PARADOXICAL FALL OF TACHYCARDIA- AND HYPOXIA-INDUCED CORONARY FLOW UNDER CONDITIONS OF SEVERE CORONARY STENOSIS IN DOGS

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It has been stated that the coronary flow paradoxically falls in response to tachycardia if the coronary artery is stenotic and "compliant". To clarify this, we measured coronary vascular resistance by cannulating the left anterior descending coronary artery in open-chest dogs. In constant flow perfusion of 41 ± 5 ml/min/100 gm, coronary perfusion pressure was decreased by pacing, while at lower flow of 14 ± 3 ml, it was increased by pacing, indicating that coronary vascular response was reversed. In constant pressure perfusion, coronary vascular resistance was reduced by pacing at high perfusion pressure, while it was paradoxically increased by pacing at low perfusion pressure. In the third experiment at constant flow perfusion, perfusing blood was changed from arterial to venous blood to induce myocardial hypoxia. At high flow, venous blood perfusion reduced coronary vascular resistance, while at low flow it increased coronary vascular resistance. All three experiments indicated that at high perfusion, tachycardia and hypoxia caused a reduction in coronary vascular resistance to meet the increased myocardial oxygen demand; however, at low perfusion, those stimuli increased coronary vascular resistance. The present study showed that the coronary vascular response is reversed at low flow and suggested that those stimuli might reduce flow further in patients with stenotic coronary artery and could be one of the mechanisms causing the development of myocardial infarction in those patients.

WE studied the coronary vascular response under severe coronary stenosis to find out if the response is different from that found in normal coronaries. Coronary vessels dilate maximally in response to myocardial ischemia in order to augment coronary flow and thereby ameliorate ischemia.¹ This metabolic mechanism

for the regulation of coronary flow is favourable in preventing myocardial ischemia. However, if the coronary artery already has severe stenosis the coronary vascular bed downstream from the stenosis will already be dilated to near maximum,¹ so there can be no further increase in coronary flow. Several reports have shown that coronary flow is decreased by pacing in these stenotic arteries.²⁻⁴ A series of experiments by Schwartz et al.⁴⁻¹⁰ resulted in their concluding that if the coronary artery at the stenotic site is "elastic" or "compliant", the tachycardia will reduce

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Measurement of coronary vascular resistances at relatively high flow and low flow

Fig. 1. Schematic illustration of the experimental design.

intravascular pressure and lead to a "passive narrowing" of the stenotic site, thereby reducing coronary flow even further. If flow is reduced, in spite of stimuli which necessitate a greater level of coronary flow, then any myocardial ischemia will only be aggravated further. As a means of investigating coronary flow responses towards ischemic stimuli (tachycardia and hypoxia), we conducted three different experiments and found that if there is severe coronary stenosis when the artery is not "elastic" or "compliant" such stimuli can result in a further decrease in coronary flow.

MATERIALS AND METHODS

Fifty-one mongrel dogs, weighing 21 ± 1 kg (mean $\pm$ standard error), were anesthetized with pentobarbital 25 ml/kg intravenously in the right decubitus position. A catheter was inserted from the right femoral artery to the thoracic aorta. The chest was opened at the left side under artificial positive pressure breathing with a tidal volume of 250–300 ml, a respiration rate of 25–30 l/min and an end-expiratory pressure of 10 cm H₂O. Arterial blood gas analysis

showed pO_2 was 98.5 ± 4.6 mmHg, pCO_2 was 32.4 ± 2.3 mmHg, pH was 7.423 ± 0.025 , hemoglobin concentration was 15.9 ± 1.0 gm/dl and oxygen saturation was $96.6 \pm 0.5\%$. After thoracotomy, the left anterior descending coronary artery was dissected, a polyethylene cannula (o.d. 20 mm, i.d. 1.2 mm, length; 0.5 cm) was inserted into the dissected portion and the artery was perfused with the arterial blood from the own left carotid artery. A larger polyethylene tube (o.d. 3.5 mm, i.d. 2.2 mm, length; 50 cm, volume; 2 ml) was used to bypass blood from the carotid artery to the coronary cannula. Using a pressure transducer (MPU-0.5, Nihon Koden, Japan) perfusion pressure was measured 0.5 cm upstream of the coronary cannula (Fig. 1). Perfusion rate was measured using an electromagnetic flowmeter (MF 46, Nihon Koden, Japan). As suggested by Folts et al.¹¹ all dogs were pretreated with 1 gm (approximately 30–40 mg/kg) of oral acetylsalicylic acid to prevent platelet aggregation. Hourly 1 mg/kg heparin was given intravenously. A Walton-Brodie type myocardial strain gauge arch (HD-1T, Nihon Koden, Japan) extended 20% of its initial length and orientated along the superficial fiber was sutured at the perfused area.¹² Positive deflections in arbitrary units during systole were considered to be actively developed tension and negative deflections were considered to be systolic bulges. A Mercury-in-Silastic gauge¹³ to measure segment length, was also sutured at the perfused area. The coronary vein accompanying the dissected coronary artery was cannulated to obtain blood samples for oxygen analysis (ABL-1 Radiometer, Denmark) and to determine lactate concentrations.

Three experiments were conducted (A; 28 dogs, B; 14 dogs, C; 9 dogs). In experiment A, using a peristaltic pump (Model 1203, Harvard Apparatus, USA) the left anterior descending artery was perfused with arterial blood from the carotid artery at a constant flow. The perfusion rate was maintained at either a relatively high flow (10.2 ± 1.1 ml/min; 41 ± 5 ml/min/100 gm) or a relatively low flow (3.9 ± 2.6 ml/min; 14 ± 3 ml/min/100 gm). In order to increase heart rate during periods of either high or low flow, pacing electrodes were sutured at the left atrium. In experiment B, the coronary artery was perfused at the animal's own carotid arterial pressure. Perfusion rate was 14.0 ± 1.0 ml/min; 41 ± 4 ml/min/100 gm, a relatively high flow. If a constricting screw was applied to the circuit,

TABLE 1 CHANGES IN CORONARY VASCULAR RESISTANCE RESULTING FROM PACING (Experiment A)

		Relatively high flow (41 ± 5)		Relatively low flow (14 ± 3 ml/min/100 gm)	
		Before pacing	After pacing	Before pacing	After pacing
Heart rate	(beats/min)	116 ± 4 ($\pm$ SE)	197 ± 3 ††	106 ± 10	182 ± 5 ††
Aortic pressure	(mmHg)	93 ± 4	86 ± 4 ††	101 ± 6	100 ± 8
Coronary perfusion pressure	(mmHg)	83 ± 8	73 ± 7 †	38 ± 2	42 ± 3 †
Coronary vascular resistance (1)	(Units)	4.82 ± 1.43	4.25 ± 1.19	4.78 ± 1.15	5.50 ± 1.37 *
Segment length at end-diastole	(mm)	14.4 ± 0.8	14.5 ± 0.8	16.5 ± 1.2	18.0 ± 1.1 *
at end-systole	(mm)	12.0 ± 0.5	12.4 ± 0.6 *	13.5 ± 0.5	14.0 ± 0.6
Force	(mm)	7.5 ± 1.4	3.9 ± 1.6 †	-0.3 ± 3.5	-2.9 ± 3.3
Coronary venous O ₂ saturation	(%)	55.6 ± 3.8	49.7 ± 3.3 †	50.5 ± 5.4	41.8 ± 4.2 *
Myocardial O ₂ extraction	(%)	48.8 ± 4.5	48.8 ± 3.7	46.1 ± 5.4	45.1 ± 4.9
Myocardial lactate extraction	(%)	-5.1 ± 11.4	-3.2 ± 10.6	6.8 ± 6.8	-33.9 ± 13.8

* $p < 0.05$; † $p < 0.01$; †† $p < 0.001$

Fig. 2. One of the original tracings in Experiment A.

Perfusion rate was higher at the upper than the lower panel. Tachycardia reduced perfusion pressure from 72 to 57 mmHg in the upper panel, while it was elevated from 32 to 35 mmHg in the lower panel. In this particular experiment, left circumflex flow (LCX CBF) was monitored for reference.

Fig. 3. Time course change of coronary vascular resistance at different coronary flow in response to pacing in Experiment A. Five experiments (1-5) were performed in this dog in which coronary perfusion (CBF) was gradually reduced from 20, 15, 5, 10.5, 5.0 to 3.0 ml/min. Pacing reduced perfusion pressure in experiment 1, 2, 3. However, in experiment 4, 5, pacing increased perfusion pressure and elevated coronary vascular resistance.

perfusion rate was relatively low (3.2 ± 0.7 ml/min; 10 ± 2 ml/min/100 gm). Heart rate was increased through stepwise pacing of approximately 20 beats/min each initiating from their own individual heart rate during periods of both relatively high and relatively low flows. In experiment C, myocardial hypoxia was induced by perfusing the myocardium with venous blood. The polyethylene tube was divided; one side went to the left atrium (arterial blood perfusion) and the other to the right atrium (venous blood perfusion). A peristaltic pump was used to

maintain a constant perfusion rate. At both relatively high (16.9 ± 2.0 ml/min; 54 ± 7 ml/min/100 gm) and relatively low flows (3.8 ± 0.4 ml/min; 12 ± 2 ml/min/100 gm), the perfusing blood was switched from (left atrial) arterial blood to (right atrial) venous blood. Each perfusion was allowed to stabilize for five minutes and measurements of aortic pressures, coronary perfusion rates, perfusion pressures, segment lengths and myocardial force tracings were taken. Samples of arterial and coronary venous blood were also obtained each time.

Coronary vascular resistance was calculated in two ways:

Coronary vascular resistance (Resistance Units) =

$$\frac{\text{Coronary perfusion pressure (mmHg)}}{\text{Coronary perfusion rate (ml/min/100 gm)}} \dots 1$$

or

$$\frac{\text{Coronary perfusion pressure} - \text{retrograde pressure (mmHg)}}{\text{Coronary perfusion rate (ml/min/100 gm)}} \dots 2$$

In experiments B and C, the polyethylene tube connected to the cannula was cramped in order to stop the flow and the resulting perfusion pressure was defined as retrograde pressure. Formula 2, therefore, gives a value which eliminates the effects of any collateral perfusion. After each experiment, 1 ml of India ink was infused into the cannula and the stained myocardium was excised for weighing and calculating of coronary blood flow in ml/min/100 gm. The paired t-test was used to test paired samples for statistical significance.

RESULTS

Experiment A (Constant rate perfusion with pacing—Table I): Examples are shown in Figs. 2 and 3. When the perfusion rate was relatively high, an increase in heart rate reduced perfusion significantly, from 83 ± 8 to 73 ± 7 mmHg, indicating that myocardial oxygen demand was augmented by pacing and that the coronary vascular bed was dilated. However, if the perfusion rate was as low as 14 ml/min/100 gm, tachycardia caused a small but significant elevation in perfusion pressure (from 38 ± 2 to 42 ± 3 mmHg). A stretching of the myocardial segment at this showed evidence of an increase in segment length (from 16.5 ± 1.2 to 18.0 ± 1.1 mm—Table I). This was accompanied by augmentation

TABLE II CHANGES IN CORONARY FLOW RESULTING FROM PACING (Experiment B)

		Relatively high flow		Relatively low flow	
		Before pacing	→ After pacing	Before pacing	→ After pacing
Heart rate	(beats/min)	119 ± 8 (± SE)	→ 180 ± 8††	119 ± 7	→ 186 ± 8†
Aortic pressure	(mmHg)	105 ± 6	→ 102 ± 7	98 ± 9	→ 101 ± 8
Coronary blood flow	(ml/min/100)	41 ± 4	→ 50 ± 5†	10 ± 2	→ 8 ± 2†
Coronary perfusion pressure	(mmHg)	87 ± 6	→ 84 ± 5	35 ± 3	→ 38 ± 3*
Retrograde pressure	(mmHg)	22 ± 2	→ 24 ± 2*	24 ± 2	→ 25 ± 2
Coronary vascular resistance (1)	(Units)	2.30 ± 0.22	→ 1.80 ± 0.15††	5.65 ± 1.11	→ 8.24 ± 1.73*
Coronary vascular resistance (2)	(Units)	1.60 ± 0.21	→ 1.27 ± 0.14†	0.61 ± 0.38	→ 2.54 ± 0.72*
Segment length at end-diastole	(mm)	13.0 ± 0.3	→ 13.1 ± 0.3	13.9 ± 0.2	→ 14.4 ± 0.4*
at end-systole	(mm)	11.7 ± 0.2	→ 11.8 ± 0.2	11.8 ± 0.3	→ 12.0 ± 0.2
Force	(mm)	6.5 ± 1.7	→ 6.1 ± 1.5	-4.4 ± 1.7	→ -6.8 ± 1.9
Coronary venous O ₂ saturation	(%)	56.6 ± 6.0	→ 57.8 ± 7.9	48.9 ± 4.6	→ 50.4 ± 4.6
Myocardial O ₂ extraction	(%)	31.2 ± 7.3	→ 36.8 ± 8.1	49.6 ± 4.6	→ 47.9 ± 4.8
Myocardial lactate extraction	(%)	18.3 ± 5.7	→ 4.2 ± 7.4	-33.1 ± 16.4	→ -32.9 ± 13.9

**p* < 0.05; †*p* < 0.01; ††*p* < 0.001

of the systolic bulge (negative deflection on the force trace).

Experiment B (Constant perfusion pressure with pacing—Table II): A peristaltic pump was not used in this experiment, but coronary perfusion was maintained by the pressure from the own carotid artery. An example is shown in Fig. 4. At the relatively high flow (41 ± 4 ml/min/100 gm), pacing caused an increase in coronary flow and a reduction in calculated coronary vascular resistance (Fig. 6 (B), open circle). Coronary vascular resistance, as calculated by both formulas, was reduced by pacing. Under a low perfusion rate of 10 ± 2 ml/min/100 gm, the opposite effect was observed. In other words, the coronary flow was further decreased and an increase in coronary vascular resistance was accompanied by a stretch of myocardial segment length.

Experiment C (Venous blood perfusion with constant rate—Table III): At a relatively high flow (54 ± 7 ml/min/100 gm), venous blood perfusion caused a marked reduction in perfusion pressure. However, at a relatively low flow (12 ± 2 ml/min/100 gm), following venous blood perfusion there was a small but significant increase in coronary perfusion pressure and vascular resistance (Figs. 5, 6). In this experiment, the paradoxical increase in coronary vascular resistance was elicited by myocardial hypoxia only at a relatively low flow.

DISCUSSION

A series of studies conducted by Berne et al¹ indicates that the coronary vascular bed dilates near maximally to meet demands for increased oxygen. The present study confirmed this theory, but only as long as coronary flow is not severely limited. In experiment A, a peristaltic pump was used to maintain a constant perfusion rate. In experiment B, constant perfusion pressure was used in order to eliminate any artifact inherent in using the peristaltic pump. In both of these experiments, tachycardia was the ischemic stimulus. In the last experiment, C, venous perfusion was used to induce an hypoxic effect on the coronary vascular bed. All three experiments were consistent in that, under severely reduced coronary flow, increased myocardial oxygen demand or myocardial hypoxia caused an elevation in coronary vascular resistance. This reaction is opposite to that found in normal coronary circulation. The paradoxical fall in coronary flow shown by Schwartz et al⁴⁻¹⁰ was also demonstrated in our experiments.

The clinical implications of the present results are as follows: In patients who have no coronary stenosis, tachycardia or hypoxia causes coronary vasodilation and increases coronary flow, both being steps in preventing myocardial ischemia. However, in patients with severe coronary stenosis and in whom coronary flow has already been reduced at rest (equivalent to the relatively low

Fig. 4. One example of Experiment B.

If the coronary perfusion (CBF) was 10 ml/min, pacing increased CBF to 11.5, decreased coronary perfusion pressure from 91 to 87 mmHg resulting significant reduction in coronary vascular resistance (lower panel). However, if CBF was as low as 4.5 ml/min, pacing reduced CBF to 4.2, elevated perfusion pressure from 40 to 44 mmHg and increased coronary vascular resistance from 3.11 to 3.33 units.

flows used in the present experiment), any physical exertion which will induce tachycardia or hypoxia will also cause an increase in coronary vascular resistance, thereby paradoxically reducing the coronary flow, aggravating the ischemia and leading towards the development of myocardial infarction. Also, we must realize that,

under these experimental conditions in which the experimental design is rather invasive and control measurements sometimes indicate lactate production, the direct translation of the present results to the clinical situation must be very cautious.

There have been several reports²⁻⁴ suggesting that coronary flow will paradoxically fall under certain conditions. Maseri et al.³ demonstrated in clinical patients that coronary flow to the poststenotic region was markedly reduced during angina. Schwartz et al. confirmed this phenomenon in open-chest dogs^{4,5,7-10} as well as in conscious dogs⁶ and concluded that the passive narrowing of the elastic stenosis of the artery is the contributory mechanism.

The possible mechanisms for inducing this increase in coronary vascular resistance are worthy of mention. Oliva and Breckinridge¹⁴ highlighted coronary vasospasm as an important mechanism in reducing coronary flow. Maseri et al.^{3,15} also reported that coronary sclerotic lesions may predispose towards coronary vasospasm. In our experiments, however, epicardial coronary artery was not spastic as visually seen. Folts et al.¹⁶ showed that obstructions resulting from platelets aggregating in the narrowed lumen caused cyclic flow reductions. Platelet aggregation and release of thromboxane (TX) A₂, a potent vasoconstrictive substance might also be responsible.¹⁵ A recent study has demonstrated that a platelet-activating factor plays the role of a "third pathway" in aggregating platelets at the stenotic coronary artery.¹⁷ In the present study, however, platelet aggregation was inhibited by aspirin administration.

There are several reports indicating that a "progressive" increase in vascular resistance occurs within the ischemic myocardium after stenosis¹⁸. Guyton et al.¹⁹ described it as an ischemia-mediated resistance increase, postulating coronary steal as a possible mechanism.

Another possible mechanism is vasospasm following coronary occlusion, involving interplay with the adrenergic nerve. Gewirtz et al.²⁰ have suggested that, in the presence of severe coronary stenosis, alpha-mediated arteriolar vasoconstriction may compete with metabolically-mediated vasodilation. Heush and Deussen²¹ concluded that with increasing severity of a stenosis there is a continuous unmasking of sympathetic vasoconstriction which may be mediated by postjunctional alpha 2-receptors. All of the above reports indicate that the vasomotor tone of the coronary vascular bed downstream from the stenosis is

TABLE III CHANGES IN CORONARY VASCULAR RESISTANCE RESULTING FROM VENOUS BLOOD PERFUSION (Experiment C)

		Relatively high flow (54 ± 7)		Relatively low flow (12 ± 2 ml/min/100 gm)	
		Arterial blood perfusion	→ Venous blood perfusion	Arterial blood perfusion	→ Venous blood perfusion
Aortic pressure	(mmHg)	132 ± 6 (± SE)	→ 132 ± 6	114 ± 3	→ 114 ± 3
Coronary perfusion pressure	(mmHg)	86 ± 8	→ 68 ± 4††	34 ± 2	→ 35 ± 2††
Retrograde pressure	(mmHg)	28 ± 1	→ 28 ± 1	24 ± 2	→ 23 ± 2
Coronary vascular resistance (1)	(Units)	24.8 ± 0.44	→ 2.20 ± 0.44††	3.54 ± 0.42	→ 3.63 ± 0.42†
Coronary vascular resistance (2)	(Units)	1.57 ± 0.14	→ 1.27 ± 0.12†	0.93 ± 0.12	→ 1.07 ± 0.12††
Segment length at end-diastole	(mm)	13.4 ± 0.6	→ 14.0 ± 0.6†	17.5 ± 0.3	→ 18.1 ± 0.4†
at end-systole	(mm)	11.5 ± 0.3	→ 11.8 ± 0.4	13.2 ± 0.3	→ 13.4 ± 0.3
Force	(mm)	6.3 ± 0.7	→ 3.5 ± 0.8††	-11.7 ± 4.7	→ -14.0 ± 4.9†
O ₂ saturation of perfusing blood	(%)	95.8 ± 0.8	→ 65.5 ± 4.8††		
pO ₂ of perfusing blood	(mmHg)	95.4 ± 4.4	→ 43.0 ± 5.9††		
Coronary venous O ₂ saturation	(%)	62.9 ± 4.5	→ 23.6 ± 4.8††	33.4 ± 4.0	→ 24.0 ± 3.5†
Myocardial O ₂ extraction	(%)	34.8 ± 4.5	→ 60.7 ± 5.3††	68.5 ± 5.0	→ 62.6 ± 3.9
Myocardial lactate extraction	(%)	-11.7 ± 9.2	→ -46.4 ± 10.7††	-55.0 ± 13.8	→ -69.0 ± 14.9

* $p < 0.05$; † $p < 0.01$; †† $p < 0.001$

different than that found in normal coronaries.

Swollen perivascular and endothelial cells that develop as a consequence of ischemia appear to obstruct capillaries²² and to increase coronary vascular resistance. This phenomenon, however, was observed in prolonged ischemia of up to 120 minutes according to Willerson et al,²² which is considerably longer than was found in this study.

Systolic myocardial compression is one of the major determinants of coronary vascular resistance.²³ In the ischemic myocardium, left ventricular size during systole and left ventricular wall tension both increase. In the present experiments, the myocardial segment was stretched during the paradoxical fall in coronary flow, suggesting that wall tension might have increased. However, since the flow during systole comprises only about 10–15% of the total flow, even if systolic compression and coronary vascular resistance increase at this time, the total reduction in coronary flow will still be negligible.²⁴ However, if there is stenosis of the coronary artery, the phasic coronary flow pattern shifts so that the ratio of systolic flow goes as high as 30–40%.²⁴ The effects of systolic compression are of considerable importance under such conditions.²³ Selwyn et al.²⁵ demonstrated angiographically that if the coronary artery is stenotic, pacing causes a cessation of flow to that artery. They

explained that acute regional ischemia resulting from pacing is associated with regional ventricular dyskinesia, increased wall tension and impaired myocardial perfusion. In our experiment, the paradoxical fall in coronary flow was accompanied by myocardial stretch and elevation in perfusion pressure, suggesting that systolic compression may be an important contributory mechanisms.

In experiments A and B, the paradoxical fall was induced by pacing. Most of the other studies^{2-4,6,10,15,25} also demonstrated that tachycardia induced this paradoxical fall. Since the diastolic period is shortened in tachycardia, the effects of systolic compression are enhanced. However, in experiment C, during which the heart rate was not altered, the paradoxical fall was still reproduced, suggesting that shortening of diastolic time is not essential.

In ischemia, left ventricular diastolic pressure is elevated and left ventricular diastolic size is enlarged. These then increase diastolic wall tension and diastolic compression of the coronary vascular bed. Freedman et al²⁶ reported that coronary collaterals to the stenotic artery disappear through exercise. They postulated that elevation of left ventricular diastolic pressure and wall tension cause an elevation in distal coronary vascular resistance and reduce coronary inflow through the collaterals. With ischemia, systolic

Fig.5. One example of Experiment C.

At high perfusion rate (left panel: 20 ml/min), venous blood perfusion reduced coronary vascular resistance from 128 to 65 mmHg, reduced coronary vascular resistance from 4.90 to 1.95 units. At low flow (2.5 ml/min: right panel), on the contrary, venous blood perfusion increased perfusion pressure from 36.8 to 38 mmHg, elevated coronary vascular resistance from 2.72 to 3.60 units.

as well as diastolic coronary vascular resistance increase and may be contributing mechanisms which lead to the paradoxical fall in coronary flow.

There are several important differences between the present results and those in previous reports by Schwartz et al.⁴⁻¹⁰ The latter observed that perfusion pressure drops at the stenotic site at the time the flow paradoxically falls and postulated that if the stenotic vessel is "elastic" or "compliant", then any intravascular pressure drop causes a passive narrowing. However, in our experiment a "rigid" polyethylene cannula was used and no such passive narrowing could take place. Our experiments suggest that this paradoxical fall in flow exists even if the artery is held rigid by atherosclerosis. Also, in the present experiment, this paradoxical fall was observed at very low levels of flow (14, 10 or 12 ml/min/100 gm), approximately one-third to one-fourth of the flow of the controls. In the experiment by Schwartz et al.⁴, the control flow (26 ± 2 ml/min) was increased to 44 ± 3 ml/min

by pacing while, if there was any stenosis, the original flow of 23 ± 2 ml/min was reduced by pacing to 15 ± 2 ml/min. In other words, the paradoxical fall was observed at the original flow of 23 ± 2 ml/min, a level not greatly different from that of the pre-stenosis. Their study may indicate that even if the flow at rest is not reduced, if there is a critical stenosis, tachycardia causes passive narrowing. On the other hand, in the present experiments this paradoxical fall was demonstrated under conditions of tachycardia whenever the original flow was already markedly reduced. This is equivalent to 90 to 99% stenosis of the coronary artery. If coronary flow falls paradoxically due to either tachycardia or hypoxia in patients with severely occluded coronary arteries the myocardium will be infarcted. A third important difference is that Schwartz et al. observed a drop in perfusion pressure concurrent with the paradoxical fall in flow, while we observed the opposite, an increase in perfusion pressure. In all three of our experiments, each with a different perfusion design, the

Fig. 6. Changes in coronary vascular resistance at relatively high and low flows in each of three experiments.

perfusion pressure was elevated slightly, but significantly, whenever the paradoxical fall was observed. Since perfusion pressure was elevated no passive narrowing at the stenotic site took place. This means that there must be an increase in vascular resistance somewhere downstream of the ventricular wall. The present study indicates that if the stenosis is severe enough to considerably reduce flow, the paradoxical fall will appear even if the stenotic site is held rigid by atheroma. In a patient with severe stenosis, physical exercise will reduce this flow further, will aggravate the ischemia and may eventually lead to myocardial infarction.

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