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## Abstract

Stress-induced changes in the resistance due to coronary arterial stenosis of a fixed diameter and in the myocardial blood flow distal to the stenosis were investigated in the open-chest dog. Myocardial blood flow in the inner and outer third of the left ventricular wall was continuously measured with heated cross-thermocouples. The circumflex coronary artery was constricted with a thick string so that myocardial reactive hyperemia was nearly eliminated. Without constriction, a 15-second occlusion of the artery produced no significant changes in the resistance of large coronary arteries. On the contrary, in the presence of coronary constriction, a brief coronary occlusion caused a sustained decrease in distal coronary pressure and subendocardial myocardial flow during reactive hyperemia, while coronary flow returned quickly to the pre-occlusion level with significant reactive hyperemia of subepicardial flow. This change resulted in a long-lasting increase in the stenosis resistance. These results suggest that stenosis resistance changes dynamically, resulting in additional myocardial ischemia especially in the subendocardial myocardial layers.

**KEYWORDS:** stenosis resistance, coronary constriction, transient myocardial ischemia, myocardial flow

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## CHANGES IN STENOSIS RESISTANCE AND MYOCARDIAL BLOOD FLOW AFTER A BRIEF CORONARY OCCLUSION IN THE DOG

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*Abstract.* Stress-induced changes in the resistance due to coronary arterial stenosis of a fixed diameter and in the myocardial blood flow distal to the stenosis were investigated in the open-chest dog. Myocardial blood flow in the inner and outer third of the left ventricular wall was continuously measured with heated cross-thermocouples. The circumflex coronary artery was constricted with a thick string so that myocardial reactive hyperemia was nearly eliminated. Without constriction, a 15-second occlusion of the artery produced no significant changes in the resistance of large coronary arteries. On the contrary, in the presence of coronary constriction, a brief coronary occlusion caused a sustained decrease in distal coronary pressure and subendocardial myocardial flow during reactive hyperemia, while coronary flow returned quickly to the pre-occlusion level with significant reactive hyperemia of subepicardial flow. This change resulted in a long-lasting increase in the stenosis resistance. These results suggest that stenosis resistance changes dynamically, resulting in additional myocardial ischemia especially in the subendocardial myocardial layers.

*Key words :* stenosis resistance, coronary constriction, transient myocardial ischemia, myocardial flow.

Coronary blood flow remains normal despite relatively severe narrowing of a coronary artery due to compensatory or autoregulatory dilation occurring in the distal vascular bed (1, 2). However, subendocardial underperfusion is induced by stenosis which causes no significant change in coronary blood flow (3). It has been reported that, in the presence of severe coronary stenosis, stimuli for the myocardium to increase the myocardial oxygen demand induced a regional myocardial maldistribution of blood flow, as was indicated by a decrease in myocardial oxygen tension, an increase in myocardial carbon dioxide tension (4), and regional myocardial dysfunction (5). Furthermore, recent studies (6, 7) have indicated that flow during stress decreased more than the resting coronary flow. These results suggest that coronary resistance across the stenosis would change dynamically with ischemic stimuli to the myocardium. However, there are few reports available concerning changes in resistance induced by stress. This study was conducted to investigate whether or not resistance across a severe stenosis

of fixed diameter would increase dynamically with a brief coronary occlusion and whether or not an increase in the coronary resistance of the stenosis would cause more myocardial ischemia distal to the stenosis.

#### METHODS

*Measurement of stenosis resistance in the dog.* Thirteen mongrel dogs of both sexes weighing 10-18 kg were used in this experiment. Pentobarbital anesthesia was induced, and the respiration was controlled to maintain blood gases within normal ranges by volume adjustment and supplemental oxygen. The circumflex coronary artery (LCx) was isolated through a left thoracotomy. An electromagnetic flow transducer (Model MFV 1200, Nihon Kodon Co.) and a pneumatic cuff occluder (Rhodes Medical Co., San Francisco) were placed around the vessel. A thick cotton string (1.0 mm in diameter by 3 cm long) for producing a coronary stenosis was loosely positioned around the vessel between the flow transducer and the occluder. A small (1.5 mm, 10 cm long), polyethylene catheter was inserted into a small branch of the LCx distal to the occluder and was used for recording the coronary pressure distal to the constriction, hereafter called the distal coronary pressure. A hard polyethylene catheter was inserted into the ascending aorta through the left carotid artery for monitoring blood pressure.

Experimental procedures were as follows. After the baseline flow was recorded, the LCx was occluded for 15 seconds by inflating the pneumatic cuff, and the hyperemic response was recorded. The coronary catheter was then inserted and the hyperemia due to the 15-second occlusion was measured again in order to verify that this catheter did not impair the flow response. After stabilization, a coronary occlusion was made for 15 seconds, and then the artery was constricted with the string so that myocardial reactive hyperemia was almost eliminated. Under coronary constriction, the peak reactive hyperemia flow (PRH) was less than 130 % of the flow level prior to total coronary occlusion. After 5 min to establish a new steady state of coronary flow and coronary pressure, the coronary occlusion was repeated twice with an interval of 5 min to establish the reproducibility of the flow response. When PRH of two occlusions of identical duration differed by more than 10 %, the data were excluded from this study. Following completion of these steps, the constriction was removed and the flow allowed to stabilize. The flow response to the 15-second occlusion was measured again for comparison to the pre-experimental response in order to demonstrate stability and responsiveness of the myocardium.

All data were continuously recorded on a Siemens-Elema Mingograph Model 804 recorder at a paper speed of 2.5 to 100 mm per second, and mean values of pressures and flows were analyzed. Stenosis resistance was calculated as the pressure gradient across the stenosis divided by the mean coronary flow. To characterize the persistent effects of each coronary occlusion on stenosis resistance, the time for the distal coronary pressure from the beginning of reflow to return to 80 % of the pre-occlusion values (T80) was measured.

*Measurement of regional myocardial flow in the dog.* This experiment was conducted in fifteen mongrel dogs. Surgical preparation was made in the same way as described above except that the distal coronary catheter was not inserted. To monitor regional myocardial blood flow (RMBF) continuously, two heated cross-thermocouple electrodes, 100  $\mu$ m in diameter (Type CTE-202, Shinei, Tokyo) were used for the assessment of the apparent myocardial thermal conductivity increment, which is directly proportional to the regional myocardial blood flow (8). These electrodes were implanted in the inner and outer third of the left ventricular wall perfused with the LCx. The position of the electrodes was verified at the end of each

experiment : if an electrode was improperly positioned, the data of the experiment were excluded. Since the heated cross-thermocouple method does not provide absolute values of RMBF, estimates of RMBF are represented in terms of the compensatory voltage ( $\mu V$ ) at the measuring point. After control recordings of a 15-second coronary occlusion and its release were recorded, the coronary artery was constricted as described. After a new steady state was established, the reactive hyperemia response to a 15-second coronary occlusion was recorded again.

### RESULTS

During neither the control period nor the coronary stenosis did the heart rate and systemic blood pressure changes significantly due to coronary occlusions. In the absence of stenosis, the pressure gradient between the ascending aorta and the branch of the LCx was less than 4 mmHg before coronary occlusion, and vascular resistance in a large coronary artery was approximately 3 % of the total resistance of the circumflex coronary bed, vascular resistance in the large coronary artery (RL) being calculated as the pressure gradient of the aorta and coronary artery divided by the coronary flow. Reactive hyperemia did not essentially affect the RL, while total and distal coronary resistance decreased markedly at the peak reactive hyperemia (Table 1).

Coronary constriction increased RL to approximately 20 % of the total vascular resistance (RT) in the coronary bed. During reactive hyperemia, following a 15-second coronary occlusion, coronary flow returned quickly to the preocclusion level and, in some cases, increased up to 30 % above the resting flow. On the contrary, slow recovery of the distal coronary pressure was observed following a rapid initial rise to approximately 65 % of the preocclusion pressure. T80 varied directly with the percent reduction in coronary perfusion pressure during the preocclusion period, where percent reduction was the quotient of the pressure

TABLE 1. EFFECTS OF A 15-SECOND CORONARY OCCLUSION ON DISTAL CORONARY PRESSURE AND STENOSIS RESISTANCE.

Heart rate (beats/min)	CBF (ml/min/100g)		Aortic pressure (mmHg)	DCP (mmHg)		SR (mmHg/ml/min/100g)		
	Preocclusion	at PRH		Preocclusion	at PRH	Preocclusion	at PRH	
<b>Without constriction (n=13)</b>								
Mean	159	74.0	230.1	100	97	87*	0.051	0.056
SD	16	9.1	40.2	14	13	12	0.023	0.024
<b>With constriction (n=26)</b>								
Mean	158	61.7	78.1	101	79	53**	0.340	0.610**
SD	19	9.6	18.9	17	15	9	0.126	0.233

CBF = coronary flow, PRH = peak reactive hyperemia, DCP = distal coronary pressure, SR = stenosis resistance with coronary stenosis and resistance of a large coronary artery without coronary stenosis, SD = standard deviation. Asterisks and double asterisks indicate statistical significance from preocclusion values of each group at the levels of  $p < 0.05$  and  $p < 0.01$ .

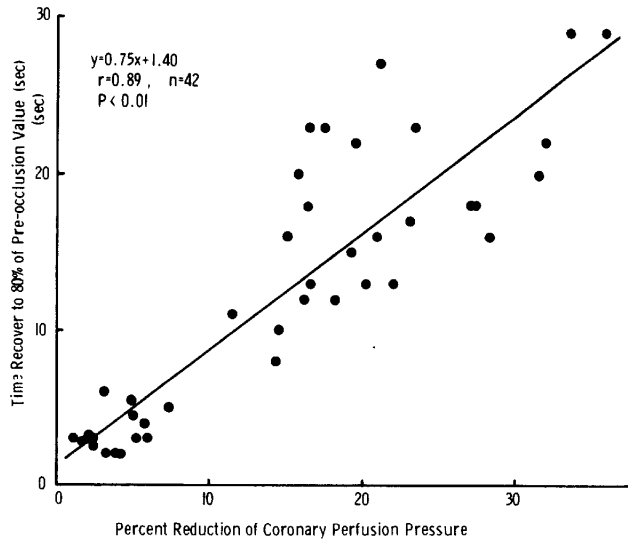


Fig. 1. Relationship between percent reduction in distal coronary pressure caused by coronary constriction and time for recovery to 80 % of preocclusion level.

gradient across the constriction divided by aortic pressure. Fig. 1 shows the relationship between percent reduction in coronary perfusion pressure (distal coronary pressure) and T80 following a 15-second coronary occlusion. Linear regression analysis revealed a close relationship represented by following equation :  $T80 = 0.74 \times (\text{percent reduction in coronary perfusion pressure}) + 1.40$ ,  $r = 0.89$ ,  $P < 0.01$ .

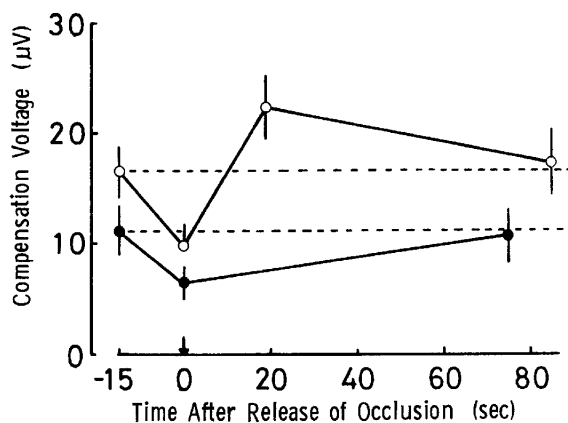


Fig. 2. Response of regional blood flow in the subendocardial (closed circle) and subepicardial (open circle) myocardium to a 15-second coronary occlusion in the presence of coronary constriction. Dash lines indicate preocclusion levels of each myocardial flow.

RMBF in the inner third of the left ventricular wall was nearly equal to that in the outer third in the absence of coronary constriction. The coronary constriction decreased RMBF in the inner third, whereas RMBF in the outer third remained unchanged when reactive hyperemia of the LCx was attenuated to less than 130 % of the preocclusion values. In the presence of coronary constriction RMBF in the outer layer returned rapidly to the preocclusion level and thereafter showed overshoot following release of the total occlusion. This result indicated that there was substantial flow reserve in the myocardium even under the condition of no or minimal reactive hyperemia in the LCx. On the contrary, RMBF in the inner layer exhibited a remarkable delayed restoration to the preocclusion level with an inconsiderable reactive hyperemia as shown in Fig. 2. The resting level was attained at  $64 \pm 12$  (mean  $\pm$  SD) seconds after reperfusion. The long-lasting redistribution of RMBF after release of the total coronary occlusion was correlated well with the sustained fall in coronary pressure distal to the constriction and with the rise in stenosis resistance.

#### DISCUSSION

A normal coronary artery has a large flow reserve to increase in flow response to vasodilatory stimuli. Without coronary constriction, the expected marked increases in coronary and regional myocardial flows were observed with insignificant changes in the resistance of large coronary arteries. In the presence of severe coronary stenosis, coronary flow showed minimal increases following brief coronary occlusion. In our experiment thick cotton string instead of wire, which has been generally used, was utilized to produce coronary constriction because an unnoticeable twist of the wire might increase stenosis resistance when the constriction was severe enough.

The sustained reduction in coronary perfusion pressure observed distal to the constriction after the release of total occlusion, despite a prompt return to the control level of coronary flow, suggests a reduction in distal coronary resistance. Furthermore, in all of the experiments in which stenosis resistance was measured, brief coronary occlusion resulted in a significant increase in the resistance of large coronary arteries. Subepicardial myocardial flow increased in response to brief occlusion, whereas subendocardial myocardial flow decreased in parallel with the fall in distal coronary pressure which led to maldistribution of blood flow across the left ventricular wall. The data suggest that when vascular resistance in the subendocardium remained unchanged the decrease in subepicardial vascular resistance was sufficient to lower pressure distal to the coronary constriction. The findings also indicate the importance of distal resistance in determining stenosis resistance. It was previously shown that the calculated hydraulic resistance of an anatomically fixed stenosis varies depending on flow, and therefore a change in resistance may not reflect a change in the severity of the stenosis (9). However, in our study the increase in stenosis resistance occurred even in experiments which

showed no excess flow after a brief coronary occlusion (11 out of 26 experiments), suggesting that the hydraulic resistance change was not the sole factor involved in the increase in stenosis resistance. Observations of Mates *et al.* (10) utilizing simulation methods for coronary circulation were different from the findings observed in this study because they assumed that the superficial coronary artery was a rigid tube. In our previous study, stenosis resistance increased in excised carotid artery but did not in rigid tubes in response to a fall in distal pressure (11). A possible explanation for the increase in stenosis resistance in response to distal vascular dilation is that passive narrowing may have occurred in the area of the stenosis. In the presence of severe stenosis, the distal coronary bed empties and coronary pressure distal to the stenosis decreases to less than 20 mmHg in association with the maximum dilation of peripheral coronary artery. The pressure in the area of stenosis should decrease since the vascular tonus of the coronary artery at the stenosis is approximately the same as that of the distal coronary artery. This lowers intraluminal pressure allowing the stenotic coronary segment to distend and causes an increase in passive narrowing which, in turn, results in an elevation of the stenosis resistance.

Although it is difficult to extrapolate from animal experiments to the clinical condition of patients, our data do imply that stenosis resistance is not fixed but changed dynamically. The vasodilatory reserve in the subepicardial myocardium was still substantial in the presence of severe stenosis which nearly eliminated myocardial reactive hyperemia and reduced resting coronary and subepicardial flow. Vasodilation in the subepicardium may lead to further coronary pressure fall by an increase in stenosis resistance resulting in more ischemia in the subendocardial layer and further vasodilation in the subepicardial myocardium. If stenosis was severe enough to decrease coronary flow with a very small decrease in stenotic area, coronary flow reduction to zero might be induced as observed by Walinsky *et al.* (12) and Schwartz and his coworkers (13). This phenomenon could explain why patients with chronic angina with significant coronary sclerosis might develop myocardial infarction as well as providing an explanation of the mechanism of angina attack induced by intravenous injection of dipyridamole (14).

A slow recovery of the distal coronary pressure in spite of a prompt return of coronary flow following a brief occlusion was observed in the presence of severe coronary constriction but was not in its absence. This persistent fall in the distal coronary pressure caused a persistent decrease in the subendocardial myocardial flow. It has been reported that, in exercise electrocardiograms, significant depression of the ST-segment lasted for 3 min or more in most patients with coronary heart disease but less than 3 min in normal subjects (15, 16). These results suggest that the recovery time from stress-induced ischemia is an important indicator of coronary heart disease.



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