

Alpha Adrenergic Vasoconstriction and Nitroglycerin Vasodilation of Large Coronary Arteries in the Conscious Dog

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ABSTRACT The effects of methoxamine and nitroglycerin on measurements of large vessel (left circumflex) coronary dimensions were examined in eight conscious dogs using an ultrasonic dimension gauge, and total coronary resistance was calculated from measurements of arterial pressure and coronary blood flow. Methoxamine (50 $\mu\text{g/kg}$ per min), after transiently increasing left circumflex coronary dimensions, induced sustained reductions in left circumflex diameter ($9\pm 2\%$) and external ($18\pm 4\%$) and internal ($27\pm 5\%$) cross-sectional areas, at a time when mean arterial pressure rose by $65\pm 5\%$, left ventricular dP/dt had decreased only slightly, and heart rate and mean coronary blood flow remained at control levels. Calculated large vessel and total coronary resistances rose similarly, i.e., by 108 ± 29 and $92\pm 14\%$, respectively. Methoxamine reduced coronary arterial wall stiffness from control at comparable stress levels, although at any common radius, wall stiffness was augmented substantially. Nitroglycerin (25 $\mu\text{g/kg}$) induced an initial decrease in coronary dimensions along with the fall in arterial pressure. However, left circumflex coronary dimensions then rose, reaching a maximum 5 min later at a time when left circumflex coronary blood flow was reduced and heart rate and left ventricular dP/dt were at control levels. At this time, significantly different effects were observed on large vessel coronary resistance, which fell by $18\pm 2\%$, and on total coronary resistance, which rose by $11\pm 4\%$. Thus, in the conscious dog, large coronary vessels not only react passively to changes in aortic pressure but also undergo substantial

active changes. Alpha adrenergic stimulation is sufficiently powerful to reduce cross-sectional area, despite the opposing elevation of distending pressure.

INTRODUCTION

The concept of coronary artery vasoconstriction is attracting increasing clinical interest as a possible mechanism, not only for Prinzmetal's variant angina (1-3), but also for typical angina pectoris and myocardial infarction (2, 3). In support of this concept are cineangiographic studies in man and studies in experimental animals (2, 3). Moreover, an important neural component of the control of the coronary circulation has been demonstrated that particularly involves alpha adrenergic control of the coronary bed (2-11). However, in these studies, changes in coronary vascular cross-sectional area have been assessed indirectly by calculation of resistance from measurements of blood flow and pressure (4-11). There are relatively few studies on sympathetic regulation of coronary vascular caliber, in which these measurements have been made directly and continuously.

The primary goal of this investigation was to determine the extent to which alpha adrenergic activation with methoxamine altered coronary vascular caliber, using an ultrasonic dimension gauge to measure the diameter of a coronary artery directly and continuously in conscious dogs. This intervention was compared with the effects of nitroglycerin, a potent coronary vasodilator. In both instances, calculations of large vessel resistance, determined from the measurement of left circumflex coronary diameter, and total coronary resistance, determined from measurements of aortic pressure and left circumflex coronary blood flow, were compared. In addition, an analysis was undertaken to assess the effects of augmented alpha adrenergic stimu-

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lation on the elastic properties of smooth muscle in the coronary arterial wall.

METHODS

Eight mongrel dogs weighing 28–38 kg were anesthetized with pentobarbital Na, 30 mg/kg i.v. The transducers were implanted through a thoracotomy in the fifth left intercostal space. One pair of miniature 7 MHz ultrasonic transducers (2×1 mm, 12 mg) was implanted on opposing surfaces of the left circumflex coronary artery 3–6 cm from its origin. The ultrasonic transducers were covered with Insl-X (Insl-X Products Corp., Yonkers, N. Y.), and attached to a Dacron (Du Pont, de Nemours & Co., Inc., Wilmington, Del.) backing. The Dacron was sutured to the outer adventitia of the coronary artery using Ethicon 6-0 suture (Ethicon, Inc., Somerville, N. J.). In the five dogs in which it was feasible, a Zepeda electromagnetic flow transducer (Zepeda Instruments, Seattle, Wash.) and hydraulic occluder were implanted 1–3 cm distally on the same vessel. In all dogs, a miniature pressure gauge (Konigsberg Instruments, Inc., Pasadena, Calif.) was implanted in the left ventricle, and heparin-filled Tygon (Norton Co., Plastics and Synthetics Div., Tallmadge, Ohio) catheters were implanted in the left atrium and descending thoracic aorta. In these eight dogs, a hydraulic occluder was implanted around the aortic root, and in two additional dogs the occluder was implanted around the descending thoracic aorta. 1 wk later, at the time of the experiment, using local anesthesia with 2% lidocaine (Astra Pharmaceutical Products, Inc., Framingham, Mass.), catheters (Intracath 3184, Deseret Pharmaceutical Co., Sandy, Utah) were advanced into the chest cavity to measure intrapleural pressure and into the right atrium through a peripheral vein to measure right atrial pressure. A Millar microtip pressure manometer (Millar Instruments, Houston, Tex.) was introduced into the aorta through the femoral artery. The Millar transducer was advanced into the left ventricle and withdrawn to the aortic root. To confirm that changes in mean aortic root and coronary arterial pressures were nearly identical, a catheter was implanted in a coronary artery during a terminal experiment in one dog. These pressures changed similarly over a wide range induced by administration of methoxamine and nitroglycerin. In two additional dogs during a terminal, open chest, anesthetized experiment, the pulse wave delay was measured between the aortic root (where pressure was measured) and the coronary artery (where diameter was measured) using two catheters of identical length to sense pressures at these two points.

Arterial pressure was measured with the Millar microtip manometer, which was calibrated before and after the experiment by a mercury manometer and cross calibrated during the experiment with the aortic pressure measurements derived from the aortic catheter attached to a Statham P23 Db or Id manometer (Statham Instruments, Inc., Oxnard, Calif.). Right and left atrial and intrapleural pressures were measured with Statham P23 Db and P23 V manometers. Left ventricular pressure was measured with the implanted miniature gauge, which was calibrated *in vitro* with a mercury manometer and cross calibrated *in vivo* with measurements of pressure from the aortic and left atrial catheters. Coronary blood flow was measured using a Benton square wave electromagnetic flowmeter (Benton Instruments, Cupertino, Calif.). Zero blood flow was assessed by inflating the coronary artery occluder.

Phasic coronary diameter was measured instantaneously and continuously with an improved ultrasonic dimension gauge (12, 13). The instrument generates a voltage linearly proportional to the transit time of acoustic impulses travel-

ing at the sonic velocity of $\sim 1.5 \times 10^6$ mm/s between the 7 MHz piezoelectric crystals, thus giving a record of instantaneous external coronary arterial diameter. To measure these relatively small dimensions accurately, the instrument used in this study was further modified to minimize the acoustic disturbance generated by the electrical excitation of the transmitting crystal. This was accomplished by placing 1,000-ohm rheostats in parallel with the crystals at the exciter output and receiver input. These rheostats were adjusted to minimize the ringing observed in the receiving crystal, without substantially affecting the amplitude of the received echo. In addition, the basic 1 MHz repetition rate of the dimension gauge was changed to 2 MHz. This doubled the amplitude of the output voltage and also permitted precise calibrations in 0.5- μ s steps. The frequency response of the dimension gauge is flat to 100 Hz. The drift of the instrument is minimal and in these experiments never exceeded 0.01 mm in 6 h. To further ensure data reliability, repeated calibration references were obtained regularly throughout the experiment, and the received ultrasonic signal was monitored continuously on an oscilloscope. Any major change in alignment of the crystals would be detected in the received signal and invalidate the experiment.

The experiments were conducted with the conscious dogs lying quietly 1 wk after operation. Measurements of left circumflex coronary arterial diameter, aortic root pressure, left ventricular pressure, dP/dt , intrapleural pressure, right and left atrial pressures, left circumflex coronary blood flow, and heart rate were continuously recorded. Aortic pressure was raised mechanically by inflating the aortic hydraulic occluder. Nitroglycerin was administered in a bolus, 25 μ g/kg i.v. At least 1–2 h recovery time was allowed for nitroglycerin. Methoxamine was administered as the only intervention or last because recovery was never fully complete even 2 h later. These interventions were carried out in six dogs on the same day and in the other two dogs on different days. At the end of the experiments, the animals were sacrificed to confirm placement of the ultrasonic transducers, to determine coronary arterial wall thickness, and to examine the vessel histologically. Significant fibrosis at the crystal implant site was not observed in these eight dogs.

The data were recorded on a 14-channel tape recorder (Bell & Howell Co., Datatape Div., Pasadena, Calif.) and played back on two multichannel oscillographs (Gould-Brush, Cleveland, Ohio). The pulse wave delay between the rise in aortic pressure and the rise in coronary diameter was calculated by playing back the simultaneous signals on the oscillograph at rapid paper speed after setting the lengths of the oscillograph pens identically (Fig. 1). Mean pressures and coronary diameters were assessed using RC-filters with 2-s time constants. Left ventricular dP/dt was derived by differentiating the left ventricular pressure signal using a Philbrick operational amplifier (Teledyne Philbrick, Dedham, Mass.), connected as a differentiator and having a frequency response of 700 Hz. A triangular wave signal with known slope (rate of change) was substituted for the pressure signal to calibrate the differentiator directly. Heart rate was measured continuously with a cardiometer triggered by the left ventricular pressure pulse.

While external diameter was measured continuously, the internal radius was calculated using two techniques. The first technique involved determining at autopsy the thickness and mass of a segment of coronary artery with known length from the point at which the piezoelectric crystals were located. Thus, wall volume could be calculated as the quotient of mass and density ($d = 1.06$ g/cm³). After the wall volume, one wall thickness value, and external diameter were known, the internal changing diameter was calculated. The second tech-

nique involved determining the wall thickness directly by microscopic examination of a cross section of the vessel. An index of large vessel hydraulic resistance at the crystal site was derived, on a per-unit length basis, from Poiseuille's formula: large vessel resistance = $8 \mu / \pi R_i^4$, where μ , the viscosity, is taken to be constant and R_i is the internal radius (14). Total left circumflex coronary resistance was calculated as the quotient of mean aortic root pressure and mean left circumflex coronary blood flow. Changes in intrapleural and right atrial pressures were neglected in these calculations because they were negligible in comparison with aortic pressure.

An effective diastolic incremental elastic modulus (E_{inc})¹ for the coronary vessel wall was derived from measurements of external diameter and pressure. A stress (σ) equal to the difference between circumferential and radial stresses at mid-wall was calculated according to the formula: $\sigma = 2P_i(R_i R_o / R)^2 / (R_o^2 - R_i^2)$. E_{inc} was calculated according to the formula: $E_{inc} = 0.75 R d\sigma / dR$, where P_i is the distending pressure, R_i and R_o are the inner and outer radii, respectively, and $R = (R_i + R_o) / 2$ is the midwall radius. The derivation and validation of these expressions have been published previously (15). Changes in the elastic behavior of the coronary artery wall that are associated with smooth muscle activation were assessed using data derived from the diastolic phase of the pressure-diameter loop, which was plotted on a storage oscilloscope (Tektronix model T 912, Tektronix, Inc., Portland, Oreg.). The delay between the aortic root pressure and coronary diameter waveform was minimized by an analog delay circuit connected in series with the oscilloscope. The relationships between E_{inc} and σ and between this stress and midwall radius were examined. Transients associated with atrial and isovolumic left ventricular contraction and with aortic valve closure were excluded. Limiting the analyses to diastole afforded a means of minimizing viscous influences because the strain rates are relatively low over this interval of the cardiac cycle.

Mean \pm SEM were calculated. Changes from control were analyzed statistically using the paired *t* test (16).

RESULTS

Description of the phasic waveform. Representative waveforms for simultaneous aortic root pressure, left circumflex coronary diameter and blood flow, and left ventricular pressure are shown in Fig. 1 at rapid paper speed. The pulsatile change in phasic waveform from diastole to systole averaged $8.70 \pm 1.85\%$ of the mean value. In general the phasic waveform for coronary diameter followed that for arterial pressure. However, at the end of diastole, coincident with atrial systole, and then during isovolumic ventricular contraction, downward deflections were apparent on the coronary diameter waveform. These might be related to concomitant changes in atrial or ventricular dynamics because reductions in coronary blood flow secondary to atrial and ventricular contraction also can be observed at these points in the cardiac cycle.

The phasic waveform for arterial pressure leads that for coronary diameter, which, in turn, leads that for

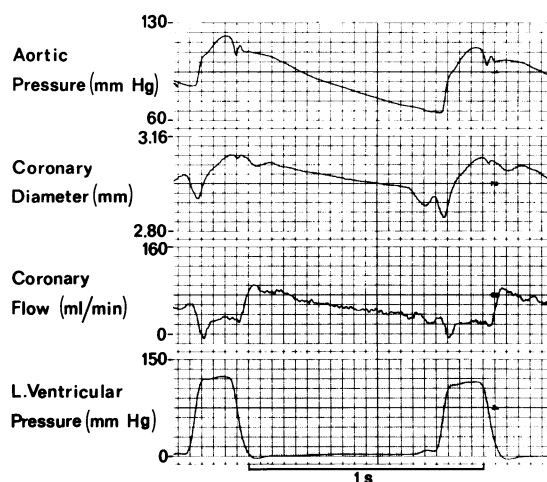


FIGURE 1 The phasic waveforms for aortic root pressure, left circumflex coronary artery diameter, blood flow, and left ventricular pressure are shown at rapid paper speed. Before construction of this figure, the pens on the oscilloscope were aligned to illustrate accurately the ~ 10 ms delay between the rise in aortic pressure and the rise in coronary artery diameter. This delay most likely reflects the fact that the coronary dimension measurements are made distal to the measurement of aortic root pressure. Note the similar features of the aortic pressure and coronary diameter waveforms. The waveform for coronary diameter was similar to that of coronary blood flow in that both showed downward deflections with atrial systole and isovolumic ventricular contraction. The marked sinus arrhythmia is characteristic of the conscious dog.

coronary blood flow. These delays are most likely the result of the difference in placement of transducers. The pressure and diameter transducers were ~ 5 – 7 cm apart, and the coronary blood flow transducer was 1–3 cm more distal. The delay between the rise in aortic pressure and coronary diameter averaged 8.1 ± 0.6 ms. This value agreed closely with the delay calculated from the two acute preparations, in which pressures in the aortic root and coronary artery at the site of the diameter transducers were recorded simultaneously. In these latter experiments, the pulse wave delay for arterial pressure was found to be 9 ms.

Effects of methoxamine (50 μ g/kg per min) (Fig. 2). Although measurements were made continuously, data were averaged during the initial increase in left circumflex coronary diameter, which occurred ~ 1 min after the onset of the infusion (early response), reflecting the passive response to pressure elevation and at 10 min, just before cessation of the infusion (late response), reflecting the active changes in coronary vasomotion (Table I). Because heart rate tended to fall as a result of arterial baroreceptor reflex effects, a steady-state response at 10 min, when heart rate was close to the control value, was purposely selected. In six animals, it was possible to identify responses when heart rate was precisely at the control level.

¹ Abbreviations used in this paper: E_{inc} , effective diastolic incremental modulus; σ , stress (difference between the circumferential and radial wall stresses).

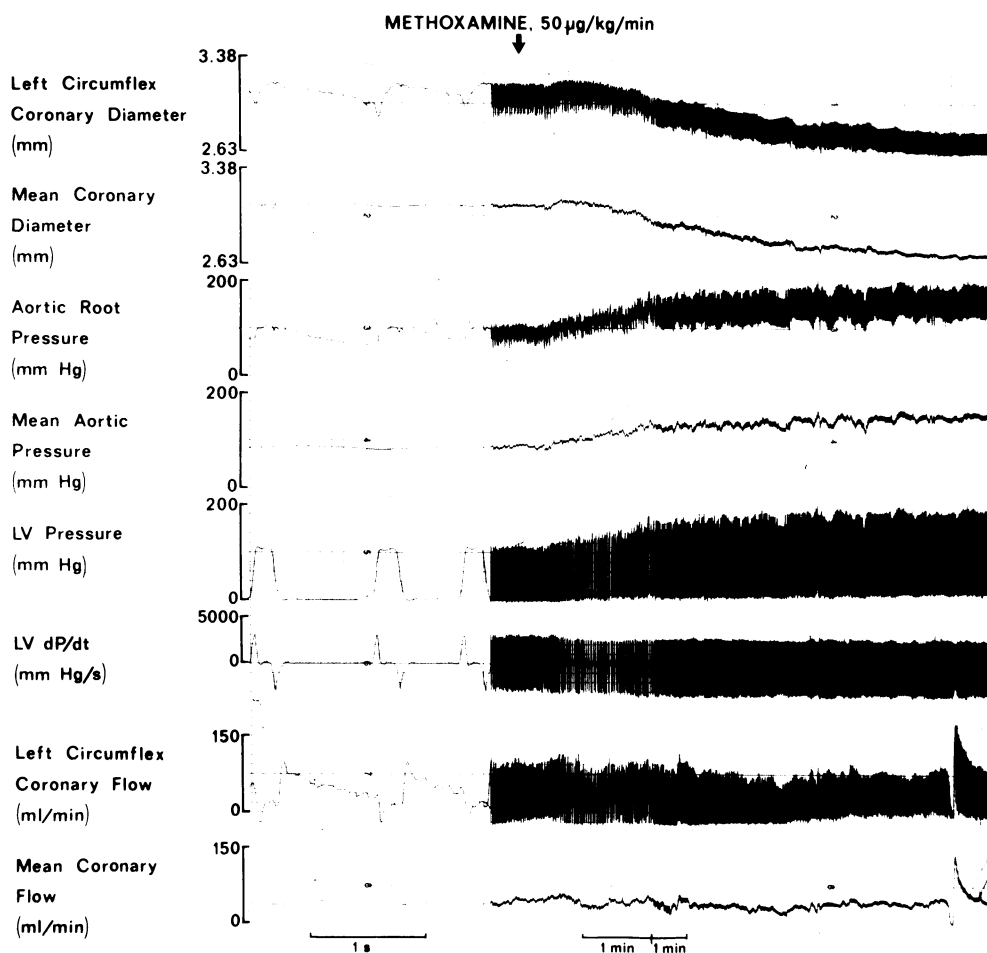


FIGURE 2 The effects of a 10-min infusion of methoxamine, $50 \mu\text{g/kg}$ per min, in a conscious dog are depicted on simultaneous and continuous measurements of phasic and mean left circumflex coronary artery diameter, aortic root pressure, left ventricular pressure, left ventricular dP/dt , and phasic and mean left circumflex coronary blood flow. Methoxamine increased coronary diameters only initially and transiently and then induced striking sustained reductions in coronary diameters at a markedly elevated aortic pressure. A mechanical zero for the blood flow recording is shown at the end of the experiment. The marked sinus arrhythmia is characteristic of the conscious dog.

Methoxamine increased mean external left circumflex coronary diameter transiently at 1 min (Fig. 2). At 10 min, methoxamine had reduced mean external left circumflex coronary diameter by $9 \pm 2\%$ below control, resulting in reductions in external and internal cross-sectional areas of 18 ± 4 and $27 \pm 5\%$, respectively. Mean arterial pressure rose by 1 min and was $65 \pm 5\%$ above control at 10 min. Left ventricular systolic and diastolic pressures also rose. At 10 min, left ventricular dP/dt was reduced by $12 \pm 3\%$, whereas heart rate and mean left circumflex coronary blood flow were not significantly different from control. However, calculated total coronary vascular resistance was elevated by $92 \pm 14\%$, $P < 0.01$, and calculated large vessel resistance rose by a similar amount, i.e., $108 \pm 29\%$. All these changes, except those noted otherwise, were statistically sig-

nificant (Table I). Because methoxamine-induced vasoconstriction persisted for over 2 h, the total duration of the response was not determined.

To determine whether a biphasic response occurred with mechanical elevation of distending pressure, aortic root pressure was raised mechanically by inflating the aortic occluder. This caused coronary diameter to rise and remain elevated, even when the aortic constriction was maintained for 10 min (Fig. 3).

Effects of nitroglycerin ($25 \mu\text{g/kg}$) (Fig. 4). The peak initial changes (early response), the changes 5 min later (late response), and statistical significance are noted in Table II. The initial response to nitroglycerin was characterized by a transient reduction in mean left circumflex coronary diameter associated with the decrease in aortic pressure. This occurred just

TABLE I
Effects of Methoxamine

	Control	Change from control	
		Early	Late
Mean external left circumflex coronary diameter, mm	3.41±0.10	+0.04±0.01*	-0.32±0.07‡
Left circumflex coronary external cross-sectional area, mm ²	9.20±0.54	+0.21±0.06*	-1.62±0.36‡
Left circumflex coronary internal cross-sectional area, mm ²	6.14±0.49	+0.21±0.06*	-1.62±0.36‡
Mean aortic root pressure, mm Hg	89.9±2.4	+9.3±1.2‡	+58.3±4.6‡
Left ventricular systolic pressure, mm Hg	109.4±2.7	+11.9±1.9‡	+83.1±5.7‡
Left ventricular end-diastolic pressure, mm Hg	6.5±0.6	+1.6±0.2‡	+19.5±2.1‡
Left ventricular dP/dt, mm Hg/s	3,100±140	-70±50	-390±110*
Heart rate, beats/min	85.4±6.8	+0.3±2.4	-4.0±3.9
Mean left circumflex coronary blood flow, ml/min	41.3±3.5	+0.2±0.8	-4.6±3.2
Calculated total coronary resistance, mm Hg/ml/min	2.27±0.18	+0.19±0.04‡	+2.11±0.40‡
Calculated large vessel coronary resistance, U	269±41	-21.4±9.9	+288±82‡

* $P < 0.05$.

‡ $P < 0.01$.

before the maximal increases in heart rate, coronary blood flow, and left ventricular dP/dt . Mean external left circumflex coronary diameter subsequently rose, reaching a maximum of $3.4 \pm 0.5\%$ above control 5 min later. This resulted in increases in external and internal left circumflex coronary cross-sectional areas of 7 ± 1 and $11 \pm 2\%$, respectively. At this time, mean arterial pressure and left ventricular end-diastolic pressures were still reduced. Mean left circumflex coronary blood flow had decreased by $13 \pm 3\%$ below control, but heart rate and left ventricular dP/dt were not significantly different from control. Calculated total coronary

vascular resistance, which fell by $65 \pm 5\%$ at 15 s, was actually elevated by $11 \pm 4\%$ at 5 min, a time when large vessel resistance was reduced by $18 \pm 2\%$. These responses of large vessel and total coronary resistance were significantly different, $P < 0.01$.

At 15 min, all parameters had returned to control except for left circumflex coronary dimensions, which returned to control by 1 h.

Elastic properties. Fig. 5 shows the effects of smooth muscle activation on the midwall σ -radius relationship. The σ -radius relationships derived for each animal were all well described ($r > 0.94$) by exponential curves. Alpha adrenergic stimulation induced by methoxamine infusion caused a dramatic leftward shift of the σ -radius curve. At any common radius, derived by extrapolating the control σ -radius curve to the somewhat lower radii observed during methoxamine infusion, the level of stress was increased markedly above control.

Fig. 6 shows E_{inc} plotted as a function of stress both at resting levels of smooth muscle tone and during the later phase of peak pressor response to methoxamine infusion. As noted above, methoxamine increased mean aortic pressure by $65 \pm 5\%$. Over the common stress range between 2.0 and 4.0×10^5 dyn/cm², E_{inc} was reduced significantly from base-line levels by smooth muscle activation. It should also be noted that when E_{inc} was examined as a function of the midwall radius, it was augmented at any common extrapolated radius value under conditions of smooth muscle activation.

DISCUSSION

Previous studies on the vasoactivity of large coronary arteries have been primarily conducted in anesthe-

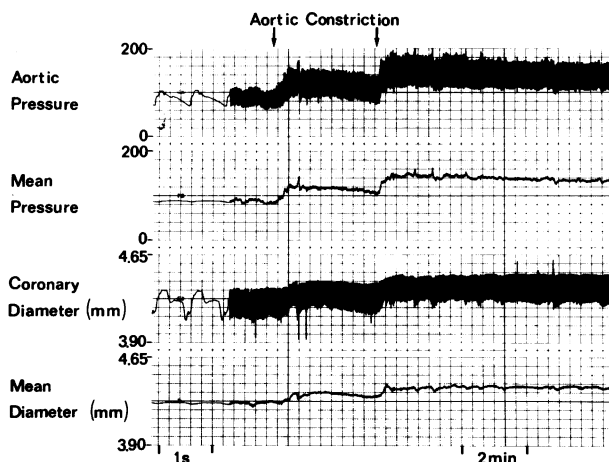


FIGURE 3 The response to constricting the descending thoracic aorta in a conscious dog is shown on phasic and mean measurements of aortic root pressure and left circumflex coronary artery diameter. In contrast to the response to methoxamine (Fig. 2), when aortic pressure was raised mechanically, a sustained rise in coronary artery diameter was observed. The arrows indicate initiation and augmentation of aortic constriction.

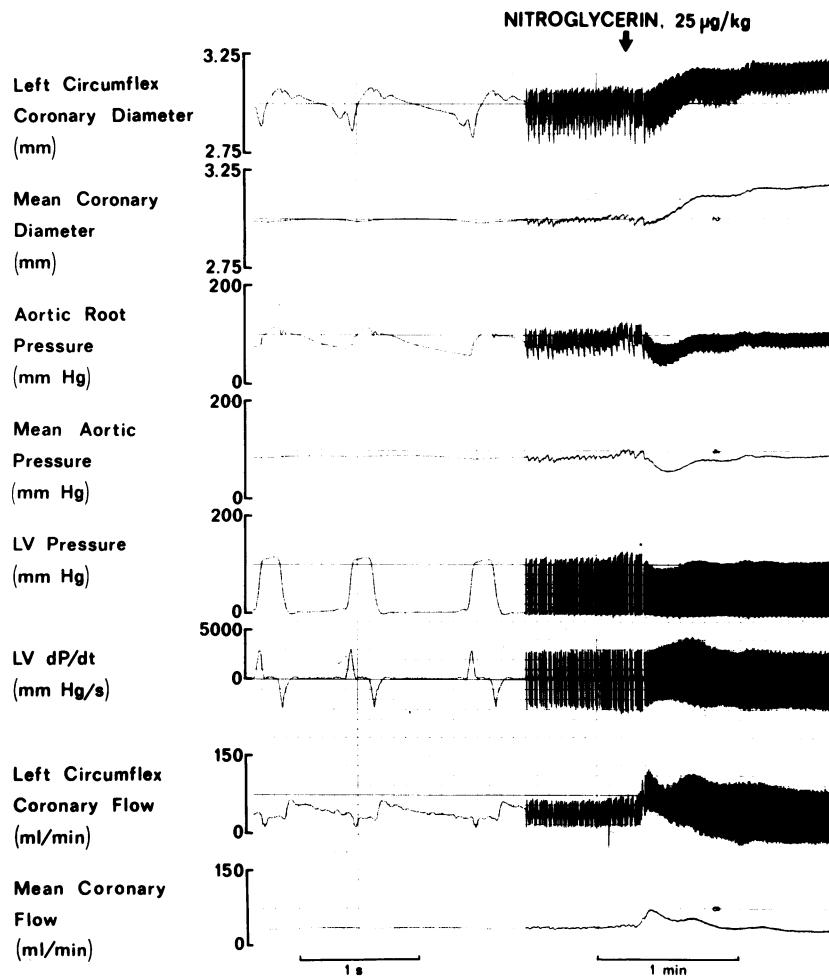


FIGURE 4 The effects of a bolus of nitroglycerin, 25 µg/kg, in a conscious dog are depicted on simultaneous and continuous measurements of phasic and mean left circumflex coronary artery diameter, aortic root pressure, left ventricular pressure, left ventricular dP/dt , and phasic and mean left circumflex coronary blood flow. Nitroglycerin induced a transient fall in coronary diameters and a striking early increase in coronary blood flow. However, coronary diameters then rose as all other measured variables returned to control levels. The marked sinus arrhythmia is characteristic of the conscious dog.

tized animal preparations with an open chest, where calculations of coronary vascular caliber have been made indirectly from measurements of coronary arterial pressures (5, 17). There are also numerous reports of changes in coronary vascular dimensions from cineangiographic studies in man (2). Studies in animals and in humans suggest that coronary vessels are responsive to neural stimuli, particularly through the sympathetic nervous system (2-9), and that coronary vasoconstriction can even lead to typical angina pectoris, Prinzmetal's variant form (1-3), and perhaps myocardial infarction (2, 3).

Our investigation provides support for the hypothesis that large coronary arteries in conscious dogs are capable of altering vascular caliber considerably in

response to alpha adrenergic activation. This study is unique in that it was conducted in conscious animals without the complications caused by premedication that occur in human studies and without those caused by general anesthesia and recent surgery in animal studies. Moreover, coronary vascular dimensions were measured instantaneously and continuously using an ultrasonic dimension gauge.

The ultrasonic dimension gauge employed in this study was modified to provide: (a) measurements of small dimensions such as occur in the left circumflex coronary artery in the dog and (b) calibrations in steps of 0.5 µs, i.e., 0.75 mm. One of the important features of this dimension gauge is its stability and lack of drift. Moreover, any drift that may have occurred in the

TABLE II
Effects of Nitroglycerin

	Control	Change from control	
		Early	Late
Mean external left circumflex coronary diameter, mm	3.36±0.09	-0.03±0.01*	+0.11±0.02*
Left circumflex coronary external cross-sectional area, mm ²	8.92±0.49	-0.17±0.03*	+0.62±0.10*
Left circumflex coronary internal cross-sectional area, mm ²	5.74±0.45	-0.17±0.03*	+0.62±0.10*
Mean aortic root pressure, mm Hg	91.0±1.4	-33.6±2.4*	-5.0±2.5
Left ventricular systolic pressure, mm Hg	112.8±2.4	-27.2±3.1*	-10.0±3.2†
Left ventricular end-diastolic pressure, mm Hg	6.3±0.5	-3.4±0.3*	-1.2±0.3*
Left ventricular dP/dt, mm Hg/s	3,170±160	+710±120*	-160±70
Heart rate, beats/min	84.0±5.3	+59.6±5.2*	+4.8±2.6
Mean left circumflex coronary blood flow, ml/min	42.9±4.9	+47.3±6.5*	-6.4±1.9†
Calculated total coronary resistance, mm Hg/ml/min	2.23±0.19	-1.45±0.13*	+0.23±0.08†
Calculated large vessel coronary resistance, U	311±45	+19.3±5.0*	-58.2±12.7*

* $P < 0.01$.

† $P < 0.05$.

electronics, which in this study was always <0.01 mm, was eliminated by periodic calibrations. It is also important that physiological variability in the measurement of phasic coronary diameter was minimal. When the animals were monitored for over 1 h without an intervention, or when the animals were studied on successive days, there were no detectable changes in coronary artery dimensions.

Several potential limitations of this technique were considered. First, the surgical implantation of the ultrasonic transducers initiates a fibrotic reaction that could limit vasomotion. To minimize this potential

problem, experiments were conducted 1 wk postoperatively at a time when histological examination did not reveal substantial fibrosis postmortem. Second, even though the transducers were small and lightweight, they must have interfered to some degree with normal vessel motion. However, inspection of the phasic waveform for coronary diameter, which demonstrated considerable motion during the cardiac cycle, together with the observations that substantial reductions in coronary dimensions occurred with methoxamine, and that substantial increases occurred with nitroglycerin,

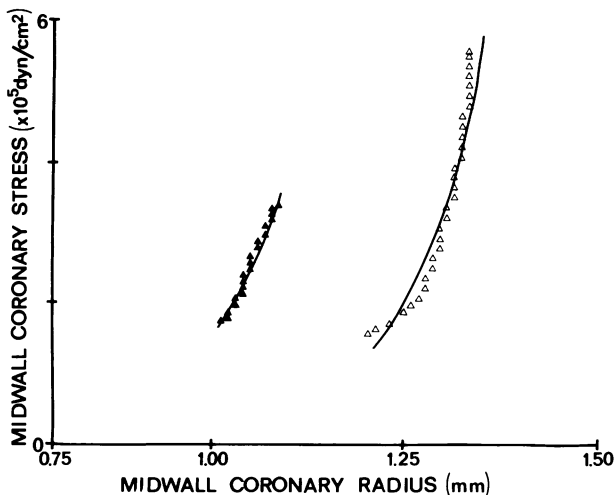


FIGURE 5 Midwall stress-radius relationships for the left circumflex coronary artery of conscious, chronically instrumented dogs are shown in the absence of alpha adrenergic activation (Δ) and in the presence of methoxamine (\blacktriangle). Note that stress represents the difference between the circumferential and radial wall stresses at midwall.

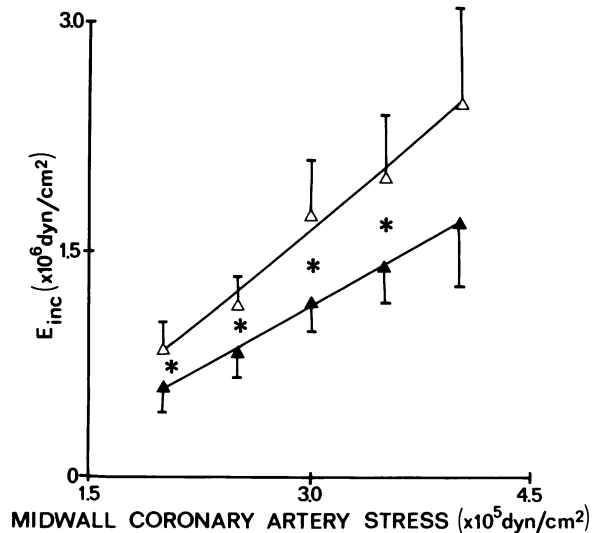


FIGURE 6 Mean (\pm SEM) values of midwall stress and E_{inc} for the left circumflex coronary artery of conscious instrumented dogs. The significant differences induced by methoxamine (\blacktriangle) from control (Δ) ($P < 0.05$) are indicated by asterisks. Note that stress represents the difference between the circumferential and radial wall stresses at midwall.

suggest that mechanical loading was not impeding vessel motion inordinately. It still should be recognized that in the absence of the loading effect of the transducers, the responses observed might have actually been greater. Moreover, the normal value for baseline coronary blood flow and the marked vasodilation that was observed in response to nitroglycerin indicate that the coronary bed distal to the ultrasonic transducers was not impaired because of this instrumentation. It is also important to note the potential errors in calculations of internal arterial cross-sectional area. A continuous recording of coronary arterial wall thickness was not obtained. Accordingly, if wall mass varied with interventions, quantitative discrepancies in calculated internal cross-sectional area could have occurred.

Because vascular dimensions changed significantly with the interventions studied, a potential limitation of blood flow measuring techniques must also be considered. This is particularly important for the CW Doppler ultrasonic flowmeter, which measures blood velocity, but less so for the electromagnetic technique, which is relatively insensitive to changes in vessel cross-sectional area. This potential problem would be most critical in acute experiments in which the measurement of blood flow is made immediately after application of the transducer. It would be of less importance in chronic experiments after the fibrotic process has fixed the vessel wall to the transducer. Our experiments were conducted only 1 wk postoperatively, at a time when fibrosis at the transducer site was minimal. For this reason, the electromagnetic technique was selected for the measurement of blood flow in this study.

In general, the coronary diameter phasic waveform resembled that of aortic pressure. The pulsatile change observed from diastole to systole in the coronary diameter phasic waveform averaged 9% of the mean diameter, a value higher than predicted from experiments in anesthetized preparations (18, 19). Late in diastole there were downward deflections in the coronary diameter waveform coincident with atrial systole and isovolumic ventricular systole. There were also times in the cardiac cycle when downward deflections in the phasic waveform for coronary blood flow were apparent (Fig. 1). However, the deflections may not be physiological because mechanical effects occurring during atrial or isovolumic systole causing rotation of the ultrasonic transducers or stretching of the coronary vessel cannot be excluded. Moreover, in these experiments the phasic waveform for the coronary diameter was delayed from that of aortic pressure by 8.1 ± 0.6 ms, which appears to be related primarily to the distance between the sites of placement of these two transducers. It is important to note that these potential criticisms of analysis of instantaneous coronary pres-

sure-diameter relations would not have a substantial impact on the major conclusions of our investigation, which relate to an alpha adrenergic-induced vasoconstriction of large coronary arteries, and are based on analysis of mean (as opposed to instantaneous) data. Moreover, to avoid the potential problems in examination of instantaneous coronary pressure-diameter relations for the study of coronary arterial elasticity, these analyses were limited to diastole up to the point of atrial systole, thereby excluding transients during atrial or ventricular contraction. Finally, to construct the instantaneous pressure-coronary diameter loops, problems caused by delay between the pressure and coronary diameter pulse were corrected by an analog circuit.

The major finding of the present investigation was that coronary vascular caliber actually fell below control levels with infusion of an alpha adrenergic agonist, methoxamine. It was expected that coronary dimensions would have increased passively in response to the elevated distending pressure induced by methoxamine infusion. Indeed, this was observed initially but only transiently with methoxamine. It was also observed throughout the time that arterial pressure was raised mechanically by inflation of an aortic hydraulic occluder (Fig. 3). However, with continued alpha adrenergic stimulation, coronary cross-sectional area rapidly returned to control levels and then fell significantly below control for the remainder of the infusion period (Fig. 2). These data indicate that alpha adrenergic vasoconstriction of the large coronary arteries is sufficiently powerful to oppose the tendency of arterial pressure to dilate these arteries. Moreover, the changes in vessel caliber cannot be ascribed to a reduction in metabolic requirements of the heart because heart rate was not significantly different from control, yet preload and afterload were both elevated. Calculated total coronary vascular resistance rose 92% with methoxamine, a value similar to the observed increase in large vessel resistance (108%). The similarity in these responses suggests that vasoconstriction was occurring throughout the coronary bed, which is consistent with the results from a recent study in anesthetized animals by Kelley and Feigl (5).

Nitroglycerin induced a biphasic response. Initially, it increased coronary blood flow and reduced total coronary vascular resistance, which was primarily caused by dilatation of small, resistance vessels. This dilatation of smaller coronary vessels was transient and was rapidly replaced by a sustained period of large vessel coronary dilatation. The peak dilatation of large vessels occurred at a time when coronary blood flow was decreased and when total coronary vascular resistance had risen significantly. Thus, in contrast to the experiments with methoxamine, in which sustained constriction occurred throughout the coronary bed,

nitroglycerin induced sustained dilatation of only large vessels concomitant with constriction in the remainder of the bed. The early period, consisting of an increase in coronary blood flow, has been characterized in both conscious and anesthetized preparations (17, 20–22) and involves dilatation resulting from a direct effect on coronary vessels, as well as secondary effects from the reflex increases in heart rate and myocardial contractility. The sustained large vessel dilatation in response to nitroglycerin has been shown previously only in anesthetized animal preparations (17, 20, 21). The later period of sustained large vessel coronary vasodilation was not a result of increased myocardial metabolic requirements because preload, afterload, heart rate, and contractility, the major determinants of myocardial oxygen demand, were all at or below control levels.

The isotropic E_{inc} concept provides a practical means of quantifying vascular wall stiffness around any operating large deformation level along the highly nonlinear load-response curve (Fig. 5). In many physiologic studies, vascular compliance is quantified in terms of an incremental modulus of volume distensibility, defined as $C_v = \Delta V / \Delta P \times 1/V$. Although E_{inc} pertains to the stiffness of the wall material only, whereas C_v pertains to the reciprocal of the stiffness of the vascular segment as a distensible structure, the two indices can be related quite readily. The relationship between these two indices is described in the Appendix.

In this investigation, under base-line conditions of smooth muscle tone, the effective diastolic incremental modulus of the left circumflex coronary artery wall was $1.7 \pm 0.4 \times 10^6$ dyn/cm² at a stress of $\sim 3 \times 10^5$ dyn/cm², (Fig. 6). Allowing for an inner diameter to wall thickness ratio of ~ 8 –10, this E_{inc} estimate is slightly lower than that implied by the modulus of volume distensibility reported by Patel and Janicki (19), which in turn is lower than the C_v values reported by Douglas and Greenfield (18). Our representative E_{inc} is an order of magnitude lower than the E_{inc} reported by Cox (23). The differences in these stiffness estimates may in part be attributed to differences in experimental design. For instance, the greatest disparities were found between our results and those of Cox (23). Whereas our studies were conducted in intact, conscious animals, the data of Cox (23) were obtained from isolated, in vitro vascular segments.

The elastic behavior of the left circumflex coronary artery of the conscious dog was altered by smooth muscle activation. Methoxamine induced a marked leftward shift in the pressure-diameter and stress-radius relationships (Fig. 5). Thus, augmented alpha adrenergic activation reduced vascular caliber for any given stress and pressure level. Moreover, smooth muscle activation raised the E_{inc} of the coronary ar-

terial wall from control when the comparison was carried out at similar radii (cf. Fig. 5), but it reduced E_{inc} when the comparison was made at similar stress (Fig. 6) or pressure levels. Thus, for any given arterial pressure level, the effective incremental modulus of the wall of the left circumflex coronary artery can be reduced considerably by the enhanced smooth muscle activation elicited by methoxamine.

In conclusion, the results of our investigation indicate that in the conscious animal, large coronary vessels not only respond passively to changes in distending pressure but also undergo substantial active changes in cross-sectional area. Whereas nitroglycerin elicits prolonged dilatation of these vessels, alpha adrenergic activation reduces coronary cross-sectional area, even when distending pressure is markedly increased.

APPENDIX

For a longitudinally tethered thin-walled vascular segment (negligible longitudinal strain), $\Delta V/V$ coincides with the incremental luminal cross-sectional area strain $\Delta A/A$, which amounts to twice the corresponding small incremental circumferential strain $\Delta R_i/R_i$; thus

$$C_v = \frac{\Delta V}{\Delta P_t} \times \frac{1}{V} \sim \frac{\Delta R_i}{\Delta P_t} \times \frac{2}{R_i}.$$

Moreover, for a thin-walled segment, $h/R_i \ll 1$, where h denotes wall thickness, we need not distinguish among inner, outer, and midwall radii. Then, the expression for E_{inc} reduces to

$$E_{inc} \sim 0.75 \frac{\Delta P_t}{\Delta R_i} \times \frac{R_i^2}{h}.$$

Combining the preceeding two equations, we arrive at the simple (albeit only approximate) relationships

$$C_v \sim \frac{0.75}{E_{inc}} \times \left(\frac{D_i}{h} \right), \quad \text{or} \quad E_{inc} \sim \frac{0.75}{C_v} \times \left(\frac{D_i}{h} \right),$$

where we have substituted the inside diameter, D_i , for twice the inner radius ($D_i = 2R_i$). It is important to note that for a thin-walled vessel, such that $h/R_i \ll 1$, the radial stress is negligible compared with the circumferential. Thus, σ becomes practically equal to the circumferential stress sustained by the wall because σ here is defined as the difference between the circumferential and radial wall stresses.

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REFERENCES

1. Prinzmetal, M., R. Kenner, R. Merliss, T. Wada, and N. Bor. 1959. Angina pectoris. I. A variant form of angina pectoris. *Am. J. Med.* 27: 375-388.
2. Hillis, L. D., and E. Braunwald. 1978. Medical progress: coronary artery spasm. *N. Engl. J. Med.* 299: 695-702.
3. Maseri, A., A. L'Abbate, G. Baroldi, S. Chierchia, M. Marzilli, A. M. Ballestra, S. Severi, O. Parodi, A. Biagini, A. Distanti, and A. Pesola. 1978. Coronary vasospasm as a possible cause of myocardial infarction. A conclusion derived from the study of "preinfarction" angina. *N. Engl. J. Med.* 299: 1271-1277.
4. Feigl, E. O. 1967. Sympathetic control of coronary circulation. *Circ. Res.* 20: 262-271.
5. Kelley, K. O., and E. O. Feigl. 1978. Segmental α -receptor-mediated vasoconstriction in the canine coronary circulation. *Circ. Res.* 43: 908-917.
6. Vatner, S. F., C. B. Higgins, and E. Braunwald. 1974. Effects of norepinephrine on coronary circulation and left ventricular dynamics in the conscious dog. *Circ. Res.* 34: 812-823.
7. Vatner, S. F., D. Franklin, R. L. Van Citters, and E. Braunwald. 1970. Effects of carotid sinus nerve stimulation on the coronary circulation of the conscious dog. *Circ. Res.* 27: 11-21.
8. Vatner, S. F., and R. J. McRitchie. 1975. Interaction of the chemoreflex and the pulmonary inflation reflex in the regulation of coronary circulation in conscious dogs. *Circ. Res.* 37: 664-673.
9. Mudge, G. H., W. Grossman, R. M. Mills, M. Lesch, and E. Braunwald. 1976. Reflex increase in coronary vascular resistance in patients with ischemic heart disease. *N. Engl. J. Med.* 295: 1333-1337.
10. Schwartz, P. J., and H. L. Stone. 1977. Tonic influence of the sympathetic nervous system on myocardial reactive hyperemia and on coronary blood flow distribution in dogs. *Circ. Res.* 41: 51-58.
11. Holtz, J., E. Mayer, and E. Bassenge. 1977. Demonstration of alpha-adrenergic coronary control in different layers of canine myocardium by regional myocardial sympathectomy. *Pfluegers Arch. Eur. Physiol.* 372: 187-194.
12. Patrick, T. A., S. F. Vatner, W. S. Kemper, and D. Franklin. 1974. Telemetry of left ventricular diameter and pressure measurements from unrestrained animals. *J. Appl. Physiol.* 37: 276-281.
13. Pagani, M., S. F. Vatner, H. Baig, D. L. Franklin, T. Patrick, W. T. Manders, P. Quinn, and A. Sherman. 1978. Measurement of multiple simultaneous small dimensions and study of arterial pressure-dimension relations in conscious animals. *Am. J. Physiol.* 4: H610-H617.
14. McDonald, D. A. 1974. Blood Flow in Arteries. The Williams & Wilkins Co., Baltimore. 2nd edition. Chapt. 2. 17-54.
15. Pagani, M., I. Mirsky, H. Baig, W. T. Manders, P. Kerkhof, and S. F. Vatner. 1979. Effects of age on aortic pressure-diameter and elastic stiffness-stress relationships in unanesthetized sheep. *Circ. Res.* 44: 420-429.
16. Armitage, P. 1971. Statistical Methods in Medical Research. Blackwell Scientific Publications, Ltd., Oxford. 116-126.
17. Winbury, M. M., B. B. Howe, and M. A. Hefner. 1969. Effect of nitrates and other coronary dilators on large and small coronary vessels: an hypothesis for the mechanism of action of nitrates. *J. Pharmacol. Exp. Ther.* 168: 70-95.
18. Douglas, J. E., J. C. Greenfield, Jr. 1970. Epicardial coronary compliance in the dog. *Circ. Res.* 27: 921-929.
19. Patel, D. J., J. S. Janicki. 1970. Static elastic properties of the left coronary circumflex artery and the common carotid artery in dogs. *Circ. Res.* 27: 149-158.
20. Fam, W. M., and M. McGregor. 1968. Effect of nitroglycerin and dipyridamole on regional coronary resistance. *Circ. Res.* 22: 649-659.
21. Cohen, M. V., and E. S. Kirk. 1973. Differential response of large and small coronary arteries to nitroglycerin and angiotensin. Autoregulation and tachyphylaxis. *Circ. Res.* 33: 445-453.
22. Vatner, S. F., C. B. Higgins, R. W. Millard, and D. Franklin. 1972. Direct and reflex effects of nitroglycerin on coronary and left ventricular dynamics in conscious dogs. *J. Clin. Invest.* 51: 3872-3883.
23. Cox, R. H. 1978. Passive mechanics and connective tissue composition of canine arteries. *Am. J. Physiol.* 5: H533-H541.