**Effects of the Rise in Aortic Pressure on
Coronary Flow Reserve in Dogs**
**Comparison between Constriction of the Descending
Thoracic Aorta and Injection of Methoxamine**

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SUMMARY

In order to investigate the effect of a rise in aortic pressure on coronary flow reserve and also on the difference of its effect according to the methods used to raise aortic pressure, this experiment was performed.

Using 7 anesthetized dogs with heart rate held constant by a pacemaker, both the resting and the peak reactive hyperemic left circumflex coronary flow were measured following raising of the aortic pressure by either descending thoracic aorta constriction or methoxamine injection.

The resting and peak reactive hyperemic coronary flows both increased linearly following the rise in aortic pressure. The magnitude of the resting flow increment and the resting coronary vascular resistance following raising aortic pressure did not differ significantly between the two different methods. However, the magnitude of the peak hyperemic flow increment and the peak hyperemic coronary vascular resistance following raising aortic pressure were significantly smaller with methoxamine injection than with aortic constriction.

These data indicate that coronary flow reserve increases proportionally with a rise in aortic pressure. However, the magnitude of the increment of coronary flow reserve is smaller following an alpha-adrenoceptor-mediated rise in aortic pressure, because the maximal coronary vasodilation was reduced by alpha-stimulated coronary vasoconstriction.

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CORONARY blood flow has been regarded as being regulated by the metabolic demands of the myocardium,¹⁾ and under maximal stress it may increase above resting levels and may reach a maximum due to maximal coronary vasodilation. This increment of coronary flow from the resting level to the maximally vasodilated level is termed "coronary flow reserve" and is thought to give information about what might happen during maximal stress.²⁾

Mosher et al,³⁾ using dogs whose coronary arteries were perfused separately from aortic pressure, featured the coronary pressure-flow diagram that is often used to describe coronary flow reserve. However, under physiological conditions with coronary arteries perfused by aortic pressure, it is not well known how much effect changing aortic pressure has on coronary flow reserve.²⁾ Coronary pressure-flow relationship in physiologically perfused coronary arteries will be changed relative to what was obtained by Mosher et al. In addition, since the coronary artery per se is subject to alpha-adrenoceptor vasoconstriction,⁴⁾⁻¹¹⁾ the rise in aortic pressure associated with alpha-adrenoceptor stimulation will modify the coronary pressure-flow relationship in comparison to the rise in aortic pressure by a means without a coronary vasoconstrictive effect.

This study was designed to investigate the effect of raising aortic pressure on coronary flow reserve under physiological conditions, and to examine how coronary flow reserve differs according to whether the increase in aortic pressure was or was not accompanied by alpha-adrenoceptor stimulation. For this purpose, by constriction of the descending thoracic aorta and by intravenous injection of methoxamine, the effects of the rise in aortic pressure on the resting coronary flow and peak reactive hyperemic flow after transient coronary occlusion were studied in dogs.

METHODS

Experimental preparation:

Seven mongrel dogs weighing 10 to 16 kg were anesthetized with sodium pentobarbital 25 mg/kg intravenously and ventilated with a Harvard respirator. The right femoral vein was cannulated for drug administration. The right femoral artery was cannulated to monitor aortic pressure using a 7F heparin-filled catheter, which was placed in the aortic arch and con-

nected to a pressure transducer (Nihon Kohden, MPU-0.5A). Lead II of the electrocardiogram was continuously recorded. A left thoracotomy was performed in the fourth intercostal space and the heart was exposed and suspended in a pericardial cradle. Atrial pacing at a rate of 130 beats/min with pacing electrodes attached to the left atrial appendage was conducted after the sinoatrial node was mechanically crushed. Blood flow through the proximal left circumflex coronary artery was measured by an electromagnetic flow probe (Nihon Kohden, FJ 2-2.5 mm ϕ) connected to a flowmeter (Nihon Kohden, MFV-1200). An 18-gauge needle was inserted into the apex of the left ventricle for left ventricular pressure measurement and connected to a pressure transducer (Nihon Kohden, MPU-0.5A). In addition, in order to produce a rise in aortic pressure, a tape was placed around the descending thoracic aorta to facilitate aortic constriction.

Experimental protocol:

Measurements of aortic pressure, left ventricular end-diastolic pressure, and left circumflex coronary flow were performed both at a resting state and peak reactive hyperemic state after a 20 sec circumflex artery occlusion in the following serial conditions: control state; after constriction of the descending thoracic aorta; and after alpha-adrenoceptor stimulation with intravenous injection of methoxamine (0.2 mg/kg). After measuring the control values, we constricted the descending thoracic aorta to almost complete occlusion for the first 5 min by tightening the tape around it (level 1). Then, we moderated the constriction for the second 5 min so that the aortic pressure attained an intermediate value between control and complete occlusion (level 2), and finally, released the constriction completely (level 3). The measurements of the parameters were done at each level of aortic constriction. Subsequently, methoxamine was injected intravenously. The dose of methoxamine was determined according to our previous study¹¹⁾ in order to raise the aortic pressure by a similar degree to that following aortic constriction. The parameters were also measured every 5 min until 20 min after the injection when the aortic pressure was stabilized.

The step-wise reduction in aortic constriction made the aortic pressure change similar to that produced by methoxamine injection, which caused the aortic pressure to elevate maximally within a minute and then attenuate gradually. Furthermore, lessening the time of constriction to less than 15 min might have minimized the influence of the preceding constriction of the thoracic aorta on the effect of methoxamine. Reductions in renal artery pressure as a result of constriction of the descending thoracic aorta would stimulate a release of renin and angiotensin formation. However, the effect

of angiotensin on vascular resistance reaches a maximum about 40 min after the reduction in renal artery pressure.¹²⁾ This is much longer than the period of time the aorta was constricted in the present study.

Data analysis:

Electrocardiogram, aortic pressure, left ventricular end-diastolic pressure and left circumflex coronary flow were recorded on an 8-channel pen recorder (Nihon Kohden, RM-6000). To appreciate the coronary pressure-flow relationship following the increase in aortic pressure, the individual values of resting coronary flow or peak reactive hyperemic flow for a given animal were normalized and plotted against the corresponding mean aortic pressure. For normalization, the values of resting and peak hyperemic coronary flow at the initial control state were used as the denominators for the values of coronary flow after aortic constriction. Also, the values of coronary flow 20 min after aortic constriction were used as the denominators for the values after methoxamine injection in each dog. This procedure was useful not only to normalize the differences in coronary flow among the individual dogs, but also to characterize the coronary pressure-flow relationship by linear regression analysis without controlling aortic pressure exactly and to calculate the "pressure-normalized flow slope", defined as the change in normalized flow associated with the change in mean aortic pressure.

Animals with an aortic pressure depression of more than 20 mmHg after a 20 sec occlusion of the circumflex coronary artery and/or arrhythmias making coronary flow unstable were excluded from this study.

All values are presented as mean $\pm$ standard error of the mean. Coronary pressure-normalized flow data were plotted and fitted by linear regression, and these pressure-normalized flow slopes were compared by analysis of covariance. The coronary vascular resistance both at resting states and at peak reactive hyperemic states following raising of the aortic pressure was calculated by dividing the mean aortic pressure by the left circumflex flow, and the mean values of these resting and peak hyperemic coronary resistances were compared respectively between aortic constriction and methoxamine injection using Student's paired t-test. The level of statistical significance was $p < 0.05$.

RESULTS

The results of a typical experiment demonstrating the effects of raising aortic pressure by constriction of the descending thoracic aorta or methoxamine injection on resting and peak reactive hyperemic coronary flow are

shown in Fig. 1. The resting flow and peak reactive hyperemic flow increased in proportion to raising aortic pressure. In comparing the effects on the coronary pressure-flow relationship of aortic constriction and methoxamine injection, the resting flow differed only slightly between the two. However, it was observed that the peak reactive hyperemic flow was smaller following methoxamine injection than following aortic constriction.

Aortic pressure, left ventricular end-diastolic pressure, resting left circumflex coronary flow and peak reactive hyperemic flow at the initial control state and the states following aortic constriction or methoxamine injection are shown in Table I. Aortic pressure was raised more by methoxamine than by aortic constriction.

Fig. 2 shows the relationships between the raised aortic pressure and the normalized resting coronary flow for all the trials involving aortic constriction and methoxamine injection. Each point represents one measurement after raising aortic pressure in a given animal. The mean aortic pressure correlated linearly with the normalized resting flow both with aortic constriction ($r=0.82$, $p<0.001$) and with methoxamine injection ($r=0.69$, $p<0.001$). The magnitude of change in normalized resting coronary flow associated with the change in mean aortic pressure (the pressure-normalized resting flow

Fig. 1. Relationship between raised aortic pressure and the resting or the peak reactive hyperemic coronary flow obtained from a representative dog.

Table I. Effects of Aortic Constriction and Methoxamine Injection on Hemodynamics and Circumflex Coronary Flow

	Control state	Aortic constriction			Methoxamine injection			
		level 1	level 2	level 3	5 min	10 min	15 min	20 min
Aortic pressure (mmHg)								
Mean pressure	94±2	138±2	123±4	99±8	152±9	140±7	136±7	132±9
Systolic pressure	107±4	169±5	147±6	120±4	173±8	157±6	155±6	148±7
Diastolic pressure	87±2	121±2	109±4	88±4	142±9	132±7	128±6	123±9
Left ventricular end-diastolic pressure (mmHg)	6±1	10±1	8±1	5±2	12±1	10±2	8±1	5±1
Circumflex coronary flow (ml/min)								
Resting flow	23±4	43±6	34±5	25±3	40±4	35±4	33±4	30±4
Peak reactive hyperemic flow	90±10	151±23	133±24	98±17	141±23	130±26	119±20	110±22

Values are mean±SE. There was no significant difference between the values of control state and level 3.

Fig. 2. Relationship between raised aortic pressure and normalized resting coronary flow following constriction of the descending thoracic aorta and methoxamine injection. Data obtained at three levels of aortic constriction in 7 dogs denoted by (●) and at 5, 10 and 15 min after methoxamine injection in 7 dogs and 20 min after in 6 dogs denoted by (○) were plotted together. Linear regression analysis shows a significant correlation in aortic constriction ($r=0.82$, $p<0.001$) and also in methoxamine injection ($r=0.69$, $p<0.001$). Curved broken lines are 95% confidence limits for regression. The pressure-normalized resting flow slope did not differ significantly between aortic constriction and methoxamine injection (1.89 vs. 1.22, N.S.).

Fig. 3. Relationship between raised aortic pressure and normalized peak reactive hyperemic coronary flow following aortic constriction and methoxamine injection. Data obtained after aortic constriction denoted by ($\blacktriangle$) and after methoxamine injection denoted by ($\triangle$) were plotted together. Linear regression analysis shows a significant correlation in aortic constriction ($r=0.76$, $p<0.001$) and also in methoxamine injection ($r=0.54$, $p<0.01$). Curved broken lines are 95% confidence limits for regression. The pressure-normalized peak reactive hyperemic flow slope was smaller with methoxamine injection than with aortic constriction (1.56 vs. 0.50, $p<0.01$).

Fig. 4. Comparisons of the resting and the peak reactive hyperemic coronary vascular resistance between aortic constriction and methoxamine injection. Data represent means $\pm$ SE. The peak hyperemic coronary resistance was greater with methoxamine injection than with aortic constriction, whereas, the resting coronary resistance did not differ between them.

slope) did not differ between aortic constriction and methoxamine injection (1.89 vs. 1.22, N.S.).

Similar linear correlations were also found between the raised aortic pressure and the normalized peak reactive hyperemic flow. The mean aortic pressure correlated with the normalized peak hyperemic flow both with aortic constriction ($r=0.76$, $p<0.001$) and with methoxamine injection ($r=0.54$, $p<0.01$), as shown in Fig. 3. However, the pressure-normalized peak hyperemic flow slope was significantly smaller with methoxamine injection than with aortic constriction (0.50 vs. 1.56, $p<0.01$).

Comparing the coronary vascular resistance following raising of the aortic pressure by aortic constriction and methoxamine injection (Fig. 4), the resting coronary vascular resistance tended to be greater with methoxamine injection than with aortic constriction, but not significantly (4.14 ± 0.62 vs. 4.51 ± 0.71 , N.S.). On the other hand, the coronary vascular resistance at peak reactive hyperemic states was significantly greater with methoxamine injection (1.07 ± 0.11 vs. 1.28 ± 0.17 , $p<0.05$).

DISCUSSION

The results demonstrated that both the resting coronary flow and the peak reactive hyperemic coronary flow increased linearly in accordance with aortic pressure elevation under physiological conditions. The magnitude of the resting coronary flow increment and the resting coronary vascular resistance did not differ significantly between aortic constriction and methoxamine injection. However, the increment in the peak reactive hyperemic flow and the peak hyperemic coronary vascular resistance were significantly smaller with methoxamine injection than with aortic constriction. Therefore, the coronary flow reserve following a rise in aortic pressure was thought to be reduced more by methoxamine injection than by aortic constriction.

Maximal coronary flow was reported to be obtained by injection of vasodilating agents such as dipyridamole,¹³⁾ papaverine,¹⁴⁾ adenosine¹⁵⁾ and ATP.^{14),15)} But, as Dole et al,¹⁶⁾ and Olsson and Gregg¹⁷⁾ reported, a 10 sec coronary occlusion was thought to be sufficient to produce a maximal reactive hyperemic flow in the dog. Also Marcus¹⁸⁾ described that a 15–20 sec coronary occlusion can produce maximal coronary vasodilation. Thus, the 20 sec coronary artery occlusion performed in this study was thought to be adequate to produce maximal coronary vasodilation.

Previous studies reported that the maximal coronary flow is influenced by heart rate,¹⁹⁾ cardiac contractility,²⁰⁾ left ventricular end-diastolic pressure³⁾ and blood viscosity.²¹⁾ In this study, because heart rate was kept constant by atrial

pacing and end-diastolic pressures were similar between aortic constriction and methoxamine injection, the effects of these parameters are considered to be negligible. As for the effects of cardiac contractility, acute occlusion of the descending thoracic aorta does not change the sympathetic activity and causes an increase in myocardial oxygen demand only because of the increase in ventricular work following the rise in aortic pressure.²²⁾ Furthermore, methoxamine, a potent alpha-adrenoceptor agonist, produced little negative inotropic action in the heart-lung preparation in doses of less than 4 mg.²³⁾ Therefore, the difference in cardiac contractility may play a small role in explaining the difference in maximal coronary flow.

Though coronary blood flow is closely regulated by myocardial metabolism,¹⁾ alpha-adrenoceptor-mediated coronary vasoconstriction,⁴⁾⁻¹¹⁾ especially by methoxamine^{8),11)} has been reported. Schwartz and Stone²⁴⁾ studied the effect of right and/or left stellectomy on myocardial reactive hyperemia and thought that reactive hyperemia is reduced by alpha-adrenoceptor-mediated vasoconstriction. In our study the magnitude of the increment in resting coronary flow and the resting coronary vascular resistance following methoxamine injection did not differ significantly from that following aortic constriction. This suggests that metabolic vasodilation linked to increased myocardial work and oxygen consumption, as well as the elevation in coronary perfusion pressure, competed with the alpha-adrenoceptor vasoconstriction induced by methoxamine and masked its vasoconstrictive action. On the other hand, as it was shown that the increment in peak reactive hyperemic flow and the peak hyperemic coronary vascular resistance following raising of the aortic pressure were smaller with methoxamine injection than with aortic constriction, with maximal coronary vasodilation the competitive metabolic effect was almost exhausted and alpha-adrenoceptor vasoconstriction is thought to be unmasked.

In conclusion, this study indicates that both the resting coronary flow and the maximal coronary flow increase in proportion to the rise in aortic pressure. However, with the rise in aortic pressure induced by alpha-adrenoceptor stimulation, the peak hyperemic flow is reduced by alpha-adrenoceptor-mediated coronary vasoconstriction. Therefore, the coronary flow reserve following the rise in aortic pressure is smaller with alpha-adrenoceptor stimulation than with mechanical aortic pressure elevation.

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