NON-UNIFORM BLOOD FLOW THROUGH THE ISCHEMIC MYOCARDIUM INDUCED BY STELLATE GANGLION STIMULATION

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The effect of electrical stimulation of the stellate ganglion on the blood flow through the ischemic myocardium was examined in anesthetized open-chest dogs. The flow was continuously monitored by heated cross-thermocouples. The anterior descending branch of the left coronary artery was constricted in order to produce various ischemic states in the anterior wall of the left ventricle.

Following stimulation, the flow through the outer half of the wall was increased before constriction, was slightly reduced during mild constriction, was markedly reduced during moderate constriction and was slightly reduced or increased during severe constriction. The flow through the inner half was not infrequently reduced before constriction, was slightly reduced or increased during mild constriction and was markedly increased during moderate or severe constriction. These flow changes had a relation to the pressure gradients between the constricted and non-constricted branch.

The flow through the zones adjacent to the constricted area was augmented by stimulation. Pretreatment with propranolol eliminated these flow changes.

These results suggest the regional difference of sympathetic regulation of the myocardial blood flow and the dependence of its modality on the severity of ischemia. It is supposed that stimulation-induced reduction in the flow through the moderately ischemic myocardium was due to 'coronary steal' and that its occurrence is dependent on the severity of constriction of the coronary artery.

BESIDES exertion, emotional and sensory stress play an important role in inciting angina pectoris.¹⁻⁴ Queerly in a certain group of patients with coronary insufficiency, stress is the sole precipitating factor of anginal attack. Since

emotional and sensory stress are accompanied by sympathetic augmentation,^{1,5,6} it has been considered that causative mechanism is an increased oxygen consumption without a sufficient increase in the coronary blood supply.⁷

In our studies, a marked decrease in the flow through the moderately ischemic myocardium was produced by stellate ganglion stimulation. This decrease was considered not due to coronary spasm,^{2,8} but due to coronary steal phenomenon. This observation is contradictory to the mechanisms hitherto considered.^{2,7,8} We,

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therefore, proffer this as a possible inciting factor for the clinically and experimentally observed events^{2,9-12}

METHODS

1. Assessments of Regional Myocardial Blood Flow

Myocardial blood flow was continuously monitored by heated cross-thermocouples. This method is based on the principle of measuring the amount of heat carried by the blood stream from a stationary heated body.¹³⁻¹⁷

The cross-thermocouples are made of constantan and copper wires with a diameter of 100μ .¹⁸⁻¹⁹ The distance between the heated and the reference junction is about 4 mm. They can easily be implanted into desired sites within

the left ventricular wall without a demonstrable damage. The radius of the temperature field around the heated junction is about 3.5 mm when a D.C. of 400 mA is delivered to the junction.¹⁸ The tissue volume within the temperature field is approximately 0.31 ml. The blood stream through this temperature field deprives the heat, and resultantly reduces the thermoelectromotive voltage and ampere.^{17,18} Therefore, the thermoelectromotive voltage and ampere can represent, although semiquantitative, the amount of the blood flow.

In our experiments, the thermoelectromotive voltage was measured as an indicator of the myocardial blood flow.

2. Experimental Procedures

Fig.1. Constriction of the anterior descending branch (Anterior D. B. or A. D. B.) was performed at each downward arrow, and electrical stimulation of the stellate ganglion was performed at each Arabic numeral. The upward arrow indicates release of constriction.

Circumflex B.: Circumflex branch

Coronary B. F.: Coronary blood flow

Coronary B. P.: Coronary blood pressure

L. V. T. a: Left ventricular tension measured at the anterior wall

R + C: Simultaneous ligation of the right coronary artery and the left circumflex branch

Note an increase in both myocardial blood flow and coronary blood flow induced by the control stimulation (1), a lessened increase in both by the second stimulation during mild constriction, and a marked and long lasting reduction in both by 4th stimulation during moderate constriction. Systolic reduction in L. V. T. a, i.e., systolic bulge, is also observed following the 4th stimulation. Elimination of the reincrease in the myocardial blood flow (the 5th tracing, but not the lowermost tracing) by R + C should also be noted.

Thirty-four mongrel dogs were used for the studies. The dogs were anesthetized with intravenous injections of pentobarbital sodium (30 to 40 mg/Kg). They were immobilized on their right decubitus position. The respiration was maintained by an endotracheal tube attached to a bird's respirator. The upper 8 ribs on the left side were resected to open the chest. After pericardiotomy, the proximal segments of the right coronary artery, the anterior descending branch and the circumflex branch of the left coronary artery were carefully freed from the surrounding tissues in order not to damage the pericoronary nerves.

The small catheters were introduced into small branches arising from the anterior descending branch and from the circumflex branch. The pressures were measured by *Statham* strain gauges connected to these catheters. A probe of electromagnetic flowmeter (Nihon Kohden) was placed on either the anterior descending or circumflex. A screw clamp was also placed on the anterior descending in order to constrict it. The threads were loosely tied around the proximal

segments of the right coronary artery and the left circumflex branch which were used to determine the supplying routs of the collateral blood flow.

A strain gauge arch was sewn onto the anterior wall of the left ventricle. Two pairs of the cross-thermocouples, which had the same character were sewn into the anterior wall.

The left stellate ganglion was freed from the surrounding tissues, the branches of its central side were transected, and was placed across the bipolar stimulating electrodes. A train of the square wave electrical pulses (0.5 msec, 20 volts, 30 cps, and 15 to 20 sec in duration) was used for stimulation of the ganglion.

The anterior descending branch was constricted stepwise by a screw clamp in order to produce various ischemic states of the anterior wall of the left ventricle.

At various grades of constriction, the same train of the electrical pulses was delivered onto the ganglion in order to observe its effect upon the blood flow through the constricted zones.

After experiments, the same train of the electrical pulses was delivered onto the left

Fig.2. A decrease in the myocardial blood flow following constriction and a reactive hyperemia after its release in both 5th and 6th tracings. An increase in the flow in both tracings induced by the control stimulation. A marked reduction in the flow in 5th tracing, whereas an augmented increase in the flow in 6th tracing which are induced by the third stimulation during constriction. Note, elimination of the reincrease by R + C in 5th tracing.

ventricular wall so as to produce ventricular fibrillation. After fibrillation occurred, the thermoelectromotive voltage of the heated cross-thermocouples was elevated and reached to a stable level in a few minutes.

This level was called zero of the myocardial blood flow. Thereafter, the wall was sectioned into slices in order to calibrate the positions of the two thermo-junctions.

In a group of the dogs pretreated with propranolol (2 mg/Kg), effect of ganglion stimulation upon the flow through the constricted and the non-constricted zones was examined. In the second group of the dogs, stimulation-induced flow changes was compared before and after administration of dipyridamole (200 μ g/Kg, I.V.) and oxyfedrine (150 μ g/Kg, I.V.). In the last group of the dogs, stimulation-induced flow changes was compared before and immediately after administration of phenoxybenzamine (5 to 10 mg) into the anterior descending branch through a catheter.

The anterior wall of the left ventricle was divided into three areas, i.e., the area from the

upper margin of the papillary muscle to the anterior descending branch and to the circumflex branch (basal area), the area between the upper margin and the lower margin of the papillary muscle (middle area), and the area from the lower margin of the papillary muscle to the apex (apical area). Each area was further divided into 4 to 5 layers, i.e., the outer layer (within 25 % in distance from the epicardium, in which the wall thickness is 100 %), the first middle layer (over 25 and within 50%), the second middle layer (over 50 and within 75%), the inner layer (over 75%), and the papillary muscle.

The measuring site in each tracing was expressed in the following way: B: basal area. M: middle area. A: apical area.

Distance of the heated junction from the epicardium (mm)/Wall thickness (mm) plus thickness of the papillary muscle (mm).

In order to avoid the influences of the luminal flow, changes in the atmospheric temperature and of the transmural temperature gradient upon the flow assessments, the obtained data was rejected when the positions of the two

Fig.3. A decreased flow by constriction and a reactive hyperemia after its release are observed in both 5th and 6th tracings.

An increased flow in 5th and a decreased flow in 6th tracing induced by the control stimulation, while a decreased flow in 5th and an increased flow in 6th tracing induced by stimulation during constriction.

TABLE I RELATIONSHIPS BETWEEN THE FLOW CHANGES INDUCED BY STELLATE GANGLION STIMULATION AND THE PERIPHERAL BLOOD PRESSURE OF THE CONSTRICTED ANTERIOR DESCENDING BRANCH

Table I-A

S B P (mmHg)	within over		120 120	100 100	80 80	60 60	40 40	20 20	0
Outer Half	Outer Layer	Inc.	1	2	2	3		1	
		Dec.		1		1	4	1	1
	First Middle Layer	Inc.	2	4	12	4	1	3	2
		Dec.		1	2	7	3	2	
Inner Half	Total Number of Exp. (%)		Inc. Dec.	3 (100) 2 (25)	6 (75) 2 (13)	14 (87) 8 (54)	7 (46) 7 (87)	1 (13) 3 (43)	2 (66) 1 (34)
	Second Middle Layer	Inc.			3				
		Dec.				1			
	Inner Layer	Inc.	1	4	2	4	4	2	2
		Dec.	1	2	3	2	2		
	Papillary Muscle	Inc.		2	5	7	1	4	1
		Dec.	1		3		1	1	
	Total Number of Exp. (%)		Inc. Dec.	1 (34) 2 (66)	6 (75) 2 (25)	10 (63) 6 (37)	12 (80) 3 (20)	5 (62) 3 (38)	6 (87) 1 (13)

Table I-B

D B P (mmHg)	within over		100 100	80 80	60 60	40 40	20 20	10 10	0
Outer Half	Outer Layer	Inc.	1	3	1		3	1	
		Dec.			1		1	4	2
	First Middle Layer	Inc.	2	4	8	6	2	1	5
		Dec.	1		1	2	6	3	2
Inner Half	Total Number of Exp. (%)		Inc. Dec.	3 (75) 1 (25)	7 (100) 2 (19)	9 (81) 2 (25)	6 (75) 7 (59)	5 (41) 7 (87)	2 (13) 4 (45)
	Second Middle Layer	Inc.			1	1	1		
		Dec.					1		
	Inner Layer	Inc.	2	3	3	1	2	6	3
		Dec.	1	2	2	1	4		
	Papillary Muscle	Inc.		1	3	5	4	2	5
		Dec.	1	1	2			1	1
	Total Number of Exp. (%)		Inc. Dec.	2 (50) 2 (50)	4 (57) 3 (43)	7 (63) 4 (37)	7 (87) 1 (13)	7 (58) 5 (42)	8 (88) 1 (12)

SBP: systolic blood pressure
DBP: diastolic blood pressure

TABLE II RELATIONSHIPS BETWEEN THE FLOW CHANGES INDUCED BY STELLATE GANGLION STIMULATION AND THE PRESSURE GRADIENTS BETWEEN THE CONSTRICTED ANTERIOR DESCENDING BRANCH AND THE NON-CONSTRICTED CIRCUMFLEX BRANCH

Table II-A

S B P G (mmHg)	over within		control	0 20	20 30	40 60	60 80	80
Outer Half	Outer Layer	Inc.	5	1		1	1	1
		Dec.				5	1	1
	First Middle Layer	Inc.	12	6	2	4	2	2
		Dec.		6	6	3		
Total Number of Exp. (%)		Inc.	17 (100)	7 (53)	2 (25)	5 (39)	3 (75)	3 (75)
		Dec.		6 (47)	6 (75)	8 (61)	1 (25)	1 (25)
Inner Half	Second Middle Layer	Inc.	1	2				
		Dec.			1			
	Inner Layer	Inc.	5	1	1	7	3	2
		Dec.	3	4	1	2		
Papillary Muscle		Inc.	6	4	4	3	1	2
		Dec.	2	2	1	1		
Total Number of Exp. (%)		Inc.	12 (70)	7 (53)	5 (62)	10 (79)	4 (100)	4 (100)
		Dec.	5 (30)	6 (47)	3 (38)	3 (21)		

Table II-B

D B P G (mmHg)	over within		control	0 20	20 40	40 60	60 80	80
Outer Half	Outer Layer	Inc.	5		1	1	1	1
		Dec.			1	1	5	1
	First Middle Layer	Inc.	12	4	5		5	2
		Dec.		3	3	6	2	1
Total Number of Exp. (%)		Inc.	17 (100)	4 (57)	6 (60)	1 (13)	6 (46)	3 (60)
		Dec.		3 (43)	4 (40)	7 (87)	7 (54)	2 (40)
Inner Half	Second Middle Layer	Inc.	1		1	1		
		Dec.				1		
	Inner Layer	Inc.	5	1	2	2	6	3
		Dec.	3	1	3	1	2	
Papillary Muscle		Inc.	6	3	3	2	5	2
		Dec.	2	2	1	1		
Total Number of Exp. (%)		Inc.	12 (70)	4 (56)	6 (60)	5 (71)	11 (84)	5 (100)
		Dec.	5 (30)	3 (44)	4 (40)	2 (29)	3 (16)	

SBPG: systolic blood pressure gradients

DBPG: diastolic blood pressure gradients

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thermo-junctions were within 2 and 1.5 mm respectively from the epicardium and the endocardium and the difference in distance of the two junctions from the epicardium was over 2 mm.¹⁸

RESULTS

The influence of implanting the cross-thermocouples into the ventricular wall on the coronary blood flow was examined in 3 preliminary experiments. Manipulation of the ventricle during implantation caused a decrease in the coronary blood flow measured by the electromagnetic flow meter. The flow was increased after implantation and returned to the control level in a few minutes. Warming the thermo-junction with D.C. had little influence on the coronary blood flow. In other 3 experiments, the influence of placing the probe of the electromagnetic flow meter and the screw clamp on the coronary artery upon the myocardial blood flow was examined. It was revealed that the influence disappeared in a few minutes.

Electrical stimulation of the ganglion was performed before constriction of the anterior descending branch. Following stimulation, an

increase in the coronary blood flow was observed in all experiments. The myocardial blood flow, however, was not necessarily increased by stimulation. Although the flow through the outer half of the wall, i.e., the outer layer and the first middle layer, was increased in all experiments, the flow through the inner half, i.e., the second middle layer, inner layer and the papillary muscle, was not infrequently reduced (see Table II).

After control experiments, constriction of the anterior descending branch was performed in order to produce various ischemic states of the anterior wall. Firstly, the branch was constricted so as to cause a fall in the diastolic blood pressure of the branch, but to maintain the systolic blood pressure and systolic myocardial tension at their control levels. Secondly, the branch was constricted so as to cause a fall in both pressures, but not to produce systolic bulge of the wall. Thirdly, the branch was constricted further so as to cause systolic bulge. The same train of the electrical pulses was delivered onto the ganglion at each stage. The typical tracings thus obtained are shown in Figs. 1, 2 and 3, and

Fig. 4. Effect of ganglion stimulation on the flow through the zones adjacent to the constricted area (6th tracing).

Note an increased flow following constriction and a further increase following stimulation.

L. M.: Adjacent to the middle area.

the relations of the induced flow changes to the peripheral pressure of the constricted branch and to the pressure gradients between the constricted branch and the left circumflex branch are summarized in Tables I and II. As Tables I and II indicate, the induced flow changes had a better relation to the pressure gradients than to the pressure of the constricted branch.

In mildly constricted condition, i.e., within 20 mmHg in systolic and 40 mmHg in diastolic pressure gradients, ganglion stimulation frequently caused an increase in the flow through both the constricted branch and the outer half of the wall. The increases, however, were always smaller than the control ones as shown in Fig.1. The induced decrease in these ranges of the gradients was usually very small.

In moderately constricted conditions, i.e., over 20 and within 60 mmHg in systolic gradients and over 40 and within 80 mmHg in diastolic gradients, however, ganglion stimulation frequently caused a marked fall in the pressures

of the constricted branch and a marked and long lasting decrease in the blood flow through both the constricted branch and the outer half of the wall (see Figs.1 and 2). In several experiments, as shown in Fig 1, the decrease in the myocardial blood flow lasted more than 15 minutes. An obvious systolic bulge was also induced in these experiments.

In severely constricted conditions, i.e., over 60 mmHg in systolic and over 80 mmHg in diastolic gradients, on the contrary, ganglion stimulation infrequently caused a decrease in the blood flow through the outer half of the wall, although it caused a decrease in the flow through the constricted branch. In several experiments, the induced decrease which was observed in moderately constricted condition was replaced by an increase (Fig.4). The induced decrease which was observed in 3 experiments was smaller than what was observed in moderately constricted condition.

Simultaneous ligation of the right coronary

Fig.5. Effect of pretreatment with propranolol on the flow changes induced by ganglion stimulation. A marked decrease in the flow through the constricted area and an augmented increase in the flow through the adjacent zones are produced by stimulation which was carried out within 7 minutes after pretreatment. Over 10 minutes, however, no obvious change in the flow is produced by stimulation.

artery and the circumflex branch was performed during the recovery from the induced decrease in order to know the vessels participated in this reincrease. It was revealed that ligation could stop the reincrease in the outer half (Figs.1. and 2).

The induced change in the simultaneously measured flow through the inner half was frequently different from that in the flow through the outer half, and its relation to the pressure gradients was consequently different. Similarly to the flow through the outer half, the flow in 7 experiments was increased by stimulation before constriction, reduced in moderately constricted conditions and was again increased in severely constricted condition. In 5 experiments, however, no decrease could be produced by stimulation, although constriction of the branch reduced the flow. The measuring sites in these experiments were not apart from the constricted branch, but they all located either in the apical or middle area. The stimulation-induced increases during constriction in these experiments were larger than the control ones (Fig.2). Before constriction, the flow through the inner half was reduced by stimulation in 5 experiments. Over 40 mmHg in both systolic and diastolic pressure gradients, however, the decrease was replaced by an increase in all these experiments (Fig.3). Resultantly, no decrease was observed over 60 mmHg in the systolic and over 80 mmHg in the diastolic pressure gradients in this half of the wall (Table II).

The flow through the marginal zones of the constricted area was measured. The flow through these zones was slightly reduced by mild or moderate constriction, but was increased by severe constriction. Ganglion stimulation caused an augmented increase in the flow through these zones.

In 5 experiments, the flow through the zones adjacent to the constricted area was simultaneously measured with the flow through the constricted area. Different to the flow through the constricted area, as demonstrated in Fig. 4, the flow through the adjacent zones was increased by constriction and was further augmented by stimulation.

The effect of pretreatment with a β -receptor blocking agent with propranolol on the flow through the constricted zones and the adjacent zones was examined in 5 experiments. In 10 to 15 minutes after administration of this agent, stimulation could induce neither a decreased

flow through the constricted zones nor an augmented increase in the flow through the adjacent zones (see Fig.5).

In similar way, the effect of pretreatment with oxyfedrine, a coronary vasodilating agent,^{2,1} on the stimulation-induced flow changes was examined. It was revealed that this agent reduced the flow changes induced by stimulating the ganglion. Pretreatment with dipyridamole, on the other hand, could not alter the induced flow changes.

An α -receptor blocking agent with phenoxybenzamine was injected into the constricted branch. It could not however prevent the decrease in the flow induced by stimulating the ganglion.

DISCUSSION

The results obtained in the present studies suggest the regional differences in the effect of stellate ganglion stimulation on the blood flow through both the non-ischemic and ischemic myocardium. The assessments of regional myocardial blood flow by heated cross-thermocouples can be influenced, as has been pointed out by several workers,¹³⁻¹⁶ by the regional differences in heat production of the myocardium, atmospheric temperature, the luminal flow and the temperature of the coronary blood. In our preliminary experiments, the magnitude of these possible influences has been examined and it was revealed that the influence of the atmospheric temperature and the luminal flow is negligible when the two thermo-junctions are located over 2 and 1.5 mm respectively from the epicardium and the endocardium, and that the influence of the regional differences in the myocardial temperature is within 2.1 μ V when the difference in distance of the two thermo-junctions from the epicardium is within 2 mm.¹⁸ Such a change in the thermoelectromotive voltage is negligibly smaller than the changes induced by various interventions. A great care was taken so as to eliminate these possible influences in the present studies. Besides, the changes in the voltage induced by ganglion stimulation were much greater than 2.1 μ V. Therefore, the changes induced by ganglion stimulation can be attributable to the flow changes. Manipulation of the coronary arteries can also cause the regional difference in the effect of ganglion stimulation on the flow by damaging the nerve bundles which run close to them. In our experiments, a great care was also taken in order not to damage them

as far as possible. An augmented development of systolic myocardial tension was produced by ganglion stimulation in all experiments. This indicates that the majority of the sympathetic nerves were left intact. Consequently, it is unlikely that the regional differences in the induced flow changes are due to lesions of the nerves.

We reported previously that sympathetic nerve has an action to increase the flow through the outer half, while to reduce the flow through the inner half of the normally perfused left ventricular wall.²² Similar tendency was also observed in the present series of experiments. We have considered that this non-uniformity in the flow change is attributable to the increased transmural pressure gradients²³⁻²⁵ and to the accumulated metabolites.²⁶

A marked and long lasting reduction in the myocardial blood flow was frequently produced by stimulation during moderate constriction of the coronary artery. This decrease could not be eliminated by pretreatment with α -blocking agent, but was easily eliminated by β -blocking agent. Besides, an augmented increase in the flow through the marginal zones and the zones adjacent to the constricted area was produced by stimulation.

It is unlikely therefore that excitation of α -receptors participated in this decreased flow. On the contrary, these results suggest the participation of β -receptors in this decrease. One possible explanation for this unexpected decrease is as follows. Sympathetic excitation causes dilatation of the non-constricted branch through excitation of β -receptor with a consequent increase in blood flow through it, whereas can not cause any effective dilatation of the constricted branch which is previously dilated submaximally or maximally by its autoregulation.²⁷ Resultantly, the flow through the constricted branch is stolen because of no change in resistance of the constricted segment and probably because of an increased heart rate, whereas the flow through the non-constricted branch increases because of its dilatation caused by β -receptor excitation and probably because of reduced vascular resistance secondary to an increased production of the metabolites and their action on the vessels in the adjacent zones.²⁸⁻³⁴

The participation of the flow through the collateral vessels, which we consider to develop immediately after constriction, can not be neglected. During severe constriction, the decrease in the flow which was observed during moderate

constriction was frequently reduced or was replaced by an increase. It seemed to us that an increased flow through the collaterals played a role in this phenomenon. It is unlikely that a decrease in the flow through the collaterals into the constricted area participated in the stimulation-induced decrease in the flow through the constricted area. In this sense, the induced decrease can not be attributed to the generally accepted mechanism of 'coronary steal' phenomenon. A reduced flow through the constricted segment with an increased flow through intact vessels is another mechanism for 'coronary steal'. Such situation is also observed in Burger's disease. Therefore, the observed decrease in the flow in our experiments can be attributed to 'coronary steal' phenomenon in this sense.

During severe constriction, an induced decrease in the flow was infrequently observed in both halves of the constricted area. It is supposed that increased pressure gradients between the constricted and non-constricted zones and augmented production of the vasoactive metabolites^{27,36,37} may have opened the collaterals, and that the increased flow through these collaterals may have overshadowed the induced decrease in the myocardial blood flow.

Our studies revealed that the change of the flow through the inner half was somewhat different from that of the flow through the outer half. A decreased flow was not infrequently observed before constriction, whereas an augmented increase was frequently observed during constriction. Besides, this augmented increase was not eliminated by ligating the major coronary arteries. It can be supposed therefore that an increased flow through the direct communications between the coronary arteries and the ventricular cavity^{27,38} played a role in this regional difference of the flow through the ischemic wall.

It has been considered that anginal attack secondary to emotional or sensory stress is due to excitation of sympathetic nerves¹ and the consequently increased oxygen requirement without a sufficient increase in oxygen supply,² or coronary spasmus.⁸ Myocardial infarction with no concomitant thrombosis or even occlusion of the coronary artery is also of a clinical interest.¹² Reological obstruction³⁹ and energy conservation principles⁷ have also been proffered as the possible mechanisms. However, these hypothesis have not yet been proved. It has been pointed out that exercise is accompanied by sympathetic

augmentation and can cause a decrease in the myocardial blood flow in a certain group of the patients with coronary insufficiency.^{40,41} In addition, Baker observed 'coronary steal' phenomenon induced by isoproterenol in the patients with coronary insufficiency.³⁵ These clinical observations and our experimental results suggest the possible participation of 'coronary steal' phenomenon in anginal attack and myocardial infarction secondary to emotional and sensory stress.

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