CYCLICAL REDUCTION IN BLOOD FLOW OF
PARTIALLY CONSTRIC TED CORONARY ARTERY IN DOGS
II. AN ARTERIOGRAPHIC STUDY

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Mechanisms for cyclical reduction in peripheral blood pressure and flow of partially constricted coronary artery of anesthetized dogs has been examined. In 64 of 97 preparations, cyclical reduction in coronary blood pressure and flow developed 3 to 32 min after the beginning of constriction. Period duration of the cyclical reduction ranged from 1 to 32 min. The cyclical reduction was frequently associated with elevation of the ST segment of surface electrocardiogram, systolic bulge of the left ventricle and excitation of afferent cardiac sympathetic nerve fibers. In the preparations in which cyclical reduction was not produced by constriction, a brief stretching of the constricted portion provoked the cyclical reduction. Segmental or diffuse narrowing of the constricted coronary artery which occurred during the reduction in pressure and flow was demonstrated by selective arteriography. Also, segmental spasm in the constricted coronary artery was demonstrated by photography. No obvious difference in the constricted portion of the artery was observed histologically between the preparations in which cyclical reduction developed and those in which cyclical reduction was not produced. The results indicate participation of vasospasm in the cyclical reduction of blood pressure and flow in partially constricted coronary artery.

In 1973, spontaneous cyclical reduction which occurred in peripheral blood pressure and flow of partially constricted coronary artery was found by us\(^1\) and the changes in surface electrocardiogram and left ventricular wall motion due to the cyclical reduction, and the effects of coronary vasodilating agents on the cyclical reduction have been examined\(^2\)\(^-\)\(^5\). However, the mechanisms for the cyclical reduction remained unclear. In this study, we examined whether the cyclical reduction could also occur in the left circumflex branch as in the case of anterior descending branch, whether the afferent cardiac sympathetic nerve fibers which participate in noiception of the heart\(^6\)\(^-\)\(^10\) could be augmented by cyclical reduction and what kinds of morphological changes could occur in the constricted coronary artery during cyclical reduction in blood pressure and flow.

METHODS

1. Surgical Preparation

Ninety-seven adult dogs were anesthetized...
with intravenous pentobarbital sodium (35–40 mg/kg). The trachea was intubated for artificial positive pressure respiration with air. The upper 7 ribs on the left side were removed. After pericardiotomy, the proximal segment of the left circumflex branch was dissected free of surrounding tissues and a magnetic flowmeter (Nihon-koden model FM-72) was placed on it. A segment 0.5 to 1 cm distal to the flowmeter was also dissected free of surrounding tissues and a silver constrictor with a form of cylinder was placed on it for partial constriction. A catheter 1 mm in external diameter was introduced in retrograde fashion into a small branch of the circumflex branch which nourished the apical area of the left ventricle to monitor the peripheral coronary blood pressure. A monopolar electrode was fixed to a portion of the left ventricle to monitor surface electrocardiogram. A strain gauge arch was sewn to the left ventricular wall to monitor the active force developed by the portion of the ventricle and was expressed as left ventricular tension. A catheter was introduced into the right femoral artery to measure systemic blood pressure.

2. Recording Action Potentials of Afferent Cardiac Sympathetic Nerve Fibers

In 5 preparations, the action potentials of the afferent sympathetic nerve fibers from the left ventricle were led from either the second or third thoracic communicating ramus of the left side by the method previously described\(^6\)–\(^10\) and the changes in firing frequency of the fibers during the cyclical reduction in pressure and flow of the partially constricted coronary artery were examined.

3. Histologic Examination

In 8 preparations in which cyclical reduction in coronary blood pressure and flow developed, both sides of the constricted portion of the circumflex branch was tied with threads and the portion was isolated. The isolated portion was fixed in 20% formalin and was stained with Carstairs platelet stain and the changes in the

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Fig. 1. Schematic representation of the experimental preparations.
Ao=aorta. PA=pulmonary artery. RV=right ventricle. LV=left ventricle. ADB=anterior descending branch. LCB=left circumflex branch.

Fig. 2. From the top: peripheral coronary blood pressure (CBP), coronary blood flow (CBF), systemic blood pressure (SBP), heart rate (HR), surface electrocardiogram (ECG) and left ventricular tension (LVT). The initial abrupt fall in CBP indicates constriction.

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TABLE 1  DIFFERENCE IN SYSTEMIC BLOOD PRESSURE AND HEART RATE BETWEEN
THE PREPARATIONS IN WHICH CYCLICAL REDUCTION IN CORONARY BLOOD
PRESSURE OCCURRED AND THOSE IN WHICH CYCLICAL REDUCTION DID
NOT OCCUR

<table>
<thead>
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<th>Cyclical Reduction</th>
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<tbody>
<tr>
<td></td>
<td>Occurred</td>
</tr>
<tr>
<td>Female</td>
<td></td>
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<tr>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18</td>
</tr>
<tr>
<td>MSBP (mmHg)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>105.0 ± 19.0</td>
</tr>
<tr>
<td>n</td>
<td>18</td>
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<tr>
<td>Male</td>
<td>109.3 ± 20.1</td>
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<tr>
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<td>23</td>
</tr>
<tr>
<td>Total</td>
<td>107.3 ± 11.2</td>
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<tr>
<td>n</td>
<td>64</td>
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<tr>
<td>HR (beats/min)</td>
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<td>128.2 ± 14.0</td>
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<tr>
<td>n</td>
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<tr>
<td>Male</td>
<td>134.0 ± 10.3</td>
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<tr>
<td>n</td>
<td>23</td>
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<tr>
<td>Total</td>
<td>132.1 ± 7.6</td>
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<td>64</td>
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n = number of preparations

Fig. 3. The top one thirds: time course of the period duration of the cyclical reduction in pressure and
flow of the partially constricted coronary artery. No significant difference in period duration
from the first to the 13th cycle.
Middle one thirds: A distinct difference in period duration observed in two preparations.
Lower one thirds: distribution of period duration of the initial three cycles.
Fig. 4. The relationship between peripheral afferent sympathetic nerve fibers of the left ventricle.

Upper photograph: during the rise in peripheral coronary blood pressure.

Lower photograph: during the fall in peripheral coronary blood pressure. The downward motion of the left ventricular tension curves indicates systolic bulge. The downward arrows correspond to QRS of electrocardiogram.

portion were compared microscopically to those of the preparations in which cyclical reduction was not produced.

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Fig. 6. From the top: an integrated action potentials of a myelinated afferent fiber, peripheral coronary blood pressure, systemic blood pressure and left ventricular tension.

Note, an increase in discharge frequency during cyclical fall in peripheral coronary blood pressure.

Fig. 7.Selective arteriography of a partially constricted coronary artery (left circumflex branch).

\( a \): before constriction. \( b \): during fall in peripheral blood pressure of the partially constricted coronary artery. \( c \): during the rise in peripheral coronary blood pressure.

\( \text{ca in } a \): a catheter used for the injection of Anglo-Conrey\textsuperscript{®}. \( \text{ca in } b \): a catheter used for measurement of peripheral coronary blood pressure. \( \text{con} \): constrictor.

Mean peripheral coronary blood pressure at the time of injection is shown at the bottom of each photograph. The black arrow in \( b \) indicates segmental narrowing adjacent to the constrictor.

4. Arteriographic Examination

In 20 preparations, a small catheter was introduced into a small branch of the proximal segment of either the left circumflex branch or the anterior descending branch for injection of 0.5 to 1 ml of Anglo-Conrey\textsuperscript{®}. A segment distal to the small branch into which the catheter was introduced was constricted by a constrictor to produce cyclical reduction in peripheral blood pressure of the branch. The contrast material was injected.
before and during occurrence of cyclical reduction and arteriography was made using 35 mm cinecamera at 80 frame/sec.

5. Color-Photographic Examination
In 5 preparations, the anterior descending branch 3 to 5 cm in length was exposed. A proximal segment of the branch was constricted and the changes in the wall of the branch associated with cyclical reduction in blood pressure were examined by photography.

RESULTS
1. The Relationship between Peripheral Blood Pressure and Flow of the Partially Constricted Coronary Artery
Cyclical reduction in peripheral blood pressure and flow of the partially constricted coronary artery occurred in 64 of 97 dogs (Fig. 2). The cyclical reduction occurred in 18 of 24 female dogs (75%) while it occurred in 23 of 40 male dogs (57%). Mean systemic blood pressure of the preparations in which the cyclical reduction occurred was higher than that of those in which cyclical reduction did not occur. However, no significant difference in heart rate was observed between these two groups (Table I).
In 33 preparations in which cyclical reduction did not occur within one hour, repeated constriction was performed, however, the cyclical reduction was produced in only two of them. In 8 preparations in which cyclical reduction was not produced by constriction, both ends of the constricted segment were stretched briefly with two pairs of forceps. In 4 of these preparations, the cyclical reduction developed immediately after cessation of stretching. However, it disappeared after one to 3 cycles. The results of these preparations were not included in Fig. 3 and Table I.

Fig. 8. The same preparation as that in Fig. 7.
The black arrow in b indicates diffuse narrowing of the branch which was not observed in c.

Fig. 9. Arteriographic changes observed in the partially constricted coronary arteries.

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pressure and flow were reduced gradually and then were increased abruptly in 59 preparations as shown in Fig. 2 while they were reduced and increased abruptly in the remaining 5 preparations.

The time course of the period duration of the cyclical reduction was examined in 12 preparations. However, no significant change in period duration was observed for up to 13th cycle. Period duration of the cyclical reduction distinctly differed preparation by preparation as shown in Fig. 3. The period duration ranged from 30 sec to 32 min and the maximum frequency was observed between 7 and 8 min (Fig. 3).

In 24 preparations, the relationship between peripheral blood pressure and flow of the constricted coronary artery was examined. In these preparations, the flow was reduced below 50 percent of the control value during the phase of fall in peripheral coronary blood pressure. On the other hand, the flow increased over 50 percent of the control value during the phase of rise in peripheral coronary blood pressure. An increase in flow over the control value was frequently observed during this phase (Fig. 4).

In the preparations in which the flow was reduced below 50 percent of the control value during the phase of fall in peripheral coronary blood pressure, elevation of the ST segment of surface electrocardiogram and passive stretching of the left ventricular wall during the systole, the systolic bulge, were frequently observed (Fig. 2). The cyclical reduction in pressure and flow continued for more than 2 hours in the majority of preparations. However, it disappeared spontaneously after 3 to 7 cycles and within one hour despite no obvious change in systemic blood pressure and heart rate in 7 preparations.

2. Excitation of Afferent Cardiac Sympathetic Nerve Fibers Synchronous to Cyclical Reduction in Coronary Blood Pressure and Flow

The relationship between the changes in discharge frequency of the afferent sympathetic nerve fibers from the left ventricle and the cyclical reduction in blood pressure of the partially constricted coronary artery was examined in 5 preparations. In all these preparations, mean peripheral coronary blood pressure was reduced below 50 percent of the control value during the phase of fall. The discharge frequency of the afferent fibers increased during each cyclical reduction in coronary blood pressure (Figs. 5 and 6).

3. Histologic Changes in the Partially Constricted Coronary Artery

In all 8 constricted segments of the coronary artery which were excised during cyclical reduction in peripheral coronary blood pressure, platelet aggregates were found in the constricted segments and/or at the inlet or outlet of the constricted segments. Also, platelet aggregates were found in all 4 constricted segments which were excised during the cyclical rise in peripheral coronary blood pressure. In addition, platelet aggregates were found in all 5 segments which were excised from the preparations in which cyclical reduction in peripheral coronary blood pressure and flow did not occur. There was no obvious difference in size and locations of the platelet aggregates between the preparations in which the cyclical reduction occurred and those in which the cyclical reduction did not occur.

4. Arteriographic Changes in the Partially Constricted Coronary Artery

Selective coronary arteriography was performed in 20 dogs in which cyclical reduction in peripheral coronary blood pressure occurred. In both anterior descending branch and circumflex branches, segmental or diffuse narrowing in the portions distal to the constricted segment was observed during the phase of fall in pressure in 20 trials of 15 preparations (Figs. 7 and 8). These changes were not observed after the peripheral coronary blood pressure rose. In 3 of these preparations, arteriography was repeated during the phase of fall in pressure. In 2 of these preparations, the site and pattern of narrowing differed cycle to cycle (Figs. 7, 8 and 9). In the remaining 5 preparations, the portions peripheral to the constrictor were not visualized, indicating complete obstruction at the constricted segment. Since the constrictors made of silver were used in this study, the changes at the constricted segment could not be examined.

5. Morphologic Changes in the Partially Constricted Coronary Artery Examined by Color-Photography

In 5 preparations, the changes in the coronary arterial wall during the cyclical reduction in peripheral coronary blood pressure were photographically examined using color films. In 2 of these preparations, segmental contraction appeared gradually and disappeared rapidly along with the cyclical changes in peripheral coronary blood pressure (Fig. 10). In the remaining 3 preparations, diffuse narrowing was observed, however, it was not examined whether the narrowing was due to active contraction of the coronary smooth muscles or passive narrowing.
due to reduction in perfusion pressure caused by obstruction at the constricted segment.

DISCUSSION

The results in this study indicate that cyclical reduction in peripheral blood pressure and flow can occur in the partially constricted left circumflex branch as in the case of anterior descending branch. The latency and period duration of the cyclical reduction observed in this study were close to those observed in our previous study.

The afferent sympathetic nerve fibers with their receptive fields in the left ventricular wall cause pseudoadaptive response in dogs and anginal pain in man. Their modality of excitation during myocardial ischemia and its relation to left ventricular wall motion and electrocardiogram have been examined by Uchida, et al. In this study, it was revealed that the afferent fibers which play an important role in nociception of the heart could be augmented cyclically and synchronously with the cyclical reduction in coronary blood pressure and flow.

In patients with Prinzmetal's variant angina pectoris, one attack is frequently composed of several small attacks and is frequently associated with elevation of the ST segment of electrocardiogram. In this group of patients, coronary vasospasm has been demonstrated. The changes in electrocardiogram, period duration of the cyclical reduction in coronary blood pressure and flow and arteriographic changes observed in this study closely resembles the clinically observed events.

Recently, Fols, et al also observed the same phenomenon in dogs and suggested participation of platelet aggregation at the constricted segment of the coronary artery in this phenomenon. In our study, however, platelet aggregates were found in all number of preparations in which the cyclical reduction occurred. In addition, platelet aggregates were also found in the preparations in which the cyclical reduction did not occur. Therefore, there is a possibility that the aggregates were formed after excision of the coronary segments. Because of this finding, we could not attribute the cyclical reduction in coronary blood pressure and flow to obstruction of the constricted segment with platelet aggregates. In this study, narrowing at various portions of the constricted coronary artery was observed arteriographically and photographically. This finding suggests that vasospasm played a role in this phenomenon. Large doses of dipyridamole and prostaglandin $E_1$, which are the potent inhibitor of platelet aggregation could not suppress this phenomenon while nitroglycerin and papaverine which are the potent coronary vasodilators and are the weak inhibitor of platelet aggregation completely eliminated this phenomenon.

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This finding also supports participation of coronary vasospasm rather than platelet aggregation in this phenomenon.

In this study, the portions distal to the constrictor was not visualized arteriographically in several preparations indicating complete obstruction at the constricted segment. Although the changes in the constricted segment could not be examined, it is likely that vasospasm also occurred at the segment.

Several mechanisms can be postulated as possible inciting factors for this phenomenon:

1. In this study, stretching the constricted segment of the coronary artery initiated the cyclical reduction in pressure and flow. It is well known that a brief stretching of the isolated carotid artery contract cyclically7,10,21,22. Cyclical contraction of the isolated coronary artery in response to a brief stretching was also observed in our preliminary study. Therefore, the constricted coronary artery may have contracted cyclically in response to cardiac motion or to mechanical stimulation by the constrictor resulting in cyclical reduction in pressure and flow.

2. The subcutaneous small arteries, portal vein and mesenteric artery contract cyclically20. Also, the isolated coronary artery contract cyclically23. Therefore, the constricted coronary artery may have contracted spontaneously and cyclically because of lowered perfusion pressure which before constriction counteracted contraction resulting in the cyclical reduction in pressure and flow.

3. There is a possibility that vasospasm due to anoxia, or due to an increase in vasoactive substances released from the myocardium or platelets such as prostaglandin E2, and thromboxan A2 caused this phenomenon. In general, both coronary blood pressure and flow were reduced gradually and then were increased abruptly in this study. Production and wasting of the vasoactive substance(s) or fatigue of the coronary smooth muscles may have produced the cyclicity. Pressure gradient across the portion of spasm acetelated relaxation, leading to the abrupt increase in pressure and flow since such an abrupt relaxation (for vascular smooth muscles) is unusual.

4. There is also the possibility that the cyclical excitation of the cardiac sympathetic or vagal nerves resulted in this phenomenon. However, this phenomenon occurred even after cardiac denervation and was not influenced by the blocking agents of alpha- and beta-adrenergic recep-

tors and atropine3,18. Therefore, it is unlikely that the adrenergic and cholinergic mechanisms participated in this phenomenon.

The cyclical reduction in coronary blood pressure did not occur in about 34 percent of the preparations although severity of constriction was changed. There was a significant difference in occurrence between female and male dogs. Also, there was a significant difference in systemic blood pressure between the group in which the cyclical reduction occurred and that in which it did not occur. On the other hand, there was no significant difference in systemic blood pressure between female and male dogs. Systemic hemodynamics, humoral or hormonal environments and the character of the coronary smooth muscles may have contributed to the inconsistent occurrence of this phenomenon.

REFERENCES


14. MURAO, S., HARUMI, K., MASHIMA, S., et al.:


