α-Adrenergic vasoconstriction reduces systolic retrograde coronary blood flow

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Mori, Morita, Tsujioka, Kimura, Ogasawara, Goto, Hiramatsu, Kajiya, and Feigl. α-Adrenergic vasoconstriction reduces systolic retrograde coronary blood flow. Am. J. Physiol. 273 (Heart Circ. Physiol. 42): H2746–H2755, 1997.—There is a paradoxical α-adrenoceptor-mediated coronary vasoconstriction whenever there is adrenergic activation of the heart, as during cardiovascular reflexes or exercise. A previous study demonstrated that this paradoxical vasoconstriction helps maintain blood flow to the vulnerable inner layer of the left ventricular wall during exercise, but the mechanism for this effect was not elucidated. The purpose of the present investigation was to test the hypothesis that α-adrenoceptor-mediated vasoconstriction lessens the to-and-fro oscillation of blood flow that occurs in the coronary arterial tree during systole and diastole. Septal coronary artery blood velocity was measured in anesthetized open-chest dogs with a 20-MHz pulsed Doppler velocimeter. Systolic retrograde velocity and diastolic forward velocity were compared during norepinephrine infusion before and after α-adrenoceptor blockade with phenoxybenzamine. Systolic arterial pressure was held constant by aortic banding; heart rate was controlled by pacing at 80, 140, and 200 beats/min; and maximum left ventricular dP/dt was unchanged by α-blockade. At each pacing rate, systolic retrograde velocity was significantly greater after α-blockade, indicating that α-vasoconstriction reduced systolic retrograde flow by changing coronary vascular impedance. Transmural blood flow was measured with microspheres in a second group of dogs during the same experimental conditions, and flow to the inner layer of the left ventricle was diminished by α-adrenoceptor blockade at a heart rate of 250 beats/min, demonstrating a beneficial effect of α-vasoconstriction. In conclusion, adrenergic α-adrenoceptor-mediated coronary vasoconstriction reduces systolic retrograde coronary flow during norepinephrine infusion. This lessens to-and-fro flow oscillation in the coronary circulation and probably is the mechanism whereby α-vasoconstriction helps maintain blood flow to the inner layer of the left ventricle during exercise.

α-Adrenergic vasoconstriction; α-adrenoceptors; coronary vascular impedance; Doppler velocimeter; phasic coronary flow

Cardiac contraction retards coronary arterial inflow and accelerates coronary venous outflow during each systole (11, 15). The systolic compressive force is greatest in the inner layers of the left ventricle than in the outer layers (14), and arterioles in the subendocardium narrow ~20% from diastole to systole, but, in contrast, arteriolar diameter in the subepicardium changes very little during the cardiac cycle (30). Hoffman and Spaan (9, 15, 27) propose that systole and diastole cause a to-and-fro oscillation of blood flow in arterial vessels that penetrate the myocardium from outside to inside. This oscillating flow only fills and empties the capacitance of the intramyocardial arterial tree without providing nutritive flow through the capillaries in the subendocardium. The result of this oscillatory flow is that the inner layer of the left ventricle is only perfused during diastole, but the outer layer is perfused throughout the cardiac cycle. This means that a high heart rate is a particular threat to the subendocardium because the duration of diastole becomes very brief during tachycardia, whereas the duration of systole shortens very little. Adrenergic activation of the heart (as during exercise) imposes an additional stress on the inner layer of the left ventricle because myocardial oxygen consumption increases manyfold, and this can only be sustained by a similar increase in coronary blood flow. In addition, intramyocardial blood volume increases when the coronary circulation is vasodilated (22).

There is a paradoxical α-adrenoceptor-mediated coronary vasoconstriction whenever there is adrenergic activation of the heart, as is observed during exercise and cardiovascular reflexes (7, 8). The α-adrenergic vasoconstriction seems paradoxical because it limits coronary flow just when the myocardial oxygen demand is greatest, and this would seem most severe in the subendocardium during tachycardia, as discussed above. The answer to the paradox is in the transmural effects of α-adrenergic vasoconstriction when coronary flow is high.

Johannsen et al. (17) observed that electrical stimulation of sympathetic fibers to the heart decreased flow to the outer layer of left ventricle, thus increasing the inner-to-outter flow ratio, but only when flow was greatly augmented by adenosine infusion. Baumgart et al. (2) observed a modest increase in the inner-to-outter flow ratio due to sympathetic stimulation combined with dipyridamole vasodilation. Huang and Feigl (16) found that regional α-adrenoceptor blockade decreased blood flow to the inner layer of the left ventricle when coronary flow was high during exercise. Thus the paradoxical α-adrenergic vasoconstriction has the ben-

IT IS WELL RECOGNIZED that the inner layer of the left ventricle is more susceptible to underperfusion than the outer layer. There are two major reasons for the vulnerability of the subendocardium: 1) coronary vessels penetrate the myocardium from outside to inside so that the inner layers of the ventricle are further from the epicardial conduit artery, and 2) cardiac contraction during systole compresses the coronary vessels in the subendocardium more than the vessels in the subepicardium.
Vasoconstriction reduces coronary flow oscillations

The effective effect of helping maintain blood flow in the inner layer of the left ventricle during tachycardia when flow is high. The postulated mechanism for this effect is that α-adrenergic vasoconstriction stiffens medium-size coronary vessels so that there is less to-and-fro oscillation of coronary blood flow with systole and diastole.

The purpose of the present investigation was to test the postulated mechanism of α-adrenergic vasoconstriction decreasing the oscillating to-and-fro flow in the intramyocardial coronary arteries during systole and diastole. Coronary flow velocity was determined in the septal coronary artery during norepinephrine infusion before and after α-adrenoceptor blockade. At the same heart rate and systolic blood pressure, the systolic retrograde flow observed in the septal artery was less when α-adrenoceptors were intact than after α-adrenoceptor blockade. This indicates that α-adrenoceptor vasoconstriction adjusts the complex impedance of the coronary circulation to reduce to-and-fro oscillation of flow during the cardiac cycle. The left ventricular transmural flow was determined with microspheres in a second group of animals with the same experimental conditions. During norepinephrine infusion and a high heart rate, inner layer blood flow was greater with α-adrenoceptors intact than with α-adrenoceptors blocked.

METHODS

General Preparation

Twenty-three adult mongrel dogs of either sex (12 for Doppler flow velocity measurements and 11 for transmural myocardial flow measurements), weighing 15–25 kg, were premedicated with an intramuscular injection of ketamine (200 mg). The dogs were anesthetized with pentobarbital sodium (30 mg/kg iv). Additional doses of pentobarbital sodium were given as needed throughout the experiment. Each animal was placed on a constant temperature blanket to maintain body temperature at 37°C. The animals were intubated and ventilated with a respirator supplemented with oxygen. Arterial blood gas and pH were measured frequently and kept in the physiological range by adjustment of ventilation rate, inspired oxygen concentration, and intra-venous infusion of 150 mM sodium bicarbonate. After median sternotomy and a left thoracotomy in the fifth intercostal space, the heart was exposed and suspended in a pericardial cradle. An adjustable snare was placed around the descending aorta and was used to match the systolic aortic pressure after α-adrenoceptor blockade to the same level as during norepinephrine infusion without α-adrenoceptor blockade. In the dogs for transmural myocardial flow measurements, a 3-F catheter of 15 cm in length was introduced into the left atrium via the appendage for injection of microspheres. Heparin (5,000 units iv) was given to prevent blood coagulation. All measurements were recorded simultaneously by using a data recorder (model R-81; TEAC) and a multichannel pen recorder (model RJ 5608; Nihon Kohden) at a paper speed of 25 mm/s.

Control of Heart Rate

Atrioventricular (AV) block was made by injection of 40% Formalin into the AV node. PACing was controlled by right ventricular pacing in AV-blocked dogs. Heart rate was set at 80 to 140 and 200 beats/min for Doppler flow velocity measurements, and 140 to 200 and 250 beats/min for transmural myocardial flow measurements. In two experiments for Doppler flow, right atrial pacing was used without AV block during bilateral vagal stimulation (5 V, 20 Hz) to slow the intrinsic heart rate below 140 beats/min to investigate whether right ventricular pacing affects septal artery flow. Heart rate was set at 100 beats/min between experimental runs.

Hemodynamic Measurements

A catheter-tip transducer (8-F; Millar, Houston, TX) introduced into the left ventricle via the left carotid artery was used to measure left ventricular pressure and maximum left ventricular dP/dt (dP/dt max). The recording of dP/dt failed in four dogs in the transmural flow measurement group. Aortic pressure was measured with a second sensing element on the catheter. In the dogs for Doppler flow velocity measurements, an electromagnetic flowmeter transducer (model FF-0201; Nihon Kohden) was placed around the circumflex coronary artery. At the end of the experiment, carbon ink was injected into the circumflex coronary artery to delineate the perfusion area. The stained area was cut out and weighed, and circumflex flow per gram tissue (ml·min⁻¹·g⁻¹) was calculated.

Doppler Flow Velocity Measurements (12 Dogs)

Adipose tissue around the septal artery was carefully removed and was limited to only one-half of the circumference of the vessel to avoid damage to the myocardium surrounding the artery (Fig. 1). Phase coronary arterial blood velocity was measured in the septal artery by using our 80-channel, 20-MHz ultrasound pulsed Doppler velocimeter. The details of this system have been described previously (18, 25). In brief, the probe of the Doppler system was placed carefully on the septal artery by using a specially designed probe holder to avoid compression of the vessel. The holder was fixed at the position where the maximum flow diameter was obtained on a velocity profile (20). The flow signal was analyzed by a fast Fourier transform (FFT) method. The envelope of septal arterial blood velocity by FFT display was detected by a computer (D4000). Systolic reverse velocity area and forward velocity area were calculated by integration from the envelope of the FFT of the septal arterial flow velocity, as illustrated in Fig. 3.

Transmural Blood Flow Measurements (11 Dogs)

Myocardial blood flow was measured by using nonradioactive microspheres made of inert plastic, which were labeled with one of the following stable elements: Nb, Br, Zr, Ba, I, Ce, and In. The method has been previously reported in detail by Mori et al. (23). In brief, six different microspheres (15 µm) were used during three different heart rates (140, 200, and 250 beats/min) before and after α-adrenoceptor blockade. In each transmural flow measurement, 2 × 10⁶ microspheres in 1 ml saline solution (containing 0.09% sodium dodecyl sulfate) were injected into the left atrium for 10 s and flushed with 4 ml saline for 40 s. Reference blood sampling with a catheter placed in the aorta via the right brachial artery was started 10 s before the injection of microspheres and continued for 120 s with a constant withdrawal rate of 4.77 ml/min. At the end of the experiment, the heart was arrested with an injection of potassium chloride intravenously. The free wall of the left ventricle was removed, and the papillary muscles and the apical one-fourth were excised. The myocardial tissue was fixed using 7.4% Formalin and was cut into four layers from...
subepicardium to subendocardium (each weight ~6–10 g). These tissue samples and reference blood samples were dissolved using 2 N KOH, and the microspheres were trapped on filter paper. Thereafter, X-ray fluorescent spectrometry was applied to the filter paper using a wavelength-dispersive spectrometer (PW 1480; Philips). The X-ray fluorescence activities of the six sets of microspheres were measured, and the blood flow values of the four layer samples were calculated using the following formula: transmural flow (ml/min) = reference flow rate (ml/min) × tissue X-ray fluorescence activity (count)/reference X-ray fluorescence activity (count).

Experimental Protocols

Doppler flow velocity measurements. Septal arterial blood velocity, circumflex coronary flow, and other hemodynamic variables were measured at pacing rates of 80, 140, and 200 beats/min under the following three conditions: 1) control without norepinephrine infusion or phenoxybenzamine, 2) during norepinephrine infusion before α-adrenoceptor blockade, and 3) during norepinephrine infusion, at the same rate for each dog, after α-adrenoceptor blockade with phenoxybenzamine. The intravenous norepinephrine infusion rate was adjusted to increase systolic blood pressure ~50% at a pacing rate of 100 beats/min. When hemodynamic variables became stable, the pacing rate was changed to 80 beats/min, and the blood velocity measurement was made for this heart rate. Then, the measurements were repeated at pacing rates of 140 and 200 beats/min. Norepinephrine infusion was stopped, and pacing rate was returned to 100 beats/min. After the recovery of hemodynamic variables, the α-adrenoceptor blocking agent phenoxybenzamine was administered (0.5 mg/kg iv over 10 min). Additional phenoxybenzamine was given (0.05 mg/kg iv) every minute until aortic systolic blood pressure decreased to ~60% of the control value. The blood velocity measurements were made at pacing rates of 80, 140, and 200 beats/min during norepinephrine infusion just as before, except a partial occlusion of descending aorta was used to maintain the systolic blood pressure at the same level as before α-adrenoceptor blockade.

Transmural blood flow measurements. Myocardial flow with other hemodynamic variables was measured at pacing rates of 140, 200, and 250 beats/min under conditions 2 and 3 for the Doppler flow velocity measurement protocol, i.e., during norepinephrine infusion before and after α-adrenoceptor blockade with phenoxybenzamine. Arterial blood pressure and left ventricular pressure were measured during the microsphere injection period with a sampling interval of 8 ms for 30 s. Mean values of systolic, diastolic pressure, and dP/dt max were calculated.

Drugs

Norepinephrine (1 mg/ml; Sankyo) was diluted to the concentration of 50 µg/ml with saline. Intravenous norepinephrine infusion was started at a rate of 0.25 µg·kg⁻¹·min⁻¹ by using an infusion pump (Auto Fuser 200ML; Med-Tech). The infusion rate of norepinephrine was adjusted so that the systolic aortic pressure was ~150% of its control value and then fixed. For an individual animal, the same dose of norepinephrine was used in all runs before and after α-blockade. The range of intravenous infusion rate of norepinephrine was from 0.25 to 0.75 µg·kg⁻¹·min⁻¹. Phenoxybenzamine (Dibenzyline, 50 mg/ml; Smith Kline & French Labs, Philadelphia, PA) was diluted with saline and administered intravenously with an initial dose of 0.5 mg/kg over 10 min. Then, an additional dose of 0.05 mg/kg was given every minute until the systolic aortic pressure decreased to ~60% of the control value. The maximum total dose was limited to 1.0 mg/kg.
Table 1. Doppler flow velocity group

<table>
<thead>
<tr>
<th>Heart Rate, beats/min</th>
<th>Control</th>
<th>Norepinephrine n</th>
<th>Norepinephrine + α-Block n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aortic blood pressure, mmHg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>112/72 ± 5/7</td>
<td>9</td>
<td>153/104 ± 9/9</td>
</tr>
<tr>
<td>140</td>
<td>117/91 ± 4/5</td>
<td>11</td>
<td>154/120 ± 6/7</td>
</tr>
<tr>
<td>200</td>
<td>108/90 ± 5/7</td>
<td>11</td>
<td>141/117 ± 5/6</td>
</tr>
</tbody>
</table>

Circumflex coronary flow, ml/min·1·g⁻¹

|                       | 80       | 104 ± 11         | 1.02 ± 0.19               | 1.35 ± 0.25  | 9             |
|                       | 140      | 1.02 ± 0.18      | 1.40 ± 0.23               | 1.87 ± 0.37  | 12            |
|                       | 200      | 1.14 ± 0.22      | 1.71 ± 0.29               | 2.49 ± 0.51  | 12            |

Left ventricular dP/dt max, mmHg/s

|                       | 80       | 1.50 ± 0.09      | 2.70 ± 0.23               | 2.69 ± 0.23  | 9             |
|                       | 140      | 1.81 ± 0.14      | 3.44 ± 0.26               | 3.61 ± 0.29  | 11            |
|                       | 200      | 1.86 ± 0.19      | 3.46 ± 0.26               | 3.62 ± 0.29  | 12            |

Septal systolic reverse flow velocity area, cm

|                       | 80       | 0.91 ± 0.17      | 1.30 ± 0.29               | 1.68 ± 0.23  | 9             |
|                       | 140      | 0.55 ± 0.16      | 0.93 ± 0.27               | 1.31 ± 0.33  | 12            |
|                       | 200      | 0.49 ± 0.18      | 0.80 ± 0.28               | 1.27 ± 0.32  | 12            |

Septal diastolic forward flow velocity area, cm

|                       | 80       | 12.75 ± 0.76     | 13.65 ± 0.78              | 13.23 ± 1.42  | 9             |
|                       | 140      | 8.96 ± 0.67      | 9.46 ± 0.60               | 9.56 ± 0.77  | 12            |
|                       | 200      | 7.26 ± 0.54      | 8.20 ± 0.63               | 8.69 ± 0.74  | 12            |

Septal systolic reverse velocity area/forward velocity area, %

|                       | 80       | 7.72 ± 1.68      | 9.79 ± 2.20               | 14.44 ± 2.77  | 9             |
|                       | 140      | 6.47 ± 1.97      | 9.63 ± 2.74               | 14.55 ± 3.30  | 12            |
|                       | 200      | 6.77 ± 2.56      | 9.67 ± 2.79               | 15.23 ± 2.88  | 12            |

Values are means ± SE; n, no. of observations. dP/dt max, maximum left ventricular dP/dt.

Statistical Analysis

The data for each variable (blood pressure, dP/dt max, flow velocity, etc.) were evaluated by analysis of variance to compare norepinephrine effects before and after α-adrenoceptor blockade, at different heart rates with adjustment for dog effects and missing values (26). A significant interaction between heart rate and α-adrenoceptor blockade was found for the variables shown in Figs. 2A and 7, in which cases the effects of α-adrenoceptor blockade were tested separately at each heart rate using a paired t-test. In Figs. 3–6, the P values are from the analysis of variance test of the main effect of α-adrenoceptor blockade.

The means and SE in Tables 1 and 2 were computed on a point-by-point basis in the usual manner to illustrate the variability of the data. The SE shown in Figs. 1–7 were calculated using residual errors from the appropriate analysis of variance.

RESULTS

Doppler Flow Velocity Group

The data are given in Table 1. As expected, norepinephrine increased blood pressure, left ventricular dP/dt max, and coronary blood flow. The increase in cardiac contractility with norepinephrine augmented the systolic retrograde flow velocity in the septal artery even though the aortic systolic pressure increased. When the same dose of norepinephrine was infused after α-adrenoceptor blockade with phenoxybenzamine, a snare around the aorta was used to match systolic aortic pressure to the same level as during norepinephrine infusion without α-blockade. As expected, coronary blood flow was increased when α-adrenoceptor-mediated coronary vasoconstriction was blocked, but left ventricular dP/dt max was not changed.

The critical comparison in this study was between norepinephrine infusion before and after α-adrenoceptor blockade. This comparison for hemodynamic measurements is illustrated in Fig. 2 and demonstrates that systolic blood pressure and dP/dt max were unchanged during α-adrenoceptor blockade. Net forward circumflex coronary artery blood flow (measured with an electromagnetic flowmeter) during norepinephrine infusion was significantly increased when α-adrenoceptor-mediated coronary vasoconstriction was blocked (Fig. 2C). The effect of α-adrenoceptor blockade on flow velocity in the septal coronary artery is shown in Fig. 3.
Note that the magnitude of systolic retrograde flow velocity is greater after \(\alpha\)-blockade at the same heart rate (200 beats/min) without a change in systolic aortic blood pressure. The septal artery velocity profiles during individual cardiac cycles before and after \(\alpha\)-blockade are also shown in Fig. 3. Figure 3 illustrates that systolic retrograde coronary velocity is faster and longer in duration when \(\alpha\)-adrenoceptor-mediated coronary vasoconstriction is blocked compared with the unblocked condition. An additional example is given in Fig. 4 in which low-level vagal electrical stimulation was used to slow the intrinsic heart rate so that the heart rate could be paced by right atrial stimulation without AV heart block. A similar augmentation of systolic retrograde flow after \(\alpha\)-adrenoceptor blockade was observed with right atrial pacing as with right ventricular pacing.

The comparison of the systolic retrograde flow velocity area and the ratio of this reverse area to the forward flow velocity area (as defined in Fig. 3), before and after \(\alpha\)-blockade, are illustrated in Fig. 5. These data represent the critical test of the hypothesis that coronary \(\alpha\)-adrenoceptor vasoconstriction lessens retrograde coronary flow during systole. Systolic retrograde flow was significantly less during norepinephrine infusion with \(\alpha\)-adrenoceptors intact than when they were blocked, without a change in systolic aortic pressure or left ventricular \(dP/dt_{max}\).

Transmural Blood Flow Measurement Group

The hemodynamic data during norepinephrine infusion and microsphere measurements are given in Table 2. Systolic aortic blood pressure was well matched before and after \(\alpha\)-adrenoceptor blockade with phenoxybenzamine as required by the experimental design (Fig. 6A). Left ventricular \(dP/dt_{max}\) during norepinephrine infusion was not changed by \(\alpha\)-adrenoceptor blockade (Fig. 6B).

The transmural blood flow data are presented in Fig. 7. As expected, at a heart rate of 140 beats/min, \(\alpha\)-adrenoceptor blockade increased coronary blood flow during norepinephrine infusion (Fig. 7A). This effect was diminished at a heart rate of 200 beats/min (Fig. 7B) and reversed at 250 beats/min (Fig. 7C). The higher blood flow occurring when \(\alpha\)-adrenoceptors are intact compared with flow when they are blocked indicates that \(\alpha\)-adrenoceptor activation is beneficial during high heart rates.
DISCUSSION

The results demonstrate that an increase in cardiac contractility due to norepinephrine infusion results in augmented retrograde systolic flow in the septal coronary artery but that this effect is lessened by simultaneous \(\alpha\)-adrenoceptor-mediated coronary vasoconstriction. Adrenergic \(\alpha\)-adrenoceptor blockade made systolic retrograde flow oscillations worse, and at a high heart rate resulted in a diminished coronary blood flow in the left ventricle despite the fact that \(\alpha\)-adrenoceptor blockade produces vasodilation during norepinephrine infusion (Fig. 7). The systolic compressive forces are greatest in the inner layer of the left ventricle (14, 30); nevertheless, \(\alpha\)-adrenoceptor activation increased inner layer flow at 250 beats/min, as illustrated by Fig. 7, using data from the whole free wall minus papillary muscles and the apical one-fourth.

With the use of a Doppler method to study flow velocity oscillations and microspheres to study transmural flow, the present findings provide a mechanism for the paradoxical observation of Huang and Feigl (16) that \(\alpha\)-adrenoceptor blockade during exercise results in less coronary blood flow to the inner layer of the left ventricle than to the outer layer. The interpretation is based on the observations of both Spaan and Hoffman (15, 21, 27) that systole and diastole create a flow oscillation in the coronary vessels that penetrate from the epicardium to the inner layer of the left ventricle. Late in diastole, blood flows from the aorta through the coronary vascular tree to all layers of the left ventricle. At the onset of systole, contraction produces retrograde flow in penetrating coronary arteries, as measured in the septal coronary artery (6). A portion of the retrograde flow from the deep layers is diverted to the outer layers that are less compressed than the deep layers (9, 30). The result is that the inner layers of the left ventricle are not perfused during systole (15). At the beginning of diastole, there is a rush of forward flow that refills the intramyocardial arteries and arterioles that have been compressed during the previous systole. After this, nutritive flow through the capillaries in the subendocardium begins. The oscillating flow that partially empties and refills the intramyocardial capacitance during systole and diastole must occur before useful flow through the capillaries in the inner layer of the left ventricle can begin. A consequence of the
postulated decrease in coronary compliance during \(\alpha\)-adrenoreceptor activation is that the intramyocardial blood volume will decrease, and this will contribute to the diminished retrograde systolic flow.

During tachycardia, the duration of diastole shortens greatly, whereas the duration of systole is only slightly abbreviated. Therefore, tachycardia may compromise coronary blood flow because the fraction of a minute spent in diastole becomes very small. The oscillatory flow that partially empties and refills the intramyocardium of observations during norepinephrine infusion. Note that the systolic reverse area (A) decreases with increasing heart rate, probably because there is a shorter diastolic period to allow capacitative filling of the coronary circulation during tachycardia. When the reverse area is normalized by the forward area (B), the effect of heart rate is no longer observed. Values are means for number (n) of observations ± SE calculated from analysis of variance.

### Table 2. Transmural flow measurement group

<table>
<thead>
<tr>
<th>Heart Rate, beats/min</th>
<th>Norepinephrine</th>
<th>(\alpha)-Block</th>
<th>n</th>
<th>Aortic blood pressure, mmHg</th>
<th>Total left ventricular flow, ml·min(^{-1}·g(^{-1})</th>
<th>Left ventricular (\text{dP/\text{dt}(_{\text{max}})}, \text{mmHg/s} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>140</td>
<td>154/121 ± 8/6</td>
<td>8</td>
<td>159/118 ± 7/4</td>
<td>8</td>
<td>1.94 ± 0.36</td>
<td>3.29 ± 0.30</td>
</tr>
<tr>
<td>200</td>
<td>132/111 ± 5/5</td>
<td>11</td>
<td>127/102 ± 5/4</td>
<td>11</td>
<td>1.96 ± 0.23</td>
<td>3.06 ± 0.32</td>
</tr>
<tr>
<td>250</td>
<td>118/99 ± 9/8</td>
<td>8</td>
<td>113/91 ± 7/7</td>
<td>8</td>
<td>2.57 ± 0.49</td>
<td>3.16 ± 0.50</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of observations.

but when adenosine vasodilation is combined with tachycardia the inner-to-outer flow ratio falls to 0.4 at a heart rate of 250 beats/min (1). The interpretation is that brief diastolic periods and oscillating flow are overcome by local metabolic vasodilation in the subendocardium during normal pacing, but this is lost during adenosine vasodilation. In other words, when local metabolic vasodilator reserve is compromised, the mechanical effects of systolic compression and oscillating transmural flow restrict flow to the subendocardium. During these conditions, \(\alpha\)-adrenoreceptor-mediated vasoconstriction of intramyocardial capacitance vessels will have a beneficial effect on transmural flow distribution, as observed by Johannsen et al. (17).

Electrical stimulation of sympathetic fibers to the heart during unstressed conditions does not alter the transmural flow distribution in the left ventricle (inner-to-outer flow ratio; see Refs. 13 and 17). In the present study, the beneficial effect of \(\alpha\)-vasoconstriction on flow in the left ventricle was observed only at a heart rate of 250 beats/min (Fig. 7); however, the highest heart rate used in the prior Doppler experiments was only 200 beats/min. It is likely that a beneficial effect occurs at lower heart rates during exercise, because myocardial oxygen consumption and coronary flow are greater during exercise than with the norepinephrine infusion used in the present experiments. As discussed above, a high coronary blood flow coupled with brief diastolic periods for filling the capacitative coronary arterial tree places the myocardium at risk for underperfusion.

An interesting aspect of previous studies is that cardiac sympathetic nerve stimulation was more effective than infused norepinephrine in sustaining flow to the inner layer of the left ventricle (2, 17). Johannsen et al. (17) postulate that there could be an interaction between adenosine and sympathetic nerve terminals that favors flow to the subendocardium. The beneficial
effects observed in the present experiments during norepinephrine infusion are probably smaller than during sympathetic nerve activation as occurs during exercise. Baumgart et al. (2) observed a modest relative increase in left ventricular inner layer blood flow during electrical stimulation of the sympathetic nerves to the heart and coronary vasodilation produced by dipyridamole but failed to find an effect under the same conditions when norepinephrine infusion was used instead of sympathetic nerve stimulation. The difference may be due to neuropeptide Y, which is coreleased with norepinephrine from sympathetic nerves. Gutterman and Morgan (12) observed that the coinfusion of neuropeptide Y with norepinephrine potentiated the norepinephrine effect of augmenting inner layer flow compared with outer layer flow in a preparation with adenosine-induced vasodilation. Norepinephrine infusion was used in the present experiment because it is not practical to obtain a long steady effect with electrical stimulation of sympathetic nerves while adjusting the aortic snare to match systolic blood pressure before and after \(\alpha\)-adrenoceptor blockade.

Adrenergic activation has been shown to decrease arterial compliance in vivo (3). The present results are consistent with Chilian et al.'s (5) observation that sympathetic coronary vasoconstriction is predominantly found in coronary microvessels larger than 100 \(\mu\)m in diameter, whereas adenosine and local metabolic vasodilation occur predominantly in coronary arterioles smaller than 100 \(\mu\)m in diameter (19). The stiffening of coronary vessels larger than 100 \(\mu\)m in diameter by \(\alpha\)-vasoconstriction will decrease the intramyocardial compliance and reduce septal artery flow oscillations as observed in the present study.

Gwirtz et al. (13) report that the intracoronary infusion of prazosin to produce \(\alpha_1\)-adrenoceptor block-
ade during electrical stimulation of sympathetic fibers to the heart improved contractile function of the inner layer of the left ventricle. These authors conclude that $\alpha_1$-adrenoceptor-mediated coronary constriction limits oxygen delivery to the subendocardium and compromises myocardial contraction. Although the experimental conditions in Gwirtz et al.'s study differ from the present investigation, the detrimental effects of $\alpha_1$-adrenoceptor vasoconstriction found by Gwirtz et al. are not supported by the present results or the literature discussed above (2, 12, 16, 17). The reason for the discrepancy is not apparent at this time.

The present investigation and the papers cited above pertain to adrenergic alterations in transmural blood flow distribution during normal conditions. In contrast, when a coronary artery stenosis is present, a transmural vascular steal may occur. A vascular steal happens when pressure distal to a stenosis is lowered by vasodilation in a parallel vascular bed. If the blood pressure at the branch point between two beds distal to the stenosis is below the autoregulatory range so that flow is pressure dependent, then vasodilation in one bed will lower the poststenotic pressure, and flow will be stolen from the other bed. A coronary transmural steal from the inner layer to the outer layer of the left ventricle will occur if there is vasodilation in the subepicardium distal to a stenosis. Conversely, vasoconstriction in the subepicardium can have an antitransmural steal effect and preserve flow to the subendocardium. $\alpha_1$-Adrenoceptor-mediated coronary vasoconstriction in the outer layer of the left ventricle can have an antitransmural steal effect (4, 24, 29). However, this antitransmural steal effect could not explain the results of Johannsen et al. (17), Baumgart et al. (2), or Huang and Feigl (16), because there was no coronary stenosis in these studies. Hence the $\alpha_1$-adrenoceptor-mediated decrease in systolic-diastolic flow oscillation demonstrated in the present study is probably the mechanism involved. Whether decreasing flow oscillations contributes to the $\alpha_1$-adrenoceptor-mediated antitransmural steal phenomenon is not revealed by the present investigation.

Goto et al. (10) made a related observation when nitroglycerin was used to dilate the coronary vasculature. Phasic flow velocity in the septal coronary artery was determined as in the present study but with the addition of an upstream stenosis or a low perfusion pressure of 40 mmHg. Intracoronary nitroglycerin infusion augmented the systolic-diastolic flow oscillation in the septal coronary artery. Similarly, Kimura et al. (20) found that adenosine-induced vasodilation enhanced flow oscillations in the septal coronary artery, with or without a proximal coronary artery stenosis. These are examples of vasodilation increasing the intramyocardial compliance and thus flow oscillations. The increase in flow oscillations with nitroglycerin or adenosine complements the present results in which $\alpha_1$-vasoconstriction decreased intramyocardial compliance and flow oscillations.

The present results are consistent with the work of Watanabe et al. (28), who compared the effects of coronary stenosis with intense coronary vasoconstriction produced by endothelin to lower coronary blood flow. Coronary stenosis produced the well-known disproportionate decrease in left ventricular inner-layer blood flow, whereas coronary constriction with endothelin decreased flow more in the outer than the inner layer of the left ventricle. The effect was not due to a greater sensitivity of coronary vessels to endothelin in the outer layer, since a uniform vasoconstriction was observed in fibrillating hearts. Watanabe et al. proposed that endothelin vasoconstriction acts by changing the dynamic interaction of systole and diastole on coronary blood flow (the subject of the present paper).

It might be argued that heart block and right ventricular pacing alter the sequence of ventricular activation sufficiently to distort the results. This was checked in two experiments in which low-level vagal stimulation was used to slow the intrinsic heart rate sufficiently so that right atrial pacing with an intact AV node could be used to obtain heart rates of 140 and 200 beats/min. The results in the vagal stimulation group were similar to the main group, and an experiment with right atrial pacing is illustrated in Fig. 4.

In conclusion, adrenergic $\alpha_1$-adrenoceptor-mediated coronary vasoconstriction reduces systolic retrograde coronary flow during norepinephrine infusion. This lessens to-and-fro flow oscillation in the coronary circulation and probably is the mechanism whereby $\alpha_1$-adrenergic vasoconstriction helps maintain blood flow to the inner layer of the left ventricle during exercise.

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