemic change occurs locally in the epicardium has not yet been reported to our knowledge. As shown in the present study, interestingly, the ischemic changes induced by AIV occlusion took place limitedly in the epicardium around the AIV, with no change in the endocardium. Thus, this finding might be called as "subepicardial infarction" in the sense corresponding to subendocardial infarction. More interestingly, in spite of these histological changes, it is difficult to distinguish from changes in ECG patterns and myocardial enzymes whether these ischemic changes occurred in the endocardium or in the epicardium, and whether these changes were due to coronary arterial occlusion or coronary venous occlusion. 

The following mechanism may be considered as the reason for the localization of the ischemic change on the epicardium. That is, the ischemic region induced by AIV occlusion is so narrow that the coronary blood flow is decreased or stopped only in the epicardium, while it is not completely obstructed in the endocardium because of the presence of Thebesian vessels resulting in continued blood supply to the endocardium (Fig. 7). In any case, it is apparent that coronary venous occlusion by thrombus formation induces advanced ischemic changes in the myocardium although no occlusive changes are observed in the coronary arteries. Therefore, the results of the present experiments strongly suggest further studies particularly on the onset mechanism of myocardial infarction. 

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