Functional Consequences and Intracoronary Localization of Alpha-Adrenergic Stimulation of the Canine Coronary Circulation

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Although alpha-adrenergic stimulation can increase coronary vascular resistance, it remains unknown whether the vasoconstriction can override intrinsic coronary regulatory influences to produce ischemia. Methoxamine, 2 to 4 mg, was infused into the circumflex coronary artery of 23 chloralose-anesthetized open chest dogs, and resulted in a 68% increase in coronary vascular resistance. The functional consequence of this increased coronary vascular resistance was assessed by gated radionuclide ventriculography and ST-T wave changes on the electrocardiogram.

In six dogs (Group I), aortic pressure changed trivially (<5 mm Hg) to allow distinction between direct effects of the flow reduction and indirect effects of increased aortic pressure. In this group, coronary blood flow decreased 33% from a control value of 44 ± 10 ml/min ($p < 0.001$) and left ventricular ejection fraction decreased from 0.54 ± 0.12 to 0.46 ± 0.10 ($p < 0.025$). In eight dogs (Group II) in which aortic pressure increased by more than 5 mm Hg, left ventricular ejection fraction decreased from 0.46 ± 0.07 to 0.39 ± 0.09 ($p < 0.002$). Pressure gradients were measured between the aorta and a distal coronary artery branch to calculate small and large vessel resistances separately in four other dogs (Group III). The resistance of small coronary arteries accounted for 92% of the total increase in coronary vascular resistance produced by methoxamine. In five other dogs (Group IV), intracoronary methoxamine, 2 mg, produced ST-T wave changes suggestive of ischemia as it increased coronary vascular resistance by 33%.

In conclusion, this study demonstrated that methoxamine caused functionally significant vasoconstriction of small coronary arteries as shown by the decreased left ventricular ejection fraction and ST-T wave changes. These findings suggest that alpha-adrenergic vasoconstriction can override coronary regulatory influences to cause ischemia.

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Primary alpha-adrenergic receptor-mediated coronary vasoconstriction and secondary metabolic vasodilation are competitive with one another (1). Alpha-adrenergic stimulation has been shown to cause increased coronary vascular resistance (2,3), narrowing of the large coronary arteries (4) and decreased oxygen tension in the coronary venous blood (5). The decrease in coronary venous oxygen tension is presumably caused by increased oxygen extraction. It is not known whether this increased oxygen extraction reflects a severe enough depression in coronary blood flow so that alpha-adrenergic stimulation actually overcomes the intrinsic coronary regulation to reduce tissue oxygenation and precipitate ischemia. Thus, the first goal of the present study was to determine whether the increase in coronary vascular resistance produced by intracoronary methoxamine causes a severe enough reduction in coronary blood flow to produce myocardial ischemia, as indicated by impaired left ventricular contractile function and ST-T wave changes on the electrocardiogram. Left ventricular dysfunction could certainly be produced by factors other than acute myocardial ischemia, so we designed this study to use left ventricular ejection as an index of the functional significance of changes in coronary vascular resistance. First, we selected methoxamine as an alpha-adrenergic agonist because it causes

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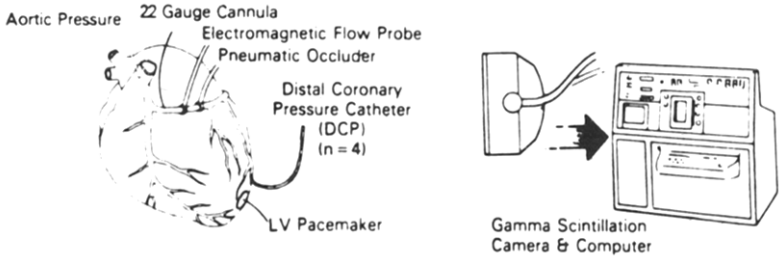

Figure 1. Experimental preparation. Instrumentation on the dog heart is shown on the **left.** The gamma camera/computer system used to measure left ventricular ejection fraction is shown on the **right.** LV = left ventricular.

no direct negative inotropic effects (6,7). Second, we selected one group of dogs (Group I) because of their trivial, (that is, less than 5 mm Hg) change in mean aortic pressure with methoxamine, to avoid the effects on cardiac function of changing afterload or baroreceptor reflexes.

The second major purpose of our investigation was to determine whether methoxamine constricted primarily large or small coronary arteries. Indirect evidence has suggested that small vessels have minimal alpha-adrenergic receptor function (8,9), and that the predominant effect of alpha-adrenergic vasoconstriction is on large vessels (4). Recently Kelley and Feigl (10) suggested a more significant role for small vessels in vasoconstriction mediated by alpha-adrenergic receptors. However, these investigators studied only small increases (not greater than 35%) in coronary vascular resistance and did not determine whether these changes were functionally significant. Thus, it could not be determined whether functionally significant changes in coronary vascular resistance sufficient to impair left ventricular contractile and electrophysiologic function require large vessel involvement, or can be mediated primarily by small vessel constrictors.

Methods

Experimental preparation. Twenty-three foxhounds weighing 25 to 35 kg were anesthetized with morphine sulfate, 3 mg/kg body weight intramuscularly, and alpha chloralose, 3 g intravenous bolus, then maintained on a 2 to 5 mg/h constant infusion of chloralose in normal saline solution. A left thoracotomy was performed and a pericardial cradle was made. A 1 to 2 cm segment of the proximal left circumflex coronary artery was isolated to place an electromagnetic flow probe proximal to a pneumatic occluder (Fig. 1). The pneumatic occluder was used to stop flow momentarily to check the balance of the flow probe. A 22 gauge catheter was inserted retrograde into the proximal left circumflex coronary artery for infusion of methoxamine. Aortic pressure was monitored through a femoral artery catheter registering mean pressure by a calibrated P23 ID transducer. A constant heart rate was maintained by pacing the apex of the left ventricle to obviate any possible changes in atrioventricular conduction, except in the five dogs in which the electrocardiogram was recorded. The dogs were paced 10 to 15% above their intrinsic heart rate to ensure pacemaker capture. Arterial blood gases were monitored periodically and maintained within normal limits by adjusting ventilation.

Left ventricular function measurements. Radionuclide angiographic studies were performed in 14 dogs given intracoronary methoxamine. These dogs were divided into two groups based on changes in mean aortic pressure. Because some dogs had trivial changes (<5 mm Hg) in aortic pressure, this design permitted evaluation of the effects of methoxamine on coronary blood flow and left ventricular function without the confounding effects of increased aortic pressure. In Group I (n = 6), aortic pressure changed by less than 5 mm Hg (Fig. 2A) and in Group II (n = 8), aortic pressure increased by 5 mm Hg or more (Fig. 2B).

When conditions were stable, stannous pyrophosphate, 3 mg, was injected intravenously, followed after 30 to 40 minutes by 20 mCi of technetium-99m. Electrocardiographic-gated blood pool scintigraphy was performed by imaging the dog with an E1 Scint model portable gamma

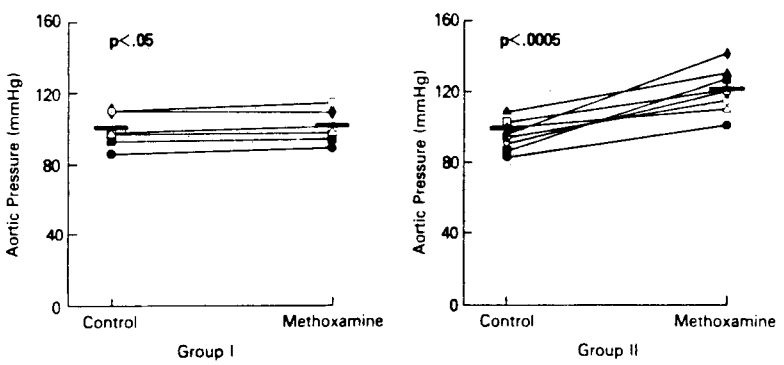

Figure 2. Mean aortic pressure during control state and during the maximal decrease in coronary blood flow after treatment with methoxamine. To isolate the effects of methoxamine on the coronary circulation independent of its effect on blood pressure, Group I dogs (n = 6) were defined as having a less than 5 mm Hg increase in mean aortic pressure (**left**) whereas Group II dogs (n = 8) showed a greater than 5 mm Hg increase (**right**). Different symbols are used for each individual dog and are consistent in all figures. The **heavy horizontal bars** show mean values. **Lines** connect **points** for the same dog.

scintillation camera. The dog was imaged in a modified left anterior oblique projection that provided the best separation between the right and left ventricles (11). The data were collected in list mode on a Hewlett-Packard computer using programs developed at the National Institutes of Health (12). Briefly, the images were acquired to 6.2 million events over 6 to 10 minutes, and the computer-based electrocardiographic-gating system constructed a cardiac image sequence representing an average cardiac cycle (12). The data were also used to construct a high temporal resolution (10 ms/frame) left ventricular time-activity curve after manually outlining regions of interest for the left ventricle and background. The time-activity curve is proportional to changes in left ventricular volume, and left ventricular ejection fraction was calculated from the following equation:

$$\frac{\text{End-diastolic counts} - \text{End-systolic counts}}{\text{End-diastolic counts} - \text{Background counts}}$$

After the baseline gated blood pool scan, measurements of coronary blood flow, aortic pressure, left ventricular pressure and heart rate were made. Intracoronary saline solution was injected as a control in six dogs and caused no change in heart rate, coronary blood flow, aortic pressure or left ventricular ejection fraction. Intracoronary methoxamine, 2 to 4 mg, was injected in 3 ml of saline solution over 1 minute, and repeat measurements, including the gated blood pool scan, were made.

Total coronary vascular resistance was estimated by the formula:

$$\frac{\text{Mean aortic pressure}}{\text{Mean coronary blood flow}},$$

where coronary back pressure is ignored, acknowledging that the value of coronary back pressure is uncertain but probably low in the open chest dog (13).

Measurement of large versus small vessel resistances. In four separate dogs (Group III) an 18 gauge coronary catheter that tapered to a 21 gauge tip was inserted in a small distal branch of the circumflex coronary artery. A differential pressure transducer monitored the difference between aortic and distal coronary artery pressure. This transducer was carefully calibrated in steps from 0 to 20 mm Hg full scale; it recorded zero pressure difference when both pressure inputs were attached to the same catheter, whether it was reading zero or aortic pressure. The 18 gauge catheter used in the coronary artery was inserted into a femoral artery in separate pilot studies, and it did not alter the value of mean pressure. If a pressure difference of less than 2 mm Hg was recorded, the animal was not used for the study, using the criteria of Kelley and Feigl (10). Several animals were prospectively judged unusable for this reason before methoxamine was given. No animals were withdrawn retrospectively.

Large (R_L) *and small* (R_S) *vessel resistances were calculated in successful experiments as follows:*

$$\text{Large vessel resistance} = \frac{\text{AoP} - \text{DCP}}{\text{CBF}} = R_L$$

$$\text{Small vessel resistance} = \frac{\text{DCP}}{\text{CBF}} = R_S,$$

where AoP = mean aortic pressure; DCP = mean distal coronary pressure and CBF = coronary blood flow. In five other dogs (Group IV), lead II of the electrocardiogram was recorded before and during methoxamine administration.

Protocol. After control measurements was obtained, each dog received intracoronary methoxamine, 2 to 4 mg, in 1 ml of normal saline solution infused over 1 minute, followed by a 3 ml flush of normal saline solution over 1 minute. After completing the methoxamine infusion, we recorded the values of mean aortic pressure and heart rate at the time of the maximal changes in mean coronary blood flow. In Groups I (n = 6) and II (n = 8) we collected radionuclide data for 6 to 10 minutes, beginning 1 minute after completion of the methoxamine infusion. In Group III (n = 4) we measured distal coronary pressure and aortic pressure at the time of maximal coronary blood flow changes due to methoxamine. In Group IV (n = 5), we measured coronary hemodynamics and recorded the electrocardiogram before and during the intracoronary methoxamine infusion (n = 5).

Analysis of data. We tested the significance of differences from control to the maximal change after methox-

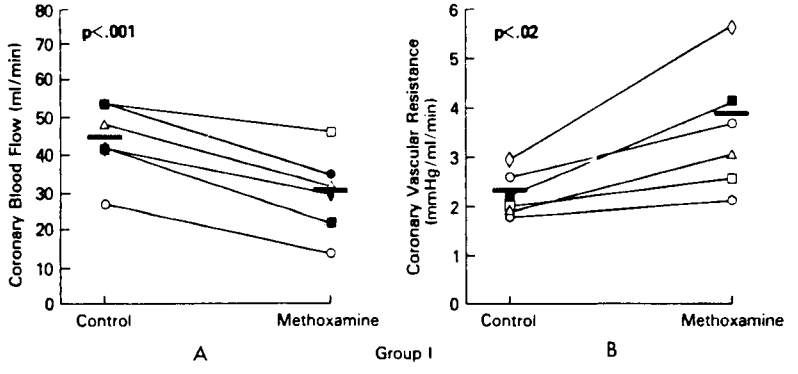

Figure 3. Coronary hemodynamics in dogs with a less than 5 mm Hg increase in aortic pressure during methoxamine infusion (Group I). **A**, Coronary blood flow decreased from the control period to the time of minimal coronary blood flow resulting from methoxamine (10 to 15 seconds after completion of the infusion). **B**, Coronary vascular resistance increased from the control period to the time of minimal coronary blood flow resulting from methoxamine.

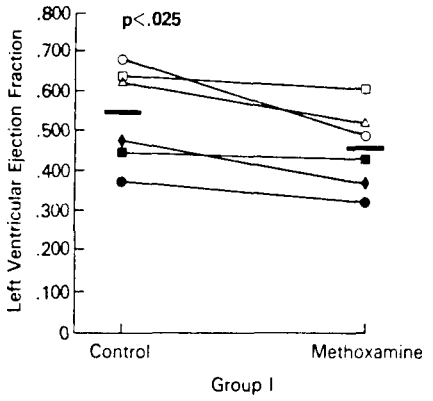

Figure 4. In Group I dogs with a less than 5 mm Hg increase in aortic pressure, left ventricular ejection fraction decreased during methoxamine treatment compared with the control state.

amine by Student's *t* test for paired data (14). Data are presented as mean ± SD. A probability (p) value of less than 0.05 was considered statistically significant but $0.05 < p < 0.10$ was reported as marginally significant.

Results

In Group I (n = 6), in which aortic pressure changed less than 5 mm Hg and heart rate was held constant by pacing so that it did not change from the control value of 97 ± 9 beats/min, coronary blood flow decreased from 44 ± 10 to 31 ± 11 ml/min ($p < 0.001$) (Fig. 3A). Coronary blood flow remained at least 20% below baseline for 15 to 45 minutes. Coronary vascular resistance increased 55% from 2.28 ± 0.43 to 3.53 ± 1.27 mm Hg/ml per min ($p < 0.02$) (Fig. 3B). Left ventricular ejection fraction decreased from 0.54 ± 0.12 to 0.46 ± 0.10 ($p < 0.025$) (Fig. 4).

In Group II (n = 8), in which aortic pressure increased by 5 mm Hg or more (an average of 23%) and heart rate was held constant so that it did not change from the control value of 116 ± 22 beats/min, coronary blood flow decreased from 50 ± 20 to 44 ± 23 ml/min ($p < 0.05$). Coronary resistance increased 70% from 2.30 ± 1.27 to 3.91 ± 2.72 mm Hg/ml per min ($p < 0.02$) (Fig. 5B). Left ventricular ejection fraction decreased from 0.46 ± 0.07 to 0.39 ± 0.09 ($p < 0.002$) (Fig. 6). Reproducibility of the left ventricular ejection fraction by gated blood pool scintigraphy of two separate data acquisitions in the same dog a few minutes apart was excellent. The absolute difference between paired serial studies separated by a saline injection was 0.01 ± 0.01 ejection fraction units (p = NS, n = 7).

Large versus small vessel resistances. *In Group III (n = 4),* aortic pressure did not change significantly (Fig. 7). Coronary blood flow decreased 28% from a control of 43 ± 31 ml/min. Methoxamine increased large vessel resistance from 0.18 ± 0.18 to 0.40 ± 0.33 mm Hg/ml per min and small vessel resistance from 2.73 ± 1.51 to 5.72 ± 4.94 mm Hg/ml per min. When expressed as percent of control, large vessel resistance increased 122 ± 106% (p = 0.08) and small vessel resistance increased 111 ± 59% from control (p = 0.05). Although the percent increases in large and small vessel resistances were similar, the increase in small vessel resistance (R_S) accounted for 92% of the increase in total coronary vascular resistance:

$$\frac{\text{Small vessel resistance}}{\text{Large vessel resistance} + \text{Small vessel resistance}},$$

where large plus small vessel resistance ($R_L + R_S$) = total coronary vascular resistance. The increase in large vessel resistance accounted for less than 8% of the total increase in coronary vascular resistance due to methoxamine. Therefore, the change in total resistance produced by methoxamine was primarily due to its effect on small vessels. Thus, small vessels exerted predominant control of coronary circulation both during control conditions and during vasoconstriction due to methoxamine (small vessel resistance = 94% of total resistance before and during methoxamine) (Fig. 8).

In Group IV, methoxamine caused a 33% increase in total coronary resistance and ST-T wave changes in all five dogs (Table 1) (Fig. 9). Intracoronary saline solution infused at the same rate had no effect.

Discussion

Previous studies. Normally, endogenous regulatory mechanisms control coronary blood flow to meet myocardial metabolic demands (15) so that any coronary vasoconstrictor

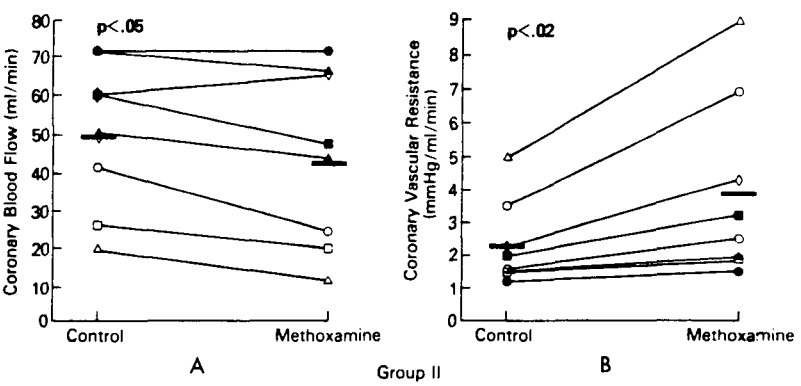

Figure 5. Coronary hemodynamics in Group II dogs with a greater than 5 mm Hg increase in aortic pressure after methoxamine administration. **A**, Coronary blood flow decreased from the control state to the time of minimal coronary blood flow resulting from treatment with methoxamine. **B**, Coronary vascular resistance increased from the control state to the time of minimal coronary blood flow resulting from treatment with methoxamine.

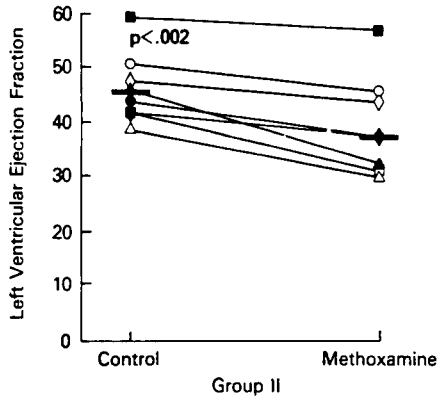

Figure 6. In Group II dogs with a greater than 5 mm Hg increase in aortic pressure, left ventricular ejection fraction decreased during methoxamine treatment compared with the control state.

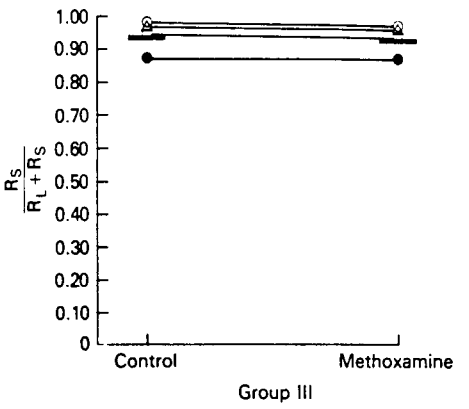

Figure 8. In Group III dogs, small vessel coronary vascular resistance expressed as a fraction of the total coronary vascular resistance did not change with methoxamine treatment (mean, 94%). This shows that small vessels exert predominant control over the coronary circulation both during the control state and during treatment with methoxamine. Small vessel resistance/(large vessel resistance + small vessel resistance $[R_S/(R_L + R_S)]$) = small vessel resistance (R_S) as a fraction of total resistance (large + small vessel resistance).

agent would directly compete with this regulatory system (1,3). The extent of this competition was studied by Feigl (5), who found that alpha-adrenergic–mediated coronary vasoconstriction is capable of lowering coronary venous oxygen tension. Mohrman and Feigl (1) corroborated this by intracoronary infusion of norepinephrine in anesthetized dogs with and without alpha-adrenergic receptor blockade; they found that the resulting alpha-adrenergic–mediated vasoconstriction restricted coronary blood flow by about 30% and caused a decrease in coronary venous oxygen tension. A decrease in coronary venous oxygen tension is compatible with, but not specific for, ischemia. Although an agent reduces coronary blood flow, increased oxygen extraction (measured by decreased venous oxygen tension) may adequately compensate for the decrease in flow (3) so that tissue oxygenation is maintained and ischemia is prevented. Alternatively, this decreased tension may reflect decreased tissue oxygenation in which the alpha-adrenergic stimulation actually overrides metabolically controlled coronary regulation so that tissue oxygenation decreases and ischemia results (3).

Infusion of norepinephrine in dogs with a fixed left main stenosis was reported (16) to cause increased oxygen demand, decreased lactate extraction and eventual cardiac failure. This study did not deal with the question of whether alpha-adrenergic stimulation, in itself, can produce myocardial ischemia, in that any ischemia produced was probably due to norepinephrine-induced increased oxygen demand in the face of a critical left main coronary stenosis. A similar study (17) showed that sympathetic nerve stimulation in the presence of a coronary stenosis severe enough to abolish reactive hyperemia caused decreased systolic segment shortening and lactate production. Propranolol blocked the increase in myocardial oxygen demand in this situation and reverted gross lactate production to a decreased lactate consumption. Administration of norepinephrine in the presence of a moderately severe coronary stenosis did not produce a decrease in coronary blood flow or evidence of myocardial ischemia in two other studies (18,19), presumably because of direct and metabolically induced coronary vasodilation. In summary, previous studies have not addressed the question of whether alpha-adrenergic stimulation, as such, could

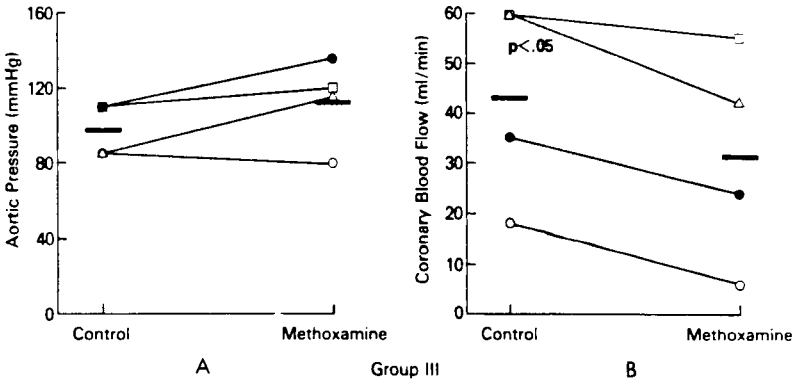

Figure 7. In Group III dogs (n = 4), in which large and small vessel resistances were studied, aortic pressure (**A**) did not change with methoxamine treatment. Coronary blood flow (**B**) decreased from the control state to the time of minimal coronary blood flow resulting from treatment with methoxamine.

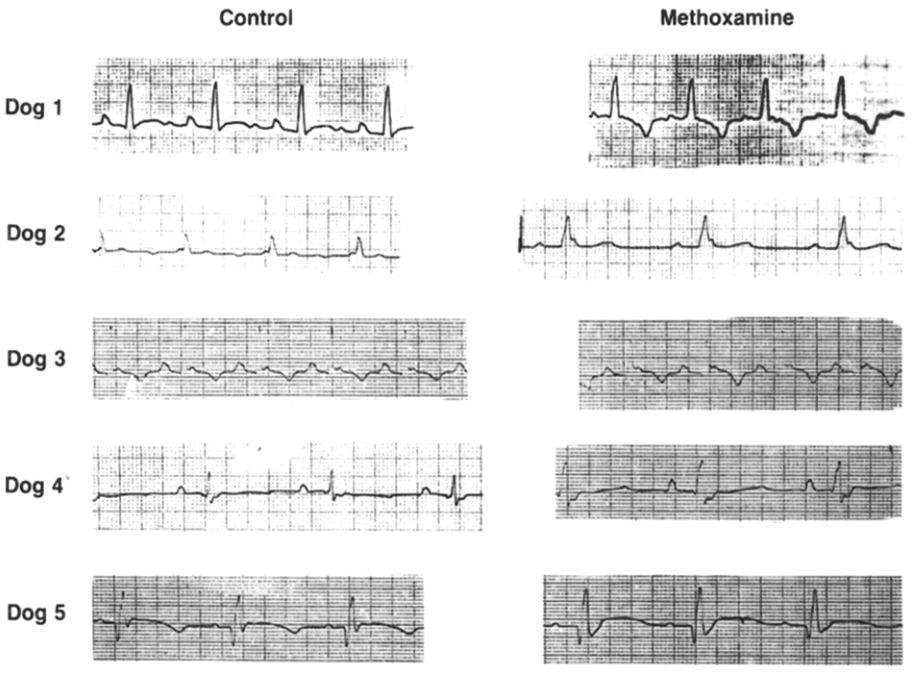

Figure 9. In Group IV dogs (n = 5), intracoronary methoxamine, 2 mg, increased coronary vascular resistance which was associated with ST-T wave changes on lead II of the electrocardiogram in each dog. Tracings are shown for each dog before (**left**) and during (**right**) methoxamine infusion. Intracoronary saline solution infused at the same rate had no effect.

constrict normal coronary arteries to produce acute myocardial ischemia.

Evidence of ischemia during methoxamine infusion. The purpose of the present study was to test the hypothesis that alpha-adrenergic receptor stimulation by intracoronary methoxamine can overcome endogenous regulatory influences so as to reduce blood flow sufficiently to produce myocardial ischemia, as manifested by left ventricular dysfunction and ST-T wave changes on the electrocardiogram. Demonstration of this functional significance of alpha-adrenergic receptor-mediated vasoconstriction is important in that it supports a potential role for alpha-adrenergic receptors in coronary vasoconstriction that is consistent with some clinical studies (20,21). Our results support the validity of the hypothesis that coronary vasoconstriction produced by methoxamine causes ST-T changes and decreases in both coronary blood flow and left ventricular ejection fraction. These findings were present in dogs in which aortic pressure and heart rate did not change and thus suggest that coronary regulation may be overcome by alpha-adrenergic stimulation to produce myocardial ischemia.

Effects of methoxamine on large versus small coronary vessels. In the second part of this study we sought to determine whether this functionally significant vasoconstriction mediated by alpha-adrenergic receptor stimulation involved predominantly the large or small coronary arteries. These results demonstrate that although the percent increase was similar for large, small and total coronary vascular resistances, the resistance of small coronary arteries accounted for over 94% of total resistance to indicate control of the coronary circulation by small arteries before and during methoxamine infusion. Because the absolute value

Table 1. Effects of Methoxamine on Coronary Hemodynamics in Dogs With Electrocardiographic Records (Group IV, n = 5).

Dog No.	Heart Rate (beats/min)		Mean Aortic Pressure (mm Hg)		Mean Coronary Blood Flow (ml/min)		Coronary Resistance (mm Hg/ml per min)	
	C	M	C	M	C	M	C	M
1	119	125	135	150	24	21	5.62	7.14
2	140	135	83	92	59	52	1.35	1.64
3	180	180	122	125	51	41	2.39	3.04
4	102	100	75	108	26	22	2.88	4.68
5	110	115	67	72	34	31	1.91	2.36
Mean	130	131	97	109*	39	33*	2.83	3.77*
±SD	±31	±30	±31	±30	±16	±13	±1.66	±2.19

*$p < 0.05$. C = control; M = methoxamine.

of the resistance of large coronary arteries is such a small percent of total resistance (6%), the increase in large vessel resistance represented a trivial contribution (8%) to the observed vasoconstriction. Thus, the primary site of the vasoconstriction was at the level of small coronary arteries, because 92% of the increase in total resistance was attributed to the increase in small vessel resistance. Vatner et al. (4) also found similar percent increases in large vessel and total resistance with methoxamine, but small vessel resistance could not be derived from their data. Although large vessel involvement was documented elegantly by ultrasound crystals, their data are consistent with our results. Although the conclusion of Zuberbuhler and Bohr (8) differs from our findings, one can question the applicability of their in vitro study in which small coronary arteries may have been less responsive to alpha-adrenergic stimulation because of damage during dissection.

Our data are consistent with those of Kelley and Feigl (10), who found similar increases in large vessel and total resistance with alpha-adrenergic stimulation. Because small vessel resistance was measured, one can calculate that the actual contribution of large vessel resistance to the increase in total resistance was less than 2%. Our results not only corroborated their study but also provide an important extension. Kelley and Feigl (10) studied small changes in total resistance that may not have been functionally significant. A functionally significant increase in resistance might require involvement of large coronary arteries to overcome endogenous regulation which occurs at the level of small arteries. Our finding that vasoconstrictor influences on small coronary arteries can cause myocardial ischemia is in agreement with clinical data (22) suggesting that constriction of small rather than large coronary arteries can cause myocardial ischemic syndromes in many patients with variable threshold angina.

Critique of methods. It is important to decide whether the observed decrease in left ventricular ejection fraction, from 0.54 to 0.46, is evidence of significant left ventricular dysfunction. Because we used several control studies with the same heart rate and aortic pressure, and imaged the same anesthetized dog in the same position over a few minutes, our serial studies are more reproducible than are clinical studies. Ejection fraction measurements on the same dog 15 minutes apart by the same observer ($n = 7$) showed an absolute difference of less than 0.01 ± 0.01 ejection fraction units (p = NS). Therefore, a decrease of 0.08 ejection fraction units from 0.54 units (15%) or 0.07 ejection fraction units from 0.46 units (15%) is quite meaningful in this highly controlled experimental environment.

A separate question is whether this decrease in left ventricular ejection fraction can be interpreted as evidence of ischemia. First, the methoxamine-induced coronary vasoconstriction was associated with ST-T wave changes on the electrocardiogram to suggest ischemia (Fig. 9). Left ventricular dysfunction certainly cannot be equated with myocardial ischemia, but this highly controlled experimental setting was designed to minimize the possibility that other potential causes could account for left ventricular dysfunction. For example, aortic pressure did not increase in Group I dogs, so the decreased ejection fraction could not be attributed to increased afterload (23), or to baroreceptor reflex inhibition of contractile function (24). Further, there is evidence that even large changes in carotid sinus pressure do not alter left ventricular function unless aortic pressure changes also (25).

Second, the possibility that intracoronary methoxamine had a direct negative inotropic effect on the heart to explain decreased left ventricular ejection fraction seems highly unlikely. Considerable evidence indicates that methoxamine has little or no direct inotropic effects over a wide dose range, and that at very high concentrations in vitro it exerts positive rather than negative inotropic effects (6,7,26–30). Lee et al. (7) reported a positive inotropic effect of methoxamine in vivo only at high doses of up to 6 mg/kg in lambs. Although Siegl et al. (31) concluded that methoxamine has a depressant effect, examination of all their published data shows that measured tension was always greater than the control value. Another study (32) reporting a negative inotropic effect of methoxamine did not control for deterioration over time of a precarious dog heart-lung preparation and used an enormous dose of methoxamine. The most conclusive study (6) showed no effect of methoxamine over a concentration range of 10^{-9} to 10^{-6} moles/liter and a positive inotropic effect over a concentration range of 10^{-6} to 10^{-3} moles/liter in cat papillary muscles. Thus, our findings strongly support the conclusion that the decrease in coronary blood flow caused ischemia, which in turn led to a reduction in left ventricular function. It is not surprising that the 55% increase in coronary vascular resistance at constant heart rate and aortic pressure would impair left ventricular function. Several studies (33–35) have found that a 10 to 20% decrease in coronary blood flow impaired cardiac contraction.

In Group III dogs, the resistances of large and small coronary arteries were determined from differential pressure measurements to provide estimates of the responses of large and small coronary arteries. The plastic catheter limited the lowest size vessel that could be cannulated to about 0.9 mm in diameter. During inflation of the pneumatic occluder on the left circumflex coronary artery, there was a large drop in pressure between the aorta and the distal coronary catheter to show that the system could detect physiologically important spasm of large coronary arteries such as is observed on angiography in humans (36). One could question the physiologic implications of methoxamine's effects, but the differences between alpha-adrenergic stimulation by cardiac nerves versus methoxamine do not appear to be large on careful analysis of the original data (24,37). Further, there

are other sources of alpha-adrenergic stimulation, such as circulating catecholamines, that can have important effects on the coronary circulation (3).

There is some evidence that alpha-adrenergic receptors in the canine coronary circulation are primarily of the alpha$_2$ subtype, whereas methoxamine stimulates primarily alpha$_1$ adrenergic receptors (38). Although the distinction between these subtypes is not clear-cut (39), these results suggest that our findings may be conservative because methoxamine is only a weak alpha$_2$-adrenergic receptor agonist. If alpha$_2$-receptors had been stimulated more strongly, then coronary vasoconstriction might have been more severe, suggesting that our study of methoxamine underestimates the potential role of alpha-adrenergic stimulation.

Clinical implications. The present study of activation of coronary alpha receptors in dogs cannot prove that alpha receptor stimulation causes ischemia in humans, but it may be relevant to support a potential mechanism for coronary artery constriction in disease states where the level of local alpha-adrenergic stimulation may be greater than in the normal state. In this context the present study is useful in demonstrating the potential for alpha-adrenergic stimulation to cause constriction of small coronary arteries and ischemia. Further, the study of alpha-adrenergic–mediated vasoconstriction suggests that it may be necessary to evaluate coronary blood flow rather than large vessel dimensions to assess the effects of alpha-adrenergic receptor stimulation in humans (20,22).

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