EXPERIMENTAL STUDY OF ACUTE CORONARY SINUS THROMBOSIS

—Clinical References to Coronary Sinus Thrombosis and Coronary Venography—

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The study was carried out to ascertain the effects caused by thrombosis in the coronary venous system.

The coronary sinus (CS) of 21 adult mongrel dogs was abruptly obstructed to produce acute CS thrombosis. These dogs were then tested for serial changes of ECG, coronary arterial blood flow (CBF), left ventricular pressure (LVP), serum enzymes originating from the injured myocardium and histological changes of myocardium. Furthermore, the clinical application of a new coronary venography procedure was investigated. The results obtained in these experiments were as follows;

(1) When the CS thrombosis was produced by the abrupt obstruction of the sinus, ECG patterns and serum enzymes originating from the myocardium showed changes similar to those of acute myocardial infarction.

(2) The histological examinations showed that the changes in myocardial infarction were characteristically similar to those of hemorrhagic infarction.

(3) Despite the complete obstruction of the coronary-venous system by thrombosis, the development of thrombosis or obstruction was not observed on the coronary-arterial side. This phenomenon is probably due to the recirculation of blood flow through the Thebesian vessels.

(4) The experiment confirmed that the clear coronary venograms were easily obtained, without any risk, by the fixation of a balloon-tipped catheter inside the CS.

VERY few studies have been done so far on the abnormalities of the coronary venous system. There are only a few studies on coronary venous (sinus) thrombosis.¹⁻⁴ This is due to the rare manifestation of thrombosis in the coronary venous system, the obscurity of its clinical sign, and/or the difficulty of a direct confirmation of

thrombosis in the coronary venous system.

On the other hand, intravascular thrombosis in the venous as well as the arterial system is influenced by the following factors: (1) stasis of blood stream, (2) alteration of coagulation and (3) local trauma or inflammation of a vessel wall.⁵

In coronary venous system, there are the Vieussens's valve, which is between great cardiac vein (GCV) and coronary sinus (CS), and the Thebesian valve between CS and right atrium.⁶ Therefore, thrombosis can occur in coronary venous system as well as in the peripheral vein.

Key words:

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Fig.1. Serial changes of ECG pattern after the CS obstruction.

Five minutes after the obstruction of the CS with a balloon and the injection of thrombin, ECG showed the elevated ST-segment in left precordial leads and was followed by the appearance of Q waves and coronary T waves.

CS: coronary sinus.

Furthermore, in practice, we often find cases which, although exhibiting ischemic ECG patterns, show normal coronary angiograms and in which the causal participations of coronary spasms are deniable^{7,8,9}. The involvement of thrombosis in the coronary venous system should probably be considered for these cases.

The authors, therefore, investigated the influences of coronary venous thrombosis on the heart as well as its clinical significance on the results obtained from the following experiments. The coronary sinuses of test animals were ob-

structed with a percutaneous catheterization in order to bring on acute CS thrombosis. Then, the animals were subjected to tests for ECG, left ventricular pressure (LVP), coronary arterial blood flow (CBF), serum enzymes escaped from injured heart muscle and histologic findings of myocardial lesions.

In addition, we also investigated whether or not, coronary venography could be conducted as safely and easily as coronary arteriography, in order to confirm coronary-venous abnormalities.

Fig. 2. Serial changes of serum enzymes after the CS obstruction.

The activities of all enzymes significantly increased compared with the control levels, and reached their peaks at 6 to 9 hours after the CS obstruction.
CS: coronary sinus.

MATERIALS AND METHODS

Twenty-one mongrel dogs, weighing from 9 to 24 kg (13 ± 2.6 kg) were used to perform the following experiments.

The animals were divided into 3 groups in order to exclude the influence of the thoracotomy on the values of serum enzymes and ECG patterns.

After venous anesthesia with pentobarbital (25 mg/kg), the dogs were intratracheally intubated and then equipped with the Harvard respirator to ventilate with room air. During the experiment, succinylcholine (0.2 mg/kg; IV) was administered.

The 7F Sones catheter was inserted into the carotid artery and placed inside the left ventricle, and the 7F balloon-tipped catheter was placed inside the pulmonary artery, which was inserted from the jugular vein.

Then the LVP and the pulmonary arterial pressure (PAP) were measured with a transducer (Bell and Howell 4-327C type).

A probe of 2 or 3 mm in diameter (Nihon Kohden FH-020T) was installed at the proximal

portion of left anterior descending coronary artery (LAD) and the CBF was measured with the electromagnetic flowmeter (Nihon Kohden MFV-1200). The San-ei Sokki Polygraph 360 system was used as a recording apparatus.

The 7F balloon-tipped catheter was used for the obstruction of the CS. ECG was recorded with 10 leads including standard limb leads, augmented unipolar limb leads and 4 precordial leads according to the method of Detweiler and his colleagues¹⁰

For both coronary arteriography and coronary venography, 76% urografin was manually injected; 1 to 2 ml for arteriography and 2 to 3 ml for the venography. The Toshiba Cine-Angio system KXO-1250 (48 frames/sec) was employed for the angiographic observation.

Group A (N = 8)

Without thoracotomy catheters were percutaneously inserted and placed inside the left ventricle and the CS. After hemodynamic stabilization, the CS was obstructed with a balloon and 100 to 300 IU of thrombin was injected from the tip of catheter to produce the CS thrombosis.

Fig.3. Histological findings after the CS obstruction. Hematoxylin-eosin stain. (b, c, d).
 a) The cutting face of heart muscle. Myocardial infarction accompanied by extensive hemorrhage in the LAD region.
 b) The cavity of the coronary vein was completely obstructed with thrombosis that was not detected in the paralleling coronary artery.
 c), d) Histological findings of epicardial side in the LAD region. These findings were accompanied by infiltration of neutrophils and extensive myocardial hemorrhage, and interstitial edema and moderate hemorrhage were recognized in normally appeared cut edge.
 CS: coronary sinus; LAD: left anterior descending artery; LV: left ventricle; RV: right ventricle; A: coronary artery; V: coronary vein; Th: thrombus

The balloon was deflated after 60 minutes and thereafter the experiment was carried out without anesthesia for 48 hours.

Throughout the experiment, ECG was serially recorded and the peripheral venous blood was collected for the measurement of such enzymes as CPK, GOT, LDH and HBD which are derived from the heart muscle.

After 48 hours, coronary angiography was done to confirm the obstruction of the left coronary artery and then the dogs were sacrificed under anesthesia. The heart was immediately resected and dipped into the 10% phosphate buffer formalin solution for histological examination.

Group B (N = 8)

Under thoracotomy on the left side, an electromagnetic-flowmeter probe was set around the

LAD. After hemodynamic stabilization, the 7F balloon-tipped catheter was percutaneously inserted into the CS and the balloon was abruptly inflated with 0.8 to 1.5 ml of air to obstruct the coronary venous blood flow, 100 to 300 IU of thrombin was immediately injected from the tip of the catheter into the CS.

Before and after the CS occlusion, the serial fluctuation of the LVP, CBF and ECG were simultaneously recorded. After 60 minutes the balloon was deflated and each parameter was recorded for additional 30 minutes.

Group C (N = 5)

The experimental procedure was similar to that of Group A. The balloon-tipped catheter was percutaneously inserted into the jugular vein and led into the CS. Under the serial recording of the LVP and ECG, the balloon was

Fig.4. Serial changes of CBF, LVP and PAP after the CS obstruction. Immediately after the obstruction of the CS, the CBF significantly decreased. It recovered slightly after the deflation of the balloon. The same phenomena were observed both in the LVP and PAP.

CS: coronary sinus; CBF: mean coronary arterial blood flow; LVP: left ventricular pressure; PAP: pulmonary arterial pressure.

inflated to occlude the CS. Immediately after this, 2 to 3 ml of 76% urografin was retrogradely and manually injected into the CS for the purpose of the coronary venography. The coronary arteriography was performed using the 7F Sones catheter.

The hemodynamic and enzymatic results obtained from these studies were analyzed with the paired *t* test of the inductive-statistic and the data showing $p < 0.05$ was judged to be statistically significant.

Each value expressed the mean $\pm$ standard deviation.

RESULTS

Group A

When 100 to 300 IU of thrombin was injected into the coronary vein, immediately after the inflation of the balloon set in the CS, some pathological changes in ECG were observed in all cases. Sixty minutes after thrombin injection the balloon was deflated. However, thrombosis remained in the CS for 48 hours in all 8 cases. In precordial leads of all cases, ECG showed elevation of ST segment followed by abnormal Q wave and then coronary T wave. Such changes in ECG pattern were quite similar to the serial changes observed in clinical cases of acute myocardial infarction (Fig. 1).

The serial changes of serum enzyme activities, such as CPK, GOT, LDH and HBD, were significant as shown in Fig. 2, and are the manifestation of myocardial necrosis. In spite of the existence of CS thrombosis, the patent coronary arteries can still be observed by angiography performed

after 48 hours while the Thebesian vessels were not observed.

Coronary venography could not be performed for the occlusion of the venous system.

In the 8 resected hearts, thrombosis was macroscopically detected inside the CS and spread over 1.5 to 3 cm length from the sinus ostium. Histological observations showed that in the cavity of the CS, the great cardiac vein, the anterior interventricular vein and small vessels were obstructed with fresh thrombus, but no abnormal findings were observed in the coronary artery parallel to the same lesions. In all cases, hemorrhagic lesions supplied from the LAD were macroscopically detectable on the cardiac surface. On the cutting section as well, transmural hemorrhage and myonecrosis were observed especially on the epicardial side. The normal appearances, however, were also recognized even in the patchy area of the epicardial side. Histopathological findings demonstrated the following: 1) severe myocardial hemorrhage on the epicardial side, 2) almost transmural hemorrhage and infiltration of neutrophils, 3) interstitial edema and moderate hemorrhage even in a cut edge with normal appearance (Fig. 3). These changes were also observed in part of the left circumflex branch area.

Group B

Before obstruction of the CS, the blood flow of the LAD was 32 to 70 ml/min, (47 ± 13.0 ml/min), after obstruction it decreased to 12 to 51 ml/min (29 ± 12.5 ml/min). The decreasing rate of the blood flow was statistically significant and was almost stable for 60 minutes throughout

Fig.5. Serial changes of LVP, PAP and CBF after the CS obstruction. These parameters significantly decreased compared with the control levels. The decreasing rate of CBF was about 40% on the average. The rebound of the blood flow was observed immediately after the balloon deflation. The same phenomena were observed both in the LVP and PAP.
CS: coronary sinus; LVP: left ventricular pressure; PAP: pulmonary arterial pressure; CBF: coronary arterial blood flow

the CS obstruction. The blood flow of the LAD increased as soon as the balloon was deflated but did not recover to the initial value. Five minutes after the inflation of the balloon, the ECG, obtained with the precordial lead reflecting the LAD region, showed ST-segment elevation, and both the LVP and the PAP decreased significantly. These changes continued during the

Fig.6. Coronary arteriogram and coronary venogram in dog.

a) A left coronary arteriographic image. (RAO 30°)

b) A coronary venographic image. (RAO 30°) The arrow shows the tip of the inflated balloon.

LAD: left anterior descending artery; LCx: left circumflex; CS: coronary sinus; AIV: anterior interventricular vein; GCV: great cardiac vein; MCv: middle cardiac vein

inflation of the balloon. After the deflation of the balloon, the elevation of ST-segment continued for long time, while the LVP and the PAP recovered in some degree (Fig. 4 and 5).

Group C

The balloon-tipped catheter inserted into the CS was rapidly inflated with air and the tip was tightly fixed inside the sinus so it will not loosen. Under these conditions, the clear coronary-venographic images were easily obtained by the manual injection of 2 to 3 ml of 76% urografin (Fig. 6). Using this procedure, coronary veno-

Fig.7. Changes of LVP, PAP and ECG at the coronary venography. After the injection of contrast medium into the CS, the LVP showed a transient slight decrease and ECG showed sporadic premature ventricular contraction (PVC) and premature atrial contraction (PAC).

CS: coronary sinus; LVP: left ventricular pressure

graphy was performed in 5 dogs, 25 times in total. Although a few ventricular premature contraction or atrial premature contraction were temporally observed for a few seconds during the injection of the contrast medium, dangerous arrhythmia was not observed. Moreover, the

decrease of the LVP, observed during the coronary venography, was a transient phenomenon (Fig. 7).

DISCUSSION

The ST-segment elevation and the T-wave inversion are usually based upon acute myocardial ischemia caused by the sudden interruption or the extreme decrease of the CBF. These abnormalities are also observed in acute myocarditis, acute pericarditis¹¹ and rare cases of idiopathic cardiomyopathy.^{12,13} In contrast, the coronary venous system has been exceptionally investigated and only a few cases of its abnormalities have been reported as special cases in clinical practice!^{14,15} However, we have noted cases with abnormal ST and T wave, despite the absence of coronary-arterial disorders, myocarditis, pericarditis and cardiomyopathy.⁷⁻⁹ Furthermore, there are no reports that have systematically examined such electrocardiographic changes from the viewpoint of CS disorders.

Therefore, for the purpose of studying whether or not CS thrombosis could be a factor in the pathogenesis of these cases, thrombosis was experimentally induced in the CS, and the following studies were done: the electrocardiographic examination and also the investigation of the serum enzymes and the histological findings of cardiac lesions. The results showed that acute

Fig.8. Schema of CS thrombosis and cardiac vessels.

Even if the coronary venous system is obstructed, the CBF is capable of being drained into the cardiac cavity through the Thebesian vessels.

CS: coronary sinus; CBF: coronary arterial blood flow

CS thrombosis caused myocardial necrosis just as in coronary-arterial thrombosis and presented the same changes in ECG and serum enzymes as in the clinical cases of acute myocardial infarction.

When the CS was obstructed with a balloon and CS thrombosis was induced by the injection of thrombin, it was found that, despite the ischemic changes in ECG, the blood flow of the LAD supplying the cardiac lesion decreased by 40% on the average, and the remaining 60% of the blood flow with the usual CBF were consistently circulating without passing through the corresponding coronary vein. The explanation of this phenomenon implies the existence of some collateral circulation. And the Thebesian vessels¹⁶ would be the only collateral circulation that is capable of playing this role (Fig. 8).

Wearn et al¹⁷ have reported that the Thebesian vessels are capable of draining about 50% of the CBF into the cardiac cavity. From their own experiments, Faxon et al¹⁸ have also reported that the left ventricular diastolic pressure could be presumably measured by means of the obstruction of CS with a balloon and they concluded that this is possible because of the existence of the Thebesian vessels.

Since the Thebesian vessels flow into the cardiac cavity, even if the coronary veins are obstructed with thrombosis, the CBF is capable of recirculating into the cardiac cavity to a certain degree and the blood supply to myocardium could be partially maintained. This hypothesis explains the results of our experiment. In all cases of experimental CS thrombosis, the angiographic image did not show any abnormal findings in the coronary artery and all dogs survived the experimental period for as long as 48 hours, despite the occurrence of myocardial necrosis similar to the myocardial lesions caused by the acute obstruction of the LAD.

The histological findings in coronary venous thrombosis seem to be characterized by the myocardial hemorrhage in addition to the sub-epicardial hemorrhage. This finding suggested that not all the coronary arterial blood flow can be drained into the cardiac cavity despite the existence of the Thebesian vessels, resulting in the partial maintenance of the blood supply for myocardial necrotic lesion.

In experiments of the B group, the CBF, which decreased by the obstruction of the CS, recovered with the deflation of the balloon after 60 minutes. This is probably due to the partly

preserved CBF, resulting from the incomplete obstruction of the CS. As for group A, the CS was suspected to be completely obstructed with the thrombosis after 48 hours.

From the biophysiological and histological investigations, it was proved that acute CS thrombosis can cause the same myocardial ischemic changes as in the coronary arterial occlusion. Even if the same phenomenon could not be immediately concluded in clinical cases, it probably suggests that the CS thrombosis should be considered as a factor in the pathogenesis of myocardial ischemia.

The results obtained in these experiments, which indicate additional information of the coronary venous system, is needed in the following clinical cases: in cases with clinical signs of myocardial infarction, despite the normal aspects of the coronary artery, accompanied with partial asynergy in the left ventricle.

Before our study, we had no means of obtaining detailed, clear coronary venograms. The venogram was scarcely considered as a venous phase of the coronary angiography. However, through our newly devised method, the detailed clear coronary venograms were easily obtained without any risk. Therefore, this method is useful to confirm the existence of coronary venous abnormalities and also valuable for the further investigations of the pathophysiological role of the coronary veins.

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