Functional Distribution of \( \alpha_1 \)- and \( \alpha_2 \)-Adrenergic Receptors in the Coronary Microcirculation

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Background. The goal of this study was to determine the functional distribution of \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic receptors in the epicardial coronary microcirculation. This goal was accomplished by intracoronary administration of the selective \( \alpha_1 \)-adrenergic agonist phenylephrine and the selective \( \alpha_2 \)-adrenergic agonist BHT-933 during measurements of coronary microvascular diameters in the beating heart.

Methods and Results. Experimental measurements were made under conditions with intact vasomotor tone and during coronary hypoperfusion (i.e., under conditions with autoregulatory mechanisms intact and blunted, respectively). Administration of selective \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic antagonists, prazosin and SKF 104078, respectively, confirmed that the agonists were preferentially activating the desired adrenergic receptor subtype because the vasoconstrictor effects of the agonists were completely blocked by the appropriate antagonist. With baseline coronary vasomotor tone intact, phenylephrine caused constriction (8±3% decrease in diameter, \( p<0.05 \)) of small coronary arteries (vessels greater than 100 \( \mu \)m in diameter) but did not produce constriction of coronary arterioles (vessels less than 100 \( \mu \)m in diameter). During coronary hypoperfusion, phenylephrine caused constriction (\( p<0.05 \)) of both small coronary arteries and arterioles, 6±2% and 11±3% decreases in diameter, respectively. BHT-933 did not cause significant changes in microvascular diameters under control conditions but substantially and selectively decreased arteriolar diameters during hypoperfusion (24±6% decrease in diameter, \( p<0.05 \)).

Conclusions. In the intact, autoregulating coronary circulation, coronary arterioles escape from the effects of adrenergic activation but coronary arteries do not; rather, they can exhibit \( \alpha_1 \)-adrenergic coronary vasoconstriction. During coronary hypoperfusion, when autoregulatory adjustments are blunted, coronary arterioles are sensitive to both \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic agonists, demonstrating significant constritor responses. Also, the magnitude of coronary \( \alpha_2 \)-adrenergic arteriolar constriction (24% decrease in diameter) is significantly greater than that of \( \alpha_1 \)-adrenergic constriction (11% decrease in diameter) (\( p<0.05 \)). Thus, \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic activation produce different constrictor effects in the coronary microcirculation under baseline conditions when autoregulatory adjustments are intact and during coronary hypoperfusion when autoregulation is blunted. The data suggest that \( \alpha_2 \)-adrenergic receptors are preferentially distributed in arterioles, whereas \( \alpha_1 \)-adrenergic receptors are located throughout the coronary microcirculation. Importantly, the data also suggest that intrinsic autoregulatory adjustments in tone (i.e., autoregulatory escape) can override either \( \alpha_1 \)- or \( \alpha_2 \)-adrenergic constriction in coronary arterioles. (Circulation 1991;84:2108–2122)

\( \alpha \)-Adrenoceptors are known to exist as two basic subtypes, \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic receptors,\(^1\) although recent studies have further reduced these subtypes into even more discrete entities based on their functional properties\(^2,3\) and genetic base sequences.\(^4-7\) Classically, identification of \( \alpha \)-adrenergic receptors was based on the relative affinity and potency of different agonists and antagonists in effector tissues, and \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic receptors

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\(^2\)Supported by the National Heart, Lung, and Blood Institute of the US Public Health Service grants HL-32788, HL-01570, and Ischemic SCOR HL-17669. Dr. Chilian is a recipient of a Research Career Development Award from the National Heart, Lung, and Blood Institute.

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\(^4\)Received July 12, 1990; revision accepted June 25, 1991.
were thought to be “postsynaptically” and “presynaptically” located, respectively. Recently, studies have challenged this concept, because presynaptic \( \alpha_1 \)-adrenergic receptors and postsynaptic \( \alpha_2 \)-adrenergic receptors have been identified. Moreover, many hemodynamic studies of whole organ preparations have documented vasoconstriction to both \( \alpha_1 \)- or \( \alpha_2 \)-adrenergic agonists, which indicated the postsynaptic location of both receptor subtypes on vascular smooth muscle. Faber extended this concept to the microcirculation and elucidated the microvascular locations of \( \alpha_1 \)- and \( \alpha_2 \)-receptors in skeletal muscle. Specifically, it was found that \( \alpha_1 \)-adrenergic receptors were located exclusively on large arterioles and small arteries, whereas \( \alpha_2 \)-adrenergic receptors were preferentially distributed on arterioles. Such heterogeneity of \( \alpha \)-adrenergic microvascular mechanisms is consistent with other aspects of microvascular specialization. Within this context, the microcirculation of skeletal muscle and other organ systems (e.g., brain) is composed of vessel groups with discrete functional and anatomical features at each microvascular level.

The coronary circulation is also composed of groups of vessels (e.g., arteries and arterioles) with distinctive physiological, anatomical, and pharmacological characteristics. Specifically, coronary arterioles and arteries demonstrate different responses to metabolic and autoregulatory stimuli, nonselective \( \alpha \)-adrenergic activation, exogenously administered serotonin, and possess varied anatomical features such as varying layers of smooth muscle. A common feature of all coronary microvascular segments is the presence of sympathetic innervation but the density of innervation appears to be different at the various vascular levels. Arteries contain a plexus of nerves with several fibers innervating a single vessel, whereas small arterioles usually have a bipolar distribution of sympathetic fibers. Despite greater innervation in arteries than in arterioles, activation of \( \alpha \)-adrenergic receptors with norepinephrine produces proportionately similar increases in arteriolar and arterial resistances.

In view of the accumulating evidence that different microvascular segments within the coronary circulation possess unique attributes and that the distribution of sympathetic nerves and vascular \( \alpha \)-adrenergic effector mechanisms is heterogeneous, I proposed that distribution of \( \alpha \)-adrenergic receptor subtypes in the coronary microcirculation would vary among different microvascular segments. Specifically, the primary hypothesis tested was that \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic receptor subtypes are nonuniformly distributed in the coronary microcirculation in a pattern similar to that observed in skeletal muscle; that is, arterioles (vessels less than 100 \( \mu \)m in diameter) would possess primarily \( \alpha_2 \)-adrenergic receptors, whereas small arteries (vessels greater than 100 \( \mu \)m in diameter) would preferentially demonstrate \( \alpha_1 \)-adrenergic responses. Under conditions of intact coronary vasmotor tone, intrinsic autoregulatory mechanisms usually enable arterioles to escape from adrenergic vasoconstriction, which would potentially obscure sites of active \( \alpha \)-adrenergic constriction. Therefore, studies were performed under two experimental conditions: 1) selective \( \alpha_1 \)- or \( \alpha_2 \)-adrenergic activation during control conditions with intact coronary vasmotor tone and 2) during coronary hyperperfusion in which intrinsic autoregulatory mechanisms are blunted. To confirm that the “preferential” agonists were specific to a certain receptor subtype, studies were also completed in the presence of \( \alpha_1 \), \( \alpha_2 \), or \( \beta \)-adrenergic antagonists. To test these hypotheses and perform the experiments, a technique was used that enabled measurement of coronary microvascular diameters in arterioles and arteries of the beating left ventricle during infusion of selective adrenergic agonists and antagonists.

**Methods**

**General Preparation**

Mongrel dogs (\( n=60 \)) of either sex weighing 3.8–12.5 kg were sedated with a combination of fentanyl 0.04 mg/kg and droperidol 2.0 mg/kg i.v. (Innovar-Vet, Haver-Lockhart, Cutter Laboratories, Shawnee, Kan.) and anesthetized with sodium pentobarbital (30 mg/kg i.v.). Animals were placed on a homeothermic blanket system to maintain body temperature at 37–39°C. A femoral artery and a femoral vein were catheterized for aortic pressure measurements, fluid and drug administration, and arterial blood gas analyses. A 5F solid-state transducer (Millar, Houston, Tex.) was introduced into the right carotid artery and advanced into the left ventricle to obtain instantaneous measurements of left ventricular pressure. Left ventricular dP/dt (LV dP/dt) was derived from the left ventricular pressure pulse.

Jet ventilation was used to eliminate cardiac movement caused by pulmonary inflation. An 18-gauge cannula was introduced into the trachea and advanced to the carina. An inspiratory tracheal tube was positioned under 1–3 centimeters of water. A solenoid valve that was triggered from LV dP/dt was connected to a pressure source (60% \( N_2 \)-40% \( O_2 \)) and regulated to 6–12 psi. The solenoid was open for only 20–35 msec during a respiratory cycle. With this ventilation system, pulmonary inflation did not produce discernible cardiac motion because of the small tidal volume. Arterial blood gases and pH were analyzed approximately every 30 minutes and were maintained within the following ranges by varying the duration that the solenoid valve was open, the position of the cannula in the trachea, the regulated pressure, and if required, administration of sodium bicarbonate: \( pCO_2 \), 25–40 mm Hg; \( pO_2 \), 100–220 mm Hg; pH, 7.34–7.44. Supplemental anesthesia was administered as required, usually about 10–15 mg/kg/hr.

The heart was exposed by a left thoracotomy through the fifth intercostal space and partially stabilized with a pericardial cradle. In experiments in
which α-adrenergic antagonists were administered, the descending thoracic aorta was isolated and a snare occluder was situated around the vessel. The snare was used to maintain aortic pressure at control levels during α-adrenergic antagonism, which would normally reduce pressure. The left circumflex coronary artery was instrumented to allow controlled reductions in perfusion pressure, intracoronary administration of fluorescent dextran for illumination of the microcirculation, and administration of adrenergic agonists and antagonists. To enable reductions in coronary perfusion pressure to the circumflex territory, a pneumatic occluder was situated around the proximal portion of the vessel. A 24-gauge catheter was introduced into the vessel downstream from the pneumatic occluder. The cross-sectional area of this catheter was 0.35 mm²; this did not produce significant obstruction of the coronary artery because coronary pressures were within 1–2 mm Hg of aortic pressures. This catheter had a “T” connection, with one end used for coronary pressure measurements and the other for intracoronary administration of drugs.

**Microvascular Preparation**

Coronary microvascular diameter measurements were accomplished in the beating heart using an intravital microscope (Leitz Ploemopak, Wild Leitz, USA, Inc.) and a Dage silicon-intensified tube (SIT) video camera (Model 66, Dage-MTI, Inc., Michigan City, Ind.). Illumination was accomplished with a computer-controlled stroboscopic light source (Chadwick-Helmuth, 100 Watt Xenon Arc, El Monte, Calif.) point-source bulb. A PDP 11/73 computer (Digital Equipment Corporation, Cambridge, Mass.) received the left ventricular dP/dt signal and was adjusted to flash the strobe once per cardiac cycle at the same point in late diastole during successive cardiac cycles. Under these conditions, the epicardial microvasculature appeared to be motionless when viewed through the microscope because the heart was illuminated for a short period of time (15–30 μsec) at the same point during the cardiac cycles. A polarizing filter was used to reduce the glare from the epicardial surface. The microscope objectives used in this preparation were the Leitz EF4 (4×, numerical aperture 0.12), Leitz L10 (10×, numerical aperture 0.22), and Leitz L20 (20×, numerical aperture 0.32).

An area of the left ventricle having a large number of vessels was identified. Cardiac motion of this area was partially restrained by inserting four 22-gauge needles attached to a rod. The myocardium within this region still contracted vigorously with restraint primarily limiting the up-and-down movement. Previous experience with this procedure has shown that neither resting blood flow nor vasodilator reserve are compromised; thus, the microvasculature does not appear traumatized.

**Microvascular Diameter Measurements**

Measurements of diameters of coronary arteries and arterioles were made during late diastole using intravital video microscopic techniques. The fluorescent images were directly digitized from the camera with a frame digitizer (Imaging Technology, Inc., Woburn, Mass.). These images were displayed on a high-resolution video monitor (Conrac Corporation, Covina, Calif.) and stored on a hard disk or transferred to magnetic tape for permanent data storage and subsequent analysis. Diameter measurements were accomplished off-line from digitized images displayed on the monitor. Cursors were aligned with the vessel edges using a digitizing tablet (SummaGraphics Corporation, Fairfield, Conn.) and a computer program was used to calculate the vessel diameter in microns. The diameter measuring system was calibrated by two independent methods. First, a standard micrometer grid (10-μm division) was used to calibrate the distance between cursors at different magnifications. Second, Fluoresbrite® (fluorescein-labeled) microspheres of different sizes (2.5, 10, 20, and 25 μm) were applied to the surface of different hearts. The diameter of the beads was measured and this value was correlated to the known value. Neither the slope nor intercept of the line was different from the line of identity. This latter method of calibration demonstrated that diameter measurements using the stroboscopic intravital microscopic techniques were accurate under the experimental conditions using epi-illumination, fluorescence microscopy.

To obtain optimal visualization of coronary arteries and arterioles, fluorescein isothiocyanate-dextran (MW, 5,000,000–2,000,000) was injected into the cannulated coronary artery as a bolus. The volume of the fluorescein isothiocyanate–dextran physiological saline solution was usually about 0.05 ml, and fluorescent-dextran concentration was 50 mg/ml. It was recently reported that coronary diameters are equivalent when measured either with polarized light or by using a fluorescent dextran; thus, the dextrans do not appear to be vasoactive. After injection of the fluorescent dextran, arteries and veins would illuminate sequentially (i.e., arteries and arterioles would illuminate initially, followed by venous and venular illumination 1–2 seconds later). This procedure enabled characterization of small coronary arteries and arterioles and engendered measurement of internal diameter because the vessel lumen was illuminated by the fluorochrome (Figure 1). The fluorescein molecule was activated and visualized using the Leitz H₂ excitation-barrier filter in conjunction with the Ploem system. A particular vessel was measured four to eight times at the same point along the vessel, using various images of a particular vessel obtained over approximately a 5–30 second period. The range of these diameter measurements typically varied less than 3% from the average value.

**Experimental Protocols**

Experimental variables were measured during the following experimental conditions: 1) microvascular.
responses to selective $\alpha_1$- or $\alpha_2$-adrenergic activation under baseline conditions ($\alpha_1$-adrenergic activation, $n=28$; $\alpha_2$-adrenergic activation, $n=17$) and during hypoperfusion ($\alpha_1$-adrenergic activation, $n=17$; $\alpha_2$-adrenergic activation, $n=13$); 2) microvascular responses to selective agonists during $\alpha_1$- or $\alpha_2$-adrenergic antagonism ($\alpha_1$-adrenergic activation, $n=4$; $\alpha_2$-adrenergic activation, $n=4$); and 3) influences of $\beta$-adrenergic blockade on coronary microvascular responses to $\alpha$-adrenergic blockade or phenylephrine infusion ($n=7$).

**Administration of $\alpha_1$- and $\alpha_2$-adrenergic agonists.** In this protocol, administration of the $\alpha_1$-adrenergic agonist phenylephrine and the $\alpha_2$-adrenergic agonist BHT-933 was accomplished by intracoronary infusion of each drug at dosage rates of 0.2 and 1.0 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$. The experimental protocol involved measurements of systemic hemodynamics (mean and phasic aortic pressures, heart rate, and left ventricular dP/dt) and coronary microvascular diameters under the following conditions: 1) baseline with coronary vasomotor tone intact; 2) administration of phenylephrine or BHT-933, 0.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; 3) administration of phenylephrine or BHT-933, 1.0 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$; 4) baseline measurement (to ensure recovery of diameters from the effects of the drugs); 5) reduction of coronary perfusion pressure to 40 mm Hg by inflation of the pneumatic occluder around the circumflex artery (hypoperfusion); 6) administration of phenylephrine or BHT-933, 0.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during hypoperfusion; and 7) administration of phenylephrine or BHT-933, 1.0 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ during hypoperfusion. This protocol was designed to assess the effects of the selective $\alpha_1$- and $\alpha_2$-adrenergic agonists on coronary microvascular diameters during baseline conditions with intact coronary vasomotor tone and during coronary hypoperfusion, when autoregulatory adjustments are blunted. Typically, images of microvascular diameters were made 3–5 minutes after administration of
the agonists was initiated, and a steady state with full adrenergic activation was assumed. Several experimental criteria were used to ensure viability of the preparations. First, measurements of microvascular diameters and hemodynamics during the first and second baseline conditions (measurements 1 versus 4) had to be within 5% of each other to ensure that the preparations were stable. Second, during reductions in coronary perfusion pressure to 40 mm Hg, coronary microvessels had to demonstrate active vasodilation. Vessels that behaved passively during reductions in perfusion pressure (i.e., decrease in diameter) may have been damaged in the experimental preparation. Passive vessels were not included in the final analysis. Third, blood gases and pH had to be within the previously described ranges. Fourth, mean arterial pressure had to be at least 70 mm Hg. Using these experimental criteria caused us to reject approximately 30% of the preparations.

**Administration of α₁- and α₂-adrenergic antagonists.** To confirm that the α₁- and α₂-adrenergic agonists were activating a specific receptor subtype, antagonists to the α₁- and α₂-adrenergic receptors were administered to determine if the constrictor effects of the specific agonists could be totally blocked or not affected by the appropriate antagonists. Measurements of coronary microvascular diameters and systemic hemodynamics during control or hypoperfusion were accomplished under the following conditions: 1) control measurements; 2) administration of BHT-933, 1.0 μg·kg⁻¹·min⁻¹; 3) administration of phenylephrine, 1.0 μg·kg⁻¹·min⁻¹; 4) baseline measurement; 5) administration of prazosin (α₁-adrenergic antagonist, 0.7 mg/kg i.v.) or SKF 104078 (preferential postsynaptic α₂-adrenergic antagonist, 0.4 mg/kg i.v.); 6) administration of BHT-933 (1.0 μg·kg⁻¹·min⁻¹) in the presence of the selective adrenergic antagonists; 7) administration of phenylephrine (1.0 μg·kg⁻¹·min⁻¹) in the presence of the antagonists; and 8) repeat diameter measurement during α₂-adrenergic antagonism. Vessels were selected for study on the basis of showing constrictor responses to the α₁- or α₂-adrenergic agonists either at normal perfusion pressures or after reductions in perfusion pressures. Ten vessels (both arteries and arterioles) from four preparations (six during hypoperfusion and four during control) were studied during α₁-adrenergic blockade, and 11 vessels from four preparations (six during hypoperfusion and five during control) were examined during α₂-adrenergic blockade. This protocol was devised to show that α₁-adrenergic activation by BHT-933 or phenylephrine was specific to the receptor subtype by showing that the constrictor effects could be completely abolished by administration of the antagonist to the same receptor, whereas antagonists to the alternative α₂-adrenergic receptor subtype would not influence constriction to the specific agonist, that is, BHT-933-induced vasoconstriction would be unaffected by prazosin. Prazosin is reported to be a selective α₁-adrenergic antagonist and SKF 104078 has been shown to preferentially antagonize postsynaptic α₂-adrenergic receptors. The ability of SKF 104078 to block postsynaptic α₁-adrenergic receptors is important because it lessens concerns about augmentation of norepinephrine release associated with presynaptic α₁-adrenergic blockade and potential complicating effects on coronary microvascular diameters (e.g., functional hyperemia). It is worth noting that some investigators have found that SKF 104078 can antagonize both presynaptic and postsynaptic α₂-adrenergic receptors; thus, the selectivity of blockade was confirmed by assessing microvascular diameters and hemodynamics before and after administration of the drug. The same criteria as for the first protocol were used (comparison of measurement 1 versus measurement 4 and measurement 5 versus measurement 8) to ensure stability of the preparations and reversibility of the responses.

**β-Adrenergic antagonism.** Because phenylephrine is reported by some investigators to be a β-adrenergic agonist in addition to an α₁-adrenergic agonist, studies (n=7) using phenylephrine as a coronary constrictor were completed in the presence and absence of β-adrenergic blockade (propranolol 1 mg/kg i.v.). β-Adrenergic blockade with propranolol significantly reduced heart rate in the preparations; thus, to compare the effects of phenylephrine before and after β-adrenergic blockade at comparable heart rates, studies were completed in animals after chemical ablation of the sinoatrial node (injection of 0.1–0.2 ml of 4% formaldehyde). After this procedure, heart rate was reduced to approximately 80–100 beats/min and was not further altered by propranolol.

The protocol for these studies was 1) control measurements (after sinoatrial nodal blockade); 2) intracoronary administration of phenylephrine (1.0 μg·kg⁻¹·min⁻¹); 3) repeat control; 4) β-adrenergic blockade (propranolol 1 mg/kg); 5) phenylephrine administration (same route and dose as in protocol 2); and 6) repeat baseline measurements during β-adrenergic blockade. Diameters between measurements 1 versus 3 and 4 versus 6 had to be within 5% of one another to ensure that the preparations were not deteriorating.

**Data Analysis**

Hemodynamic variables (systolic, diastolic, and mean arterial pressure; left ventricular dP/dt and heart rate) were compared using an analysis of variance in conjunction with Scheffe’s multiple comparison test to detect possible differences during administration of the drugs under baseline and hypoperfusion conditions. Left ventricular dP/dt was expressed as a percent of control.

Microvascular diameter responses to the α-adrenergic agonists were analyzed using three approaches. First, functional relations were constructed with the baseline diameter or diameter during hypoperfusion as the independent variable versus the percent change in coronary diameter during administration
of the adrenergic agonists (plotted as the dependent variable). Second, the percent change in microvascular diameter from baseline or during hypoperfusion during administration of the agonists in two distinct diameter classes of vessels was compared: arterioles smaller than 100 μm, arteries 100 μm or greater. Third, responses during the α-adrenergic antagonist protocol were analyzed by expressing the diameter changes during the various interventions as a percent change from control. Differences among the vessel classes and during the various interventions were analyzed using an analysis of variance in conjunction with Scheffe’s multiple comparison test.28

All data are presented as mean±SEM, and a probability level of 5% was used as the criterion for statistical significance.

### Results

**Systemic hemodynamics.** Table 1 shows systemic hemodynamics during administration of the adrenergic agonists; intracoronary administration of phenylephrine or BHT-933 did not significantly alter hemodynamics from baseline or hypoperfusion. Left ventricular dP/dt was reduced during hypoperfusion (p<0.05) but was not affected by either of the α1- or α2-adrenergic agonists. Table 2 summarizes the hemodynamic data during the α-adrenergic antagonist protocol. In this experimental series, to assess possible effects of the adrenergic antagonists on cardiac function, LV dP/dt during control and hypoperfusion was used as baseline from which to analyze the percent change. None of the interventions affected baseline hemodynamics.

In the studies (n=7) comparing the effects of phenylephrine before and during β-adrenergic blockade (after sinoatrial node ablation), aortic pressures and left ventricular dP/dt were unaffected by the agonist (mean pressure, 80±4 versus 82±6 mm Hg; LV dP/dt, 108±9%). LV dP/dt was significantly reduced (62±9% of control) after β-adrenergic blockade but was unaffected by phenylephrine.

**Coronary microvascular diameters during α1- and α2-adrenergic activation.** Figure 2 illustrates the percent change in diameter of coronary arteries and arterioles to the α1-adrenergic agonist phenylephrine plotted versus the initial diameter. Small coronary arteries (average diameter 153±18 μm) exhibited modest constrictor responses at the highest dose of phenylephrine infusion (−11±3 μm, p<0.05), whereas arterioles (average diameter 73±11 μm) did not significantly constrict. The effects of phenylephrine on coronary microvascular diameters during hypoperfusion are shown in Figure 3. Significant arteriolar constriction (negative percent change) occurred to the high dose of phenylephrine in addition to that observed in coronary arteries. The average magnitude of arterial and arteriolar constriction during α1-adrenergic activation at the high dose of phenylephrine under conditions of hypoperfusion were 11±2 μm and 8±3 μm, respectively (p<0.05).

The constrictor effects of BHT-933 (α2-adrenergic agonist) are shown in Figures 1, 4, and 5. Figure 4 illustrates the effects of BHT-933 during control, baseline experimental conditions. During these experimental conditions, the α2-adrenergic agonist did not produce significant constriction of either coronary arterioles or arteries. The effects of BHT-933 on

### Table 1. Systemic Hemodynamics for the α1- and α2-Adrenergic Activation Experiments

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>PE-0.2</th>
<th>PE-1.0</th>
<th>CPP-40</th>
<th>CPP-40 + PE-0.2</th>
<th>CPP-40 + PE-1.0</th>
</tr>
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<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>158±11</td>
<td>157±9</td>
<td>158±11</td>
<td>158±10</td>
<td>157±10</td>
<td>156±9</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>95±3</td>
<td>95±3</td>
<td>94±2</td>
<td>93±3</td>
<td>93±4</td>
<td>91±4</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>68±4</td>
<td>68±4</td>
<td>67±3</td>
<td>65±3</td>
<td>65±3</td>
<td>66±4</td>
</tr>
<tr>
<td>Mean pressure (mm Hg)</td>
<td>77±3</td>
<td>78±3</td>
<td>76±3</td>
<td>75±2</td>
<td>76±2</td>
<td>75±3</td>
</tr>
<tr>
<td>Mean coronary pressure (mm Hg)</td>
<td>76±3</td>
<td>77±2</td>
<td>76±2</td>
<td>42±1</td>
<td>41±1</td>
<td>41±1</td>
</tr>
<tr>
<td>LV dP/dt (%)</td>
<td>100</td>
<td>109±12</td>
<td>111±16</td>
<td>81±8*</td>
<td>75±9*</td>
<td>73±8*</td>
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<td>n</td>
<td>28</td>
<td>22</td>
<td>23</td>
<td>17</td>
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The only significant difference among the variables during the various protocols was a reduction of LV dP/dt at reduced perfusion pressures (*p<0.05 vs. baseline). Mean coronary pressure was not statistically analyzed because the variable was controlled, i.e., independent variable. LV dP/dt is expressed as a percent of control (100%). PE-0.2, intracoronary phenylephrine 0.2 μg·kg⁻¹·min⁻¹; PE-1.0, intracoronary phenylephrine 1.0 μg·kg⁻¹·min⁻¹; CPP-40, hypoperfusion; BHT933-0.2, intracoronary BHT-933 0.2 μg·kg⁻¹·min⁻¹; BHT933-1.0, intracoronary BHT-933 1.0 μg·kg⁻¹·min⁻¹.
arteriolar diameter during hypoperfusion are illustrated in Figure 1. The top panel shows the vessel during hypoperfusion and the bottom panel illustrates the effects of the agonist. Note the profound decrease in diameter of the microvessels in the bottom panel with some vessels decreasing their diameter by about 50%. Collectively, during coronary hypoperfusion (Figure 5), substantial constriction occurred in arterioles (15±4 μm decrease in diameter at the highest dose from a diameter of 67±7 μm, p<0.05) but not in small arteries.

Figures 6 and 7 summarize the relative constriction (percent change) of coronary arterioles and arteries during administration of phenylephrine and BHT-933. Under control conditions with intact coronary vasomotor tone, both the low and high doses of phenylephrine produced significant constriction of coronary arteries –5±1% and –8±3% change in diameter, respectively (p<0.05). Coronary arterioles, however, did not constrict. BHT-933 at either dose did not produce significant constriction of arteries or arterioles (top panel, Figure 6). Figure 7 illustrates the effects of the two α-adrenergic agonists administered during coronary hypoperfusion. Under these conditions, phenylephrine produced significant constriction of both coronary arteries and arterioles, –6±2% and −11±3% change in microvascular diameter, respectively, at the higher dose (p<0.05). BHT-933 also produced a significant decrease in coronary arteriolar diameters (24±6% decrease in diameter) of arterioles (p<0.05) but not a significant change in diameter of arteries. The percent decrease of arterial diameters during administration of BHT-933 was significantly greater than that during phenylephrine (p<0.05).

**Coronary microvascular diameters during administration of α₁- and α₂-adrenergic blockade.** Figure 8 illustrates the effects of administration of selective α₁- or α₂-adrenergic antagonists on constrictor responses to the α₁-adrenergic agonists. Vessels (arterioles and arteries) were studied at both normal and reduced perfusion pressures to facilitate the pharmacological characterization of agonist and antagonist selectivity because constriction of arterioles was augmented during hypoperfusion. However, vessels that demonstrated significant constriction were studied under either condition to ensure that the pharmacological effects were not dependent on initial tone. Because the antagonists produced similar effects under baseline conditions or during hypoperfusion, the data were combined. The top panel illustrates the effects of prazosin (α₁-adrenergic antagonist) on phenylephrine- and BHT-induced coronary microvascular constriction. Note that the antagonist did not alter resting diameter. Also, the constrictor effects of the specific α₂-adrenergic agonist phenylephrine was completely blocked by the antagonist prazosin, but that caused by BHT-933 was unaffected. The lower panel illustrates that administration of the α₂-adrenergic antagonist SKF 104078 also did not change baseline diameter and completely blocked constriction to BHT-933 but did not influence that to phenylephrine.

**Coronary microvascular diameters during administration of β-adrenergic blockade.** Because phenylephrine is reported to be a partial β-adrenergic agonist in addition to an α₁-adrenergic agonist, the possibility exists that the modest constriction produced by the drug may be, in part, due to the fact that functional hyperemia caused by β-adrenergic stimulation lessens the extent of α₁-adrenergic vasoconstriction. To examine this possibility, microvascular responses to phenylephrine were completed in the presence and absence of propranolol. In arterioles and arteries before administration of propranolol, phenylephrine decreased diameters by ±3% and ±6%, respectively (p<0.05 versus control for arteries). After
administration of propranolol, which decreased diameters of vessels by 6–10%, the decrease in coronary microvascular diameters produced by phenylephrine was 6±2% in small arteries and 0±4% in arterioles (not different from that before β-adrenergic blockade). These data indicate that by using the administration protocol and dosages of phenylephrine in the present study, β-adrenergic activation and the resulting functional hyperemia were not a confounding problem. Thus, it would appear that phenylephrine was selectively activating the α₁-adrenoceptor subtype, because the constrictor effects could be completely antagonized by prazosin but was not changed by propranolol.

**Discussion**

There are five new observations elucidated in this study. 1) With intact coronary vasomotor tone, α₁-adrenergic activation produces sustained constriction of coronary arteries but not arterioles. 2) α₂-Adrenergic activation during baseline conditions does not produce vasoconstriction of arterioles or arteries. 3) When autoregulatory adjustments are blunted during coronary hypoperfusion, α₁-adrenergic activation causes constriction by approximately the same magnitude of both coronary arterioles and arteries. 4) During hypoperfusion, α₂-adrenergic activation causes significant constriction of coronary arterioles but not coronary arteries. 5) The magnitude of

**FIGURE 2. Scatterplots showing effects of phenylephrine (PE) on coronary microvascular diameters during hypoperfusion.** The data are shown as a percent change in diameter (%Δ) plotted vs. the diameter of the microvessel at 40 mm Hg during hypoperfusion (D₄₀). For phenylephrine 0.2 μg·kg⁻¹·min⁻¹: y = -6 + 0.02x − (2.63 × 10⁻⁵)x², r = 0.13. For phenylephrine 1.0 μg·kg⁻¹·min⁻¹: y = -15 + 0.10x − (1.8 × 10⁻⁴)x², r = 0.48; p < 0.05.
arteriolar constriction during hypoperfusion is significantly greater with \(\alpha_2\)-adrenergic activation than \(\alpha_1\)-adrenergic stimulation. From these data I conclude that the functional distribution of \(\alpha_1\)- and \(\alpha_2\)-adrenergic receptors in the coronary microcirculation is different; namely, \(\alpha_2\)-adrenergic receptors are located primarily in coronary arterioles, whereas \(\alpha_1\)-adrenergic receptors are located throughout the coronary microcirculation. Also, it is noteworthy to emphasize that with intact coronary vasomotor tone, when coronary autoregulatory mechanisms are intact, arterioles escape from the constrictor effects of either \(\alpha_1\)- or \(\alpha_2\)-adrenergic agonists. In contrast, coronary arteries do not show such escape mechanisms; rather, they demonstrate sustained constriction to \(\alpha_1\)-adrenergic agonists under these experimental conditions.

These observations and conclusions are critically related to several factors, including the experimental model and methodology, \(\alpha_1\)- and \(\alpha_2\)-adrenergic coronary constriction, and relation between adrenergic vasoconstriction and autoregulatory adjustments in coronary tone.

**Critique of the Experimental Model and Methodology**

An important aspect of this study that requires emphasis pertains to the experimental model. All the
measurements of microvascular diameters during selective α-adrenergic activation or antagonism were made in the subepicardial microcirculation. Because many reports have previously indicated that there are transmural differences of α-adrenergic effects across the wall of the coronary circulation under a variety of experimental conditions including exercise, coronary vasodilation, and hypoperfusion, it is important to highlight that the present results are not necessarily indicative of endocardial microvascular influences of adrenergic stimulation.

The experimental protocols ensured that the preparation was not deteriorating during the course of a study. This is evident because systemic hemodynamics and arterial blood gases did not change during the course of a study. The excellent agreement between separate control measurements of microvascular diameters during the protocols ensured that vascular caliber did not change by more than 5%, indicating a stable preparation. Moreover, using the criterion that vessels had to dilate during reductions in coronary perfusion pressure enabled the study of vessels with tone (i.e., vessels that were not damaged during the preparatory procedures). Collectively, it would appear that the present measurements were completed under the most physiological conditions possible in the setting of an anesthetized, open-chest preparation.

Accuracy of the experimental measurements is also critical for evaluation of the data. Microvascular diameter measurements were accomplished using objective lenses with magnifications of 20×, 10×, and 4× with resolving powers of 1.3, 2.6, and 6 μm, respectively. The higher power objectives are used for vessels less than 250 μm in diameter. It is worth emphasizing that fluorescence techniques were used to enhance visualization of microvessels because the fluorochrome illuminates the internal diameter of the lumen and readily enables edge detection. Also, the fluorochrome does not appear to possess vasoactive effects because in a previous study, it was reported that measurements of microvascular diameter made with either polarized light or fluorescence microscopy are comparable.

It could be argued that interpretations of results from exogenous administration of the α1- or α2-adrenergic agonists in a preparation that was not denervated could have been problematic because endogenously released catecholamines were already activating α1- and α2-adrenoceptors. This apparently was not a problem because administration of the selective α1- or α2-adrenergic antagonists, in doses sufficient to block the effects of exogenously administered antagonists, did not change baseline diameters (Figure 8); thus, resting tone appeared minimal. It is also important to emphasize that administration
of the antagonists did not affect hemodynamics, including LV dP/dt or microvascular diameters; thus, presynaptic release of norepinephrine and the associated changes in myocardial metabolism were not confounding factors.

A limitation of the data was that only diameters of microvessels were measured. This is important to mention because without measurements of microvascular pressures, it is difficult to assess passive versus active changes in vascular caliber. For instance, during α₁-activation under conditions of hypoperfusion, diameters of both small arteries and arterioles decreased. It is possible that the decrease in arteriolar diameter was, in part, passive because of the upstream (arterial) constriction and the probable lessening of downstream (arteriolar) pressure. Although passive changes in arteriolar caliber may have contributed to the decrease in diameter, active mechanisms must also have been involved. This conclusion was based on the observation that the percent decrease in arteriolar diameter was greater than that of arteries. If passive mechanisms were solely responsible, the decrease in arteriolar diameter would have been less than that of arteries. It is worth emphasizing that arteriolar constriction to BHT-933 must have been active because the caliber of upstream arteries was not changed.

Myocardial blood flow measurements were not accomplished in the present study, which hampers some of the interpretations. For instance, the condition of the epicardium during hypoperfusion is not known (e.g., whether this area is ischemic). Based on previous measurements from this laboratory, a reduction of perfusion pressure to 40 mm Hg caused a 20–30% reduction in subepicardial blood flow but arterioles still possessed pharmacological vasodilator reserve. Importantly, vessels at 40 mm Hg appeared to have their autoregulatory ability exhausted, because further reduction in perfusion pressure to 30 mm Hg caused passive collapse. This was the reason 40 mm Hg perfusion pressure (hypoperfusion) was used as the forcing to blunt intrinsic autoregulatory adjustments and reveal sites of α-adrenergic coronary arteriolar constriction. However, as shown in Table 1, LV dP/dt decreased during hypoperfusion, indicating that most likely deeper layers within the left ventricular wall were not receiving adequate perfusion.

A problem confounding the correlation between regional microscopic measurements of microvascular dynamics and myocardial blood flow relates to the tremendous spatial heterogeneity of coronary blood flow and vasodilator reserve. An implication of the spatial heterogeneity is that not all vessels of a certain class in the microcirculation have similar pressure and flow profiles. Thus, flow measurements should be extrapolated to the microvascular measurements only if certain assurances (such as that they are representative of the same perfusion territory) can be provided. Otherwise, any such correlations should be made with caution. It is likely that heterogeneity of the coronary microcirculation may be a contributing factor to the variations in responses shown in the present study (e.g., Figure 2) and in previous reports.

Another aspect of this study warrants critique. Administration of phenylephrine or BHT-933 was used to activate α₁- or α₂-adrenergic receptors, respectively. It is critical for interpretations of the data that these agonists were activating only the desired α-adrenergic subtype. Each of the agonists is selective for only a certain dose range, but it is worth emphasizing that the affinity of the agonists is about 30- to 100-fold greater for their specified α-adrenergic receptor subtype at doses producing physiological effects.
importantly, administration of the \( \alpha_1 \) - or \( \alpha_2 \)-adrenergic antagonists completely blocked the constrictor effects of agonists to the same receptor subtype but antagonists to the alternative receptor subtype did not alter vasoconstriction (Figure 8). It would appear that each of the agonists was activating only their specific receptor subtype at the administered dose.

**\( \alpha_1 \)- and \( \alpha_2 \)-Adrenergic Coronary Constriction**

Activation of \( \alpha \)-adrenergic receptors is known to produce coronary vasoconstriction sufficient to compete with the vasodilator effects of myocardial metabolism. Pharmacological administration of catecholamines and other sympathomimetic agonists has been shown to produce \( \alpha \)-adrenergic coronary constriction. Also, physiological interventions that activate the sympathetic nervous system were found to produce \( \alpha \)-adrenergic coronary vasoconstriction. Recently, these efforts have been extended to elucidate the relative contribution of \( \alpha_1 \) - and \( \alpha_2 \)-adrenergic vasoconstriction during the physiological conditions. For instance, two laboratories have found that \( \alpha \)-adrenergic tone during exercise was mediated exclusively by \( \alpha_1 \)-adrenoceptor activation. In contrast, Seitelberger and colleagues found that during exercise in the presence of a stenosis, \( \alpha \)-adrenergic tone resulted from \( \alpha_2 \)-adrenoceptor stimulation. Within the last several years, other laboratories have found that both \( \alpha_1 \) - and \( \alpha_2 \)-adrenergic activation could produce coronary vasoconstriction. Within this context, Woodman and Vatner found that norepinephrine-induced coronary vasoconstriction was equally mediated by \( \alpha_1 \) - and \( \alpha_2 \)-adrenergic receptors. On the other hand, different laboratories have found that \( \alpha \)-adrenergic coronary vasoconstriction is mediated primarily by the \( \alpha_2 \)-adrenergic receptor subtype.

At the present, there is no general consensus regarding the exact magnitude and contribution of the different receptor subtypes modulating \( \alpha \)-adrenergic responses of the coronary circulation to a variety of physiological and pharmacological interventions.

To date, there have been only a few in vivo studies describing segmental locations of \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic coronary vasoconstriction. Kelley and Feigl reported that large arteries and distal resistance vessels responded in a proportionately similar manner to norepinephrine; they used a segmental preparation to calculate epicardial and small vessel resistance. Using a preparation in which measurements of coronary blood flow were used to calculate coronary resistance and epicardial sonomicrometry was used to assess arterial responses, Heusch and colleagues reported that \( \alpha_2 \)-adrenergic coronary constriction occurred primarily in large epicardial arteries, whereas \( \alpha_2 \)-adrenergic effects predominated in the distal resistance vessels. In contrast, Vatner and colleagues found that the \( \alpha_1 \)-adrenergic agonist methoxamine produced constriction of large epicardial coronary arteries and increased coronary vascular resistance. Because of the differences between these latter two studies, the relative distribution of \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic receptors is not easily resolved. It is worth emphasizing that all of these previous segmental studies have lumped all coronary vessels less than 1,000–500 \( \mu \)m in diameter into a single compartment and could not distinguish between \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic vasoconstriction at levels within the coronary microcirculation. Thus, adrenergic effects of small arteries, arterioles, and muscular venules, etc. were lumped into a single compartment. The present study has extended these observations to the microcirculation by demonstrating \( \alpha_1 \)-adrenergic constriction of both small arteries and arterioles and exclusive \( \alpha_2 \)-adrenergic constriction of arterioles. I would like to emphasize that the distribution of coronary vascular resistance is such that small arteries (vessels greater than 100 \( \mu \)m in diameter) and arterioles constitute about 40% and 50% of total coronary vascular resistance, respectively. Thus, modulation of arterial and/or arteriolar tone by \( \alpha \)-adrenergic activation would have the potential to substantially redistribute coronary resistance.

The physiological implications of redistributed resistance in the coronary circulation as a consequence of \( \alpha \)-adrenergic activation raise some interesting possibilities about the significance of coronary sympathetic innervation. Under normal physiological conditions, it appears that the coronary circulation escapes from \( \alpha_2 \)-adrenergic constrictor tone but not from \( \alpha_1 \)-adrenergic tone because there was sustained constriction in small arteries. During intense sympathoadrenal drive with augmented myocardial oxygen demands, functional hyperemia occurring simultaneously with sustained constriction in small arteries would tend to limit increases in hydrostatic pressure in small arterioles and exchange vessels. Perhaps confining the increase in hydrostatic pressure within certain limits in these small vessels prevents gross alterations in water and solute exchange. On the other hand, \( \alpha_2 \)-adrenergic activation can produce intense coronary vasoconstriction if autoregulatory adjustments are blunted. Constriction of coronary arterioles, and the limitation of oxygen delivery that would subsequently occur, could be a reason to account for increased vulnerability of the ischemic coronary circulation to adrenergic vasoconstriction.

Studies of isolated coronary arteries have also been used to approach \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic vasomotion in different sizes of coronary arteries. These studies have generally provided evidence that epicardial arteries possess greater or exclusive sensitivity to \( \alpha_1 \)-adrenergic agonists than to \( \alpha_2 \)-adrenergic agonists. Reasons for discrepancies between these in vitro studies and the in vivo results are easily reconciled in view of the present results, which indicate the location of \( \alpha_2 \)-adrenergic receptors is within the microcirculation in arterioles less than 100 \( \mu \)m in diameter. Thus, it is not surprising that the in vitro studies failed to document \( \alpha_2 \)-adrenergic constrictor mechanisms.
Muntz and colleagues\textsuperscript{[58–60]} have used a different technique to distinguish \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic receptor subtypes in the coronary microcirculation. These investigators used receptor autoradiography of \( \alpha_1 \)- and \( \alpha_2 \)-adrenoceptors and found preferential distribution of \( \alpha_2 \)-adrenergic receptors on coronary arterioles in the canine heart but a relatively uniform number of \( \alpha_1 \)-adrenergic receptors throughout the coronary circulation. These "microanatomical" results corroborate the results of functional \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic vasoconstriction. I have also found preferential distribution of \( \alpha_2 \)-adrenergic receptors on coronary arterioles, whereas \( \alpha_1 \)-adrenergic receptors are located throughout the coronary circulation.

Recently, in a preliminary communication Kurz et al\textsuperscript{[61]} reported that epicardial perfusion of the \( \alpha_2 \)-adrenergic agonist BHT-933 produced constriction of coronary arteries but not arterioles. It is difficult to reconcile the differences between this study and the preliminary results of Kurz et al, but a few important aspects of the two studies may account for the differences. First, without blunting intrinsic autoregulatory adjustments, arterioles may have escaped from adrenergic vasoconstriction during perfusion of BHT-933. This alone may account for these investigators to have failed to observe \( \alpha_2 \)-adrenergic arteriolar constriction. Kurz et al also found small arteries constricting significantly during \( \alpha_2 \)-adrenergic activation but selectivity of the \( \alpha_2 \)-adrenergic agonist was not established in their study; that is, a selective \( \alpha_2 \)-adrenergic antagonist was not administered. This latter point is important because high doses of BHT-933 can activate \( \alpha_1 \)-adrenergic receptors; thus, without abolishing autoregulatory responses or evaluating agonist specificity, it is difficult to evaluate their data.

Relation Between Adrenergic Vasoconstriction and Autoregulatory Adjustments in Coronary Tone

For over two decades, it has been appreciated that \( \alpha \)-adrenergic vasoconstriction is related to the intrinsic level of coronary vasomotor tone. Within this context, Bassenge and colleagues\textsuperscript{[62]} found that the change in coronary vascular resistance during \( \alpha \)-adrenergic coronary activation was a function of coronary perfusion pressure. At low perfusion pressures, \( \alpha \)-adrenergic activation induced vasoconstriction, whereas at normal and high perfusion pressures, activation caused a decrease in coronary vascular resistance. Heusch and Duessen\textsuperscript{[51]} also found that the magnitude of \( \alpha \)-adrenergic coronary constriction was a function of basal coronary vasomotor tone. These investigators found that stimulation of cardiac stellate nerves caused more pronounced coronary constriction when reactive hyperemic responses were abolished during the production of a severe coronary stenosis. Also, it is noteworthy to indicate that these same investigators found that the \( \alpha \)-adrenergic vasoconstriction was mediated exclusively by \( \alpha_2 \)-adrenoceptors because it was blocked by the \( \alpha_2 \)-adrenergic antagonist rauwolscine. Production of a severe stenosis to impair coronary vasodilator reserve has also been shown to enhance \( \alpha_2 \)-adrenergic vasoconstriction sufficient to impair myocardial function in exercising dogs.\textsuperscript{[67]} This conclusion was based on the observation that \( \alpha_1 \)-adrenergic antagonism improved subendocardial function and coronary flow during exercise in the stenotic region. In addition, Liang and coworkers\textsuperscript{[63]} reported \( \alpha_1 \)-adrenergic tone in the hyperperfused myocardium. These investigators reported that the \( \alpha_1 \)-adrenergic antagonist prazosin increased coronary blood flow and myocardial oxygen consumption. Their results supported the hypothesis that \( \alpha_1 \)-adrenergic constriction during hypoperfusion is of sufficient magnitude to impair contractile function of the myocardium. Collectively, these results suggested that reductions in coronary vasomotor tone either through exercise and/or production of a stenosis augmented \( \alpha \)-adrenergic coronary vasoconstriction. This concept is compatible with the present study because I found that coronary arterioles are sensitive to both \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic agonists during hypoperfusion, when intrinsic autoregulatory adjustments in coronary tone were blunted. Thus, hypoperfusion, which impairs coronary vasodilator reserve and blunts intrinsic autoregulatory adjustments, prevents arteriolar escape from adrenergic constriction.

Studies of exercising animals under physiological conditions (without a stenosis) also suggested that adrenergic constriction may be related to the level of coronary vasomotor tone. Specifically, a greater magnitude of \( \alpha \)-adrenergic vasoconstriction was observed at higher levels of blood flow.\textsuperscript{[29,43]} It is also worth emphasizing that the relation between myocardial oxygen consumption and oxygen delivery was shifted to a greater extent at higher rates of oxygen delivery, also suggesting that competition between dilator and constrictor stimuli may be magnified and shifted toward constriction at higher rates of coronary blood flow and lower vascular resistance.

Another aspect of my results should be reiterated: These studies were confined to measurements of coronary microvascular responses in the subepicardium of the left ventricle. Several studies have shown transmural differences in \( \alpha \)-adrenergic coronary vasoconstriction, with the subepicardium demonstrating greater constriction during exercise or hypoperfusion.\textsuperscript{[29–32]} Although these results should be extrapolated, only with caution, to the subendocardial microcirculation, I emphasize that these results have revealed the subepicardial site of \( \alpha \)-adrenergic constriction to \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic agonists under conditions with intact vasomotor tone and during hypoperfusion with low, intrinsic vasomotor tone.

Conclusions

In this study, \( \alpha_1 \)- and \( \alpha_2 \)-adrenergic constriction was found to occur at different sites within the epicardial coronary microcirculation. In the presence of basal vasomotor tone, with autoregulatory mechanisms intact, coronary arterioles escape from adrenergic constriction and small coronary arteries dem-
onstrate exclusive $\alpha_1$-adrenergic vasoconstriction. With autoregulatory adjustments blunted during hypoperfusion, coronary arterioles respond to $\alpha_1$- and $\alpha_2$-adrenergic activation. Moreover, the magnitude of $\alpha_2$-adrenergic vasoconstriction in coronary arterioles is approximately threefold greater than that of $\alpha_1$-adrenergic activation. From these results, I conclude that $\alpha_1$- and $\alpha_2$-adrenergic receptors are nonuniformly distributed in the coronary microcirculation with a greater number of $\alpha_2$-adrenergic receptors occurring in arterioles, whereas a relatively equal number of $\alpha_1$-adrenergic receptors is located throughout the coronary microcirculation.

Acknowledgments

The author would like to acknowledge Susan Gard for preparation of the manuscript and Smith Kline & French for the gifts of BHT-933 and SKF 104078.

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Key Words: dog · α-adrenoceptors · α-adrenergic constriction · phenylephrine · BHT-933 · microcirculation
Functional distribution of alpha 1- and alpha 2-adrenergic receptors in the coronary microcirculation.
W M Chilian

_Circulation._ 1991;84:2108-2122
doi: 10.1161/01.CIR.84.5.2108

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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