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Abstract

The effects of intravenous infusion of isoproterenol on stenosis resistance were studied in the anesthetized open-chest dog. The circumflex coronary artery (LCx) was isolated near its origin and an electromagnetic flow transducer was placed around the vessel for measuring coronary flow. A polyethylene catheter was inserted into the small branch of LCx for monitoring distal coronary pressure. LCx was constricted with a thick cotton string to a degree of obstruction that eliminated reactive hyperemia following a 20-second coronary occlusion. The coronary resistance across the stenotic segment (RL) was calculated as the pressure gradient across the stenosis divided by coronary flow. Isoproterenol was infused intravenously in a dose to keep the heart rate at a level 25-30% above the control with and without coronary constriction. For maintaining the ascending aortic pressure at the pre-isoproterenol level, the descending thoracic aorta was constricted with a tape. In the absence of coronary constriction, the vascular resistance of large coronary arteries was not affected by isoproterenol with a significant increase in coronary flow. In the presence of coronary stenosis, isoproterenol markedly increased RI regardless of additional aortic constriction. The magnitude of the increase in RL during aortic constriction varied directly with the percent increase in the pressure gradient across the coronary stenosis. Pacing-tachycardia essentially did not affect RL. These results suggest that isoproterenol increased the vascular resistance of the stenotic segment with fixed caliber.

KEYWORDS: coronary cinstriction, open-chest dog, distal coronary pressure

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INCREASE IN THE RESISTANCE OF STENOTIC CORONARY SEGMENT BY INTRAVENOUS INFUSION OF ISOPROTERENOL

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Abstract. The effects of intravenous infusion of isoproterenol on stenosis resistance were studied in the anesthetized open-chest dog. The circumflex coronary artery (LCx) was isolated near its origin and an electromagnetic flow transducer was placed around the vessel for measuring coronary flow. A polyethylene catheter was inserted into the small branch of LCx for monitoring distal coronary pressure. LCx was constricted with a thick cotton string to a degree of obstruction that eliminated reactive hyperemia following a 20-second coronary occlusion. The coronary resistance across the stenotic segment (R_L) was calculated as the pressure gradient across the stenosis divided by coronary flow. Isoproterenol was infused intravenously in a dose to keep the heart rate at a level 25-30 % above the control with and without coronary constriction. For maintaining the ascending aortic pressure at the pre-isoproterenol level, the descending thoracic aorta was constricted with a tape. In the absence of coronary constriction, the vascular resistance of large coronary arteries was not affected by isoproterenol with a significant increase in coronary flow. In the presence of coronary stenosis, isoproterenol markedly increased R_L regardless of additional aortic constriction. The magnitude of the increase in R_L during aortic constriction varied directly with the percent increase in the pressure gradient across the coronary stenosis. Pacing-tachycardia essentially did not affect R_L. These results suggest that isoproterenol increased the vascular resistance of the stenotic segment with fixed caliber.

Key words: coronary constriction, open-chest dog, distal coronary pressure.

Stress-induced myocardial ischemia in the presence of coronary stenosis is usually considered to be due to a disproportionate increase in flow to the myocardium relative to the myocardial oxygen requirement. It has been believed that the resistance of coronary stenosis was essentially fixed and that, with constant flow, coronary perfusion pressure distal to the stenotic segment depended solely on the pressure proximal to the stenosis. Recent studies (1, 2), however, raised the possibility of dynamic changes in stenosis resistance in response to various vasodilatory and vasoconstrictory stimuli. Isoproterenol which dilates cor-

onary artery directly and through vasoactive metabolites from the myocardium in response to an increase in myocardial oxygen usage (3), changed subendocardial myocardial ischemia in the presence of coronary stenosis (4, 5). However, the effects of isoproterenol on coronary resistance of the stenotic segment were not measured. Thus, the purpose of the present study was to determine whether or not intravenous isoproterenol affected the stenosis resistance of coronary artery.

METHODS

Twelve mongrel dogs of either sex weighing 13-18 kg were anesthetized with 30 mg/kg of intravenous injection of sodium pentobarbital. The respiration was controlled to maintain blood gases within normal ranges by volume adjustment and supplemental oxygen. The chest was opened and the left circumflex coronary artery (LCx) was isolated near its origin. An electromagnetic flow transducer (Model MFV 1100, Nihonkoden, Tokyo) and a pneumatic cuff occluder were placed around the vessel to obtain a zero flow reference. A thick cotton string was also placed around the vessel between the flow probe and the cuff occluder to create coronary stenosis. A small polyethylene tube, 1.5 mm in outer diameter, 10 cm long, was cannulated into a small branch of the LCx distal to the constrictor for measuring distal coronary pressure. The distal coronary pressure and the ascending aortic pressure were monitored with electromanometers (Model RMP-6004, Nihonkoden, Tokyo).

Experimental protocol was as follows: After the baseline flow was recorded, the LCx was occluded for 20 seconds with an inflating pneumatic cuff and the hyperemia response was recorded. The coronary catheter was then inserted and reactive hyperemia to a 20-second occlusion was repeated in order to verify that this catheter did not impair the flow response. After stabilization, 0.10 μg/kg of l-isoproterenol was injected into the femoral vein and thereafter additional isoproterenol was infused to keep the heart rate at a level of 25-30 % above the control. Then, to avoid the effect of an isoproterenol-induced pressure fall on coronary resistance, the descending thoracic aorta was constricted for raising the central aortic pressure to the pre-isoproterenol level. The experiments were conducted in the control condition and in the presence of coronary constriction at the degree of obstruction which nearyl eliminated reactive hyperemia following a 20-second coronary occlusion. Following completion of these steps, the constrictor, a cotton string, was removed and the flow allowed to stabilize. The coronary flow response to a 20-second occlusion was observed again for comparison to the pre-experimental response to demonstrate stability and responsiveness of the myocardium. If either the baseline or the peak hyperemia flow rate differed by more than 10 % between pre- and post-experimental runs, the data from the dog were excluded.

To test the effect of tachycardia induced by isoproterenol on stenosis resistance, the left atrium was electrically paced in three dogs in the presence of the critical stenosis described above. Surgical preparation and instrumentation were the same as in the study of isopproterenol infusion except for the pacing electrodes on the left atrial appendage. The pacing rate was set at 185/min which is the same level as isoproterenol-induced tachycardia. After a steady state was obtained, the coronary flow and pressures were recorded. All data were recorded continuously with a Siemens-Elema Mingograph (Model 808) at a paper speed of 2.5 mm/sec. The resistance of the coronary segments was calculated as follows:

R_T= (aortic pressure) / (coronary flow), R_S= (distal coronary pressure) / (coronary flow), R_L= $R_T - R_S$, where R_T was the total resistance of the LCx, R_S was the resistance of small coronary arteries and R_L was the resistance of a large coronary segment either with or without coronary stenosis.

RESULTS

In the absence of coronary constriction, isoproterenol rapidly increased heart rate and coronary flow, and decreased aortic pressure and distal coronary pressure, resulting in a marked reduction in the total and the small vascular resistance in the LCx. Resistance of the large coronary segment was, however, increased slightly from 0.04 ± 0.01 mmHg/ml/min/100g to 0.07 ± 0.02 mmHg/ml/min/100g. With additional aortic constriction to raise the central aortic pressure to the pre-infusion level, R_L almost returned to the level before isoproterenol infusion (Table 1).

The effect of isoproterenol on coronary hemodynamics in the dog with coronary constriction are summarized in Table 2. Coronary constriction reduced coronary flow and distal coronary pressure by approximately 13 % and 31 %, respectively, without significant changes in aortic pressure or heart rate. R_L increased from 0.024 ± 0.001 mmHg/ml/min/100g to 0.53 ± 0.21 mmHg/ml/min/100g with the constriction, while R_S decreased by 19 %. Intravenous infusion of isoproterenol in the presence of critical stenosis caused a marked increase in heart rate by 29 % and decreases in aortic pressure, distal coronary pressure and coronary flow by approximately 20 %. R_L augmented markedly in association with a significant decrease in R_S. With aortic constriction, coronary flow also returned completely to the pre-isoproterenol level. R_S was

TABLE 1. EFFECTS OF ISOPROTERENOL ON CORONARY RESISTANCE IN THE ABSENCE OF CORONARY STENOSIS.

		Heart rate	BP	CBF	DCP	BP -DCP	Coronary resistance		
							R_T	R_L	R_S
Before isoproterenol	Mean	155	98	88.4	93	5.0	1.13	0.04	1.06
	SD	17.7	18.5	13.5	18.7	1.6	0.29	0.02	0.31
During isoproterenol	Mean	205**	67**	123.1**	63**	4.4	0.58**	0.07*	0.51**
	SD	24.5	15.0	33.5	16.8	2.5	0.12	0.02	0.13
Isoproterenol plus aortic constriction	Mean	194**	99	154.8**	92	6.4	0.67	0.04	0.63**
	SD	17.4	16.6	35.4	16.1	3.6	0.21	0.02	0.21

BP = blood pressure in the ascending aorta, CBF = coronary blood flow, DCP = distal coronary pressure, R_T = total coronary resistance in the circumflex coronary artery, R_L = coronary resistance in the large arterial segment of the circumflex coronary artery, R_s = coronary resistance in the small coronary artery of the circumflex coronary bed.

Significantly different from the values before isoproterenol: **$P < 0.01$, *$P < 0.05$.

TABLE 2. EFFECTS OF ISOPROTERENOL ON CORONARY RESISTANCE IN THE PRESENCE OF CORONARY STENOSIS.

		Heart rate	BP	CBF	DCP	BP -DCP	Coronary resistance		
							R_T	R_L	R_S
Before constriction	Mean	151	108	73.8	106	1.8	1.49	0.02	1.47
	SD	16.8	12.5	10.1	11.3	0.8	0.16	0.01	0.14
After constriction	Mean	153	109	64.6	76	33	1.72	0.53	1.19
	SD	15.2	8.3	9.0	9.5	8.8	0.32	0.21	0.16
During isoproterenol	Mean	198**	82**	50.6**	41 **	41**	1.77*	0.89**	0.87**
	SD	22.4	18.5	18.1	8.1	15.7	0.61	0.46	0.27
Isoproterenol plus aortic constriction	Mean	185**	110	69.4	57**	52**	1.64*	0.84**	0.84**
	SD	19.3	8.9	19.1	7.5	10.5	0.47	0.32	0.17

Significantly different from the values after constriction: $^{**}P < 0.01$, $^{*}P < 0.05$.
Abbreviation; See Table 1.

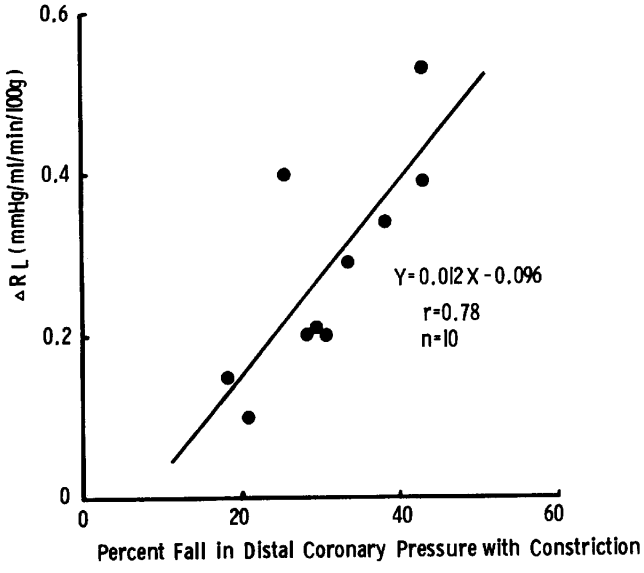

Fig. 1. Relationship between percent fall in coronary perfusion pressure caused by coronary constriction and the magnitude of the increase in R_L during aortic constriction after isoproterenol infusion. A close linear relation was observed in the two variables.

significantly less than the pre-isoproterenol and equal to the pre-aortic constriction values. On the contrary, incomplete restoration of distal coronary pressure was noticed after recovery of aortic pressure to the pre-isoproterenol level, resulting in a marked elevation in R_L in comparison to the control R_L. The magnitude

TABLE 3. EFFECTS OF ATRIAL PACING ON CORONARY RESISTANCE IN THE PRESENCE OF CORONARY STENOSIS.

		Heart rate	BP	CBF	DCP	BP -DCP	Coronary resistance		
							R_T	R_L	R_S
Dog 1	Control	156	107	54.5	73	34	1.97	0.63	1.34
	Pacing	185	110	56.2	73	37	1.96	0.66	1.30
Dog 2	Control	147	96	60.3	72	24	1.60	0.40	1.20
	Pacing	185	94	62.6	68	26	1.50	0.41	1.09
Dog 3	Control	159	113	52.1	84	29	2.17	0.56	1.61
	Pacing	185	90	44.2	64	26	2.04	0.59	1.45

Abbreviation; See Table 1.

of the increase in R_L during aortic constriction after the isoproterenol infusion varied directly with a percent increase in pressure gradient across the stenosis, as shown in Fig. 1. The regression equation is represented as follows: $R = 0.012 \times (\triangle \% DCP) - 0.096$, where $\triangle R$ is the magnitude of the increase in R_L and $\triangle \%$ DCP is the percent fall in the distal coronary pressure by the coronary constriction.

The results for the study of pacing tachycardia obtained from three dogs are summarized in Table 3. The tachycardia increased R_L in all of three dogs, but the magnitudes of the increments were not large enough to explain the change caused by isoproterenol infusion.

DISCUSSION

The present study demonstrated that intravenous injection of isoproterenol resulted in significant augmentation of R_L with critical coronary stenosis. Isoproterenol has a potent positive inotropic and chronotropic effect. Our previous study (6) indicated a significant effect of changes in aortic pressure on the stenosis resistance of the coronary artery: a fall in aortic pressure caused a rise in stenosis resistance. To avoid the effect of pressure changes on the stenosis resistance, the blood pressure in the ascending aorta was kept constant during isoproterenol infusion with constriction of the descending thoracic aorta. In this study, the heart rate increased by approximately 30-40 beats/min with isoproterenol infusion. Schwartz and his coworkers (7) reported a decline in blood flow through stenotic coronary arteries during pacing-induced tachycardia. However, it is unlikely that tachycardia was responsible for an increase in R_L after isoproterenol because, in contrast to the results of Schwartz *et al.*, our experiment revealed that pacing tachycardia caused a minimum increase in R_L in association with a slight rise in coronary flow and a mild fall in R_S. The different results of pacing tachycardia on R_L between the two studies, we believed, would

be due to the different methods for coronary constriction. In the preliminary study in our laboratory in which a wire snare was used to produce coronary obstruction according to Schwartz (8, 9), the results obtained were quite similar to their findings, while no reduction in coronary flow was observed since we utilized a cotton string for coronary constriction which moved independent of cardiac motion. From the results, even a minimum twist of the snare by changing cardiac motion or intraluminal pressure of the artery was considered to cause enhancement of coronary obstruction. Therefore when coronary stenosis is so severe that even an invisible twist of the snare causes significant increase in the stenosis resistance, the snare should be completely free of cardiac motion just like a short cotton string. Increase in myocardial compression to intramyocardial coronary vessels, extravascular compression, causes a rise in coronary resistance in the subendocardial myocardium: subendocardial myocardial blood flow decreases even with an increase in total coronary flow (10). Tachycardia caused by isoproterenol infusion further accelerates the maldistribution of myocardial blood flow (11). However, these effects were not responsible for an increase in R_L, because R_L consisted of the resistance in epicardial coronary arteries which was free of extravascular compression.

It has been shown that the pressure loss is related to the flow velocity through a stenosis: pressure loss increases directly with a rise in the flow velocity (12, 13). In the present study, however, flow velocity changes were also unlikely for pressure loss across the stenosis because flow velocity was essentially constant or rather decreased after isoproterenol infusion. Recent studies (14, 15) on sympathetic regulation of coronary vascular tone have demonstrated that alpha adrenergic control plays a major role in large coronary arteries and beta adrenergic regulation in small coronary arteries. Alpha adrenergic stimulation is powerful enough to reduce the cross-sectional area of the large coronary artery (16). Isoproterenol hardly affects alpha adrenoceptors. Although reflex stimulation of alpha adrenoceptors could be induced in response to systemic hypotension, central aortic pressure was held at the control level during isoproterenol infusion, and furthermore, the large coronary artery utilized for measuring R_L was free of adjacent tissue including autonomic nerves. Thus alpha adrenergic vasoconstriction is an unlikely cause of an increase in R_L in this study.

Isoproterenol dilates the coronary artery with stimulation of coronary beta adrenoceptors and through metabolic vasodilation in response to an increase in myocardial oxygen requirement (3). Santomore and Walinsky (17) have proposed that the reduction in distal coronary pressure causes a mechanical collapse of the wall at the stenotic segment of coronary artery, passive narrowing of segmental stenosis. Our previous study (18) suggested that the wall elasticity plays an important role in the increment of R_L occurring after the brief coronary occlusion. On the contrary, Brown (19) and Doemer and his colleagues (20) observed an increase in the cross-sectional area of coronary stenosis after adminis-

tration of coronary vasodilators in man. Thus, the mechanism(s) for a rise in stenosis resistance was quite controversial.

Whatever the mechanism concerned, a rise in resistance actually occurs after intravenous infusion of isoproterenol. In the presence of coronary stenosis, maldistribution of myocardial blood flow caused by isoproterenol was considered to be the effect of isoproterenol-induced increases in intramyocardial pressure, namely rises in extravascular compression in the subendocardial myocardium (10). However, our study revealed that the maldistribution of flow arose, at least in part, from an increase in pressure loss across the coronary stenosis that would intensify subendocardial myocardial ischemia resulting from coronary stenosis.

REFERENCES

1. McAlpin, R.N.: Relationship of coronary arterial spasm to sites of organic stenosis. *Am. J. Cardiol.* **46**, 143-153, 1980.
2. Logan, S.E.: On the fluid mechanics of human coronary artery stenosis. *IEEE (Inst. Electr. Electron. Eng.) Trans. Biomed. Eng.* **51**, 327-334, 1975.
3. Saito, D, Nixon, D.G., Vomacka, R.B. and Olsson, R.A.: Relationship of cardiac oxygen usage, adenosine content, and coronary resistance in dogs. *Circ. Res.* **47**, 875-882, 1980.
4. Buckberg, G.D. and Ross, G.: Effects of isoprenalline on coronary blood flow, its distribution, and myocardial performance. *Cardiovasc. Res.* **7**, 429-437, 1973.
5. Ueda, M.: Effect of sympathomimetic amines on distribution of blood flow in the normal and in the ischemia myocardium. *Okayama Ishi* **90**, 641-660, 1978 (in Japanese).
6. Saito, D., Yasuhara, K., Kusachi, S., Takeda, H., Hyodo, T. and Haraoka, S.: Study on resistance changes in coronary stenosis and myocardial blood flow distal to the stenosis in the dog (abstract). *J. Jpn. Coll. Angiol.* **21**, 717, 1981.
7. Schwartz, J.S., Carlyle, P.F. and Cohen, J.N.: Decline in blood flow in stenotic cororary arteries during increased myocardial energetic demand in response to pacing-tachycardia. *Am. Heart J.* **101**, 435-440, 1981.
8. Schwartz, J.S., Carlyle, P.F. and Cohen, J.N.: Effect of dilation of the distal coronary bed on flow and resistance in severely stenotic coronary arteries in the dog. *Am. J. Cardiol.* **43**, 219-224, 1979.
9. Schwartz, J.S., Carlyle, P.F. and Cohen, J.N.: Effect of coronary arterial pressure on coronary stenosis resistance. *Circulation* **61**, 70-76, 1980.
10. Buckberg, G.D., Fixler, D.E., Archie, J.P. and Hoffman, J.I.E.: Experimental subendocardial ischemia in the dogs with normal coronary arteries. *Circ. Res.* **30**, 67-81, 1972.
11. Raff, W.K., Kosche, F. and Lochner, W.: Extravascular coronary resistance and its relation to microcirculation: Influence of heart rate, enddiastolic pressure and maximal rate of rise of intraventricular pressure. *Am. J. Cardiol.* **29**, 598-603, 1972.
12. Gould, K.L.: Pressure-flow characteristics of coronary stenosis in unsedated dogs at rest and during coronary vasodilation. *Circ. Res.* **43**, 242-253, 1978.
13. Young, D.F., Cholvin, N.R. and Roth, A.C.: Pressure drop across artificially induced stenosis in the femoral arteries in dog. *Circ. Res.* **36**, 735-743, 1975.
14. Feigl, E.O.: Sympathetic control of coronary circulation. *Circ. Res.* **20**, 262-271, 1967.

15. Hortz, J., Mayer, E. and Bassenge, E.: Demonstration of alpha-adrenergic coronary control in different layers of canine myocardium by regional myocardial sympathectomy. *Pfluegers Arch. Eur. J. Pyhsiol*, **372**, 187-194, 1977.
16. Vatner, S.F., Pagani, M., Manders, W.T. and Pasipoulariders, A.D. : Alpha adrenergic vasoconstriction and nitroglycerin vasodilation of large coronary arteries in the conscious dog. *J. Clin. Invest.* **65**, 5-14, 1980.
17. Santomore, W.P. and Walinsky, P.: Altered coronary flow response to vasoactive drugs in the presence of coronary arterial stenosis in the dog. *Am. J. Cardiol.* **45**, 276-285, 1980.
18. Saito, D., Yasuhara, K., Takeda, H., Hyodo, T., Yamada, N., Uchida, T., Haraoka, S. and Nagashima, H.: Increase in stenotic resistance following a brief coronary occlusion in the anesthetized open-chest dog. *Acta Med. Okayama* **36**, 199-205, 1982.
19. Brown, G.M., Bolson, E., Frimer, M. and Dodge, H.T.: Angiographic distinction between variant angina and non-vasospastic chest pain (abstract). *Circulation* **57**, 58 (suppl. II), II-122, 1978.
20. Doemer, T.C., Brown, G.B., Bolson, E., Frimer, M. and Dodge, H.T.: Vasodilatory effects of nitroglyerin and nitroprusside in coronary arteries (abstract). *Am. J. Cardiol.* **43**, 416, 1979.