Responsiveness of the Coronary Circulation to Brief vs Sustained Alpha-adrenergic Stimulation

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SUMMARY The effects of brief and sustained pharmacologic alpha-adrenergic stimulation on the coronary arterial circulation were compared in awake pigs. Phenylephrine was administered into the left anterior descending coronary artery (LAD) either as a bolus (eight pigs) or as a 15-minute infusion (eight pigs), with myocardial blood flow measured by the radioactive microspheres technique. Flow in the distribution in the LAD was compared with flow in myocardium perfused by the left circumflex coronary artery (LCF) as the ratio LAD/LCF. This technique corrects for systemic factors capable of modifying oxygen demand, and hence myocardial blood flow, in both zones. After a phenylephrine bolus (50–100 µg), LAD/LCF fell significantly, whereas no change was observed after the sustained infusion (5–10 and 50–100 µg/min). Four additional pigs were pretreated with i.v. adenosine to raise myocardial blood flow in excess of demand before sustained stimulation. In this setting LAD/LCF fell significantly during the sustained phenylephrine infusion.

Brief alpha-adrenergic stimulation could overcome normal flow regulatory mechanisms and resulted in constriction of coronary resistance vessels. Such changes did not occur after sustained stimulation and suggest an ability of the coronary circulation to offset chronic vasoconstrictive effects. When the myocardium is overperfused, sustained alpha-adrenergic stimulation does not jeopardize myocardial oxygenation and its vasoconstriction potential is unmasked.

CORONARY BLOOD FLOW can be directly influenced by alpha-adrenergic tone in both awake and anesthetized animals using both pharmacologic and neurogenic stimulation. Recent human studies also imply a role in regulating the coronary vascular bed. In patients with coronary artery disease, and presumably little autoregulatory reserve, cold-induced alpha-adrenergic stimulation increases coronary vascular resistance despite an increase in myocardial oxygen demand. Furthermore, patients with transplanted, and therefore denervated, hearts respond sluggishly to an increased myocardial oxygen demand imposed by atrial pacing, suggesting that withdrawal of alpha-vasoconstrictor tone may be a fundamental mechanism of coronary vasoregulation.

The potent nature of this adrenergic influence is emphasized by experiments that demonstrate the capability of alpha-adrenergic tone to vasoconstrict the coronary vascular bed of normal animals even in the face of increased myocardial metabolic demand.

Most experimental demonstrations of pharmacologic alpha-adrenergic coronary vasoconstriction have been brief, using either the bolus or very rapid infusion technique of drug administration. In the clinical setting, however, alpha-adrenergic stimulation may not be so transient. Pharmacologic agents with alpha-constrictive potential are usually administered as sustained infusions. Furthermore, the non-alpha-adrenergic, initial vasoconstriction during continuous intracoronary administration of angiotensin in the anesthetized dog is attenuated with time. This observation raises the question of tachyphylaxis with respect to sustained coronary vasoconstrictor stimulation. Accordingly, the objective of this investigation was to compare the responsiveness of the coronary circulation to brief vs sustained alpha-mediated vasoconstrictor stimulation. A further objective was to conduct this investigation in an awake animal, free of the effects of anesthesia and the denervation resulting from thoracic surgery.

**Methods**

Twenty-three farm-bred pigs (32–51 kg) were sedated (ketamine 10 mg/kg i.m.), intubated, and anesthetized with halothane (0.5–1.25%) and nitrous oxide using an anesthesia ventilator. Incisions were made in the right and left groins and in the right neck. Femoral arteries and veins and the right common carotid artery were identified and isolated. Under fluoroscopic guidance, polyethylene catheters were advanced into the descending aorta, the left atrium, the main pulmonary artery and inferior vena cava from the femoral arteries and veins, respectively. A modified coronary angiography catheter was introduced into the right carotid artery and engaged in the left coronary artery. A specially prepared endhole Teflon catheter (1.0 mm o.d., 0.52 mm i.d., Cook Catheter Co.) was advanced through the angiography guiding catheter to the mid-left anterior descending...
coronary artery (LAD). Initially to confirm that the coronary cannula was not occlusive or subintimal in location, radiopaque contrast material was injected through the coronary cannula, with attention to the washout or disappearance as an indication of satisfactory blood flow. The guiding catheter was then removed, leaving the intracoronary cannula in place. The pigs were heparinized and the incisions closed. All catheters were secured to the skin by suture and tape. Anesthesia was discontinued and the pigs were permitted to regain consciousness.

The second stage of the investigation was performed with the pigs completely awake and resting comfortably in a specially constructed enclosure. The enclosure permitted animal comfort as well as ready access to all catheters and electrocardiographic leads. The interval between the stage of instrumentation and the stage of drug administration was at least 4 hours.

Arterial pressure was measured with a fluid-filled catheter and Statham P23Db transducer. Pressure and ECGs were recorded continuously on a multichannel recorder.

Regional myocardial blood flow was determined by the radioactive microsphere technique. Microspheres (diameter 15 ± 2 μm (mean ± sem) labeled with chromium-51, rubidium-103, tin-113, cobalt-57, scandium-46 and niobium-95 were suspended in 10% dextran-0.01% Tween 80 to a final concentration of approximately $4 \times 10^8$ microspheres/ml. The suspension was sonically disrupted for 15 minutes with an ultrasonic probe (Heat Systems Ultrasonics, Inc.). Dispersion was verified microscopically just before each injection. Approximately $4 \times 10^8$ spheres were injected for each blood flow determination. Injections over 5-10 seconds into the left atrial catheter were immediately followed by a 10-ml normal saline flush. Fifteen seconds before each injection, withdrawal of the reference arterial blood sample was begun at 18 ml/min and continued for 2 minutes.

**Study Protocols**

All pigs were pretreated with propranolol, 1 mg/kg intravenously 30 minutes before the control data collection period in order to minimize potential beta-adrenergic influences. The effect of brief alpha-adrenergic stimulation was assessed by the bolus injection of intracoronary phenylephrine in eight pigs. Normal saline was infused at 0.123 ml/min into the coronary cannula throughout the study to maintain cannula patency. Control hemodynamic and radioactive microsphere myocardial blood flow determinations were then made 5 seconds after a 1-ml injection of normal saline into the LAD cannula. Fifteen minutes later, a 1-ml solution of phenylephrine, 50 or 100 μg, was similarly injected into the coronary cannula. Flow and hemodynamic measurements were repeated in an identical manner. In five of these pigs, myocardial blood flow was also measured after a second phenylephrine bolus administered at the end of a sustained 15-minute intracoronary phenylephrine infusion (50 μg/min).

The effect of sustained alpha-adrenergic stimulation was determined in another group of eight pigs. Control measurements were obtained during intracoronary saline infusion. Then phenylephrine was infused at the same rate as saline for two 15-minute periods at doses of 5–10 and 50–100 μg/min. Repeat hemodynamic and myocardial blood flow values were obtained without interruption of the infusions.

To study the action of sustained alpha-adrenergic stimulation in a setting where the protective effect of autoregulation would be minimized, phenylephrine was infused after pretreatment with i.v. adenosine in four additional pigs. After obtaining control values during intracoronary saline infusion, an i.v. infusion of adenosine was initiated and regulated to reduce mean arterial blood pressure approximately 20 mm Hg. When a hemodynamic steady state was achieved, myocardial blood flow was again determined while continuing the intracoronary saline infusion. Then phenylephrine was infused into the coronary cannula at a dose of 50 μg/min for 15 minutes. Myocardial blood flow and hemodynamic values were measured during each infusion.

In every pig, a smaller quantity of labeled microspheres (approximately 300,000), not previously used in the experiment, was injected into the coronary microcannula after final drug infusion. Thus, myocardium in which the vasculature received the drug infusion was separately labeled.

Pigs were then sacrificed and hearts sectioned. Each transmural section was divided in half and labeled as endocardial and epicardial samples. Each sample was fixed and subjected to counting in a gamma well counter (Packard Instruments Company, Inc.). Differential spectrometric data from the gamma counter were printed on teletype link and simultaneously punched on paper tape. The tape, along with information of tissue weights, reference arterial blood volumes, withdrawal times and radioactive count totals, was processed by a digital computer (PDP-11/40, Digital Equipment Corp.). Background and crossover counts were corrected and simultaneous equations solved for sample flow values. Program subroutines allowed assembly of samples according to the presence of the final intracoronary microsphere.

Sections in the distribution of the LAD, which were labeled with the intracoronary spheres, were designated as LAD. Unlabeled sections in the distribution of the left circumflex coronary artery (LCF) were designated as LCF, a control zone. The simultaneous blood flows of each of these two zones was compared as a ratio, i.e., LAD/LCF, to evaluate the effect of each intervention. This technique corrects for any temporal variation in systemic factors that could influence myocardial blood flow. Such influences would simultaneously affect both perfused and nonperfused zones of myocardium. This is an important consideration in an awake animal, particularly during the prolonged phenylephrine infusion.

To determine a mean flow for each zone, individual section flows within each zone were multiplied by individual section weights, summed and divided by the total weight of the composite zone.

Four null hypotheses were tested statistically: No
true differences existed in heart rate, blood pressure or myocardial blood flow during the intracoronary administration of (1) saline bolus vs phenylephrine bolus (50–100 μg); (2) saline infusion vs phenylephrine infusion (5–10 μg/min) vs phenylephrine infusion (50–100 μg); (3) phenylephrine infusion (50 μg/min) alone vs phenylephrine infusion plus superimposed phenylephrine bolus (50–100 μg); and (4) saline infusion vs saline infusion during IV adenosine vs phenylephrine infusion (50–100 μg/min) during i.v. adenosine. Hypotheses 1 and 3 involved one treatment with paired observations, so we used the t test for paired samples. Hypotheses 2 and 4 were tested by two-way analysis of variance. Pigs were considered as a second factor in order to remove the influence of interanimal differences. Tukey's method was used to compare multiple means if analysis of variance confirmed that at least one pair of means was significantly different.

Results

Effects of Intracoronary Phenylephrine as a Bolus Injection

After phenylephrine bolus, six of the eight pigs had reduced myocardial blood flow within the distribution of the LAD. This change, however, was not statistically significant (table 1). LAD/LCF, however, declined in every pig, with a significant (p < 0.01) reduction for the group, from 1.02 ± 0.08 (mean ± sp) to 0.92 ± 0.08 (fig. 1). No change was noted in the transmural distribution of blood flow within either zone. Mean arterial blood pressure increased slightly after the administration of intracoronary phenylephrine because of a mild systemic effect in some pigs. A small but significant reduction in LAD/LCF, 1.00 ± 0.06 to 0.94 ± 0.08 (p < 0.05), also occurred in the five pigs that received a phenylephrine bolus during a sustained infusion.

Effect of Intracoronary Phenylephrine as a Sustained Infusion

After the two 15-minute periods of intracoronary phenylephrine infusion, no change was observed in blood flow to either perfused or nonperfused myocardium (table 2). Neither LAD/LCF (fig. 1) nor the endocardial/epicardial flow ratio within either zone was affected. Arterial blood pressure was unchanged at 5–10 μg/min but increased significantly at 50–100 μg/min. The heart rate was unchanged.

Effect of Intracoronary Phenylephrine Administered as a Sustained Infusion After Pretreatment with I.V. Adenosine

Intravenous adenosine reduced mean arterial blood pressure, from 132 ± 10 to 105 ± 12 mm Hg, and elevated heart rate (table 3). Blood flow to myocardium in the distribution of both the LAD and LCF increased significantly without changing LAD/LCF (fig. 2). During adenosine, the sustained infusion of intracoronary phenylephrine (50 μg/min) decreased LAD/LCF in each pig (fig. 2).

Discussion

In this investigation brief alpha-adrenergic stimulation caused coronary vasoconstriction and a reduction in myocardial blood flow. After the bolus injection of
TABLE 2. Effect of Sustained Intracoronary Phenylephrine Infusion

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Phenylephrine (µg/min)</th>
<th>Phenylephrine 5-10</th>
<th>Phenylephrine 50-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial blood flow (ml/100 g/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>140 ± 42</td>
<td>143 ± 48</td>
<td>163 ± 50</td>
<td></td>
</tr>
<tr>
<td>LCF</td>
<td>139 ± 45</td>
<td>139 ± 54</td>
<td>153 ± 50</td>
<td></td>
</tr>
<tr>
<td>LAD/LCF</td>
<td>1.02 ± 0.08</td>
<td>1.03 ± 0.12</td>
<td>1.09 ± 0.16</td>
<td></td>
</tr>
<tr>
<td>Endocardial/epicardial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>1.08 ± 0.07</td>
<td>1.09 ± 0.07</td>
<td>1.08 ± 0.08</td>
<td></td>
</tr>
<tr>
<td>LCF</td>
<td>1.12 ± 0.03</td>
<td>1.13 ± 0.07</td>
<td>1.15 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>115 ± 21</td>
<td>114 ± 15</td>
<td>126 ± 12 *</td>
<td></td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>97 ± 25</td>
<td>101 ± 30</td>
<td>99 ± 29</td>
<td></td>
</tr>
</tbody>
</table>

Values are mean ± sd.
LAD and LCF refer to values within the distribution of the left anterior descending and left circumflex coronary arteries.
*p < 0.05 comparing values of phenylephrine, 50-100 µg/min, to control and phenylephrine, 5-10 µg/min.

phenylephrine in the LAD, myocardial blood flow in the distribution of that vessel was consistently reduced compared with flow in the LCF distribution. The magnitude of flow reduction was mild and was not accompanied by an alteration in transmural flow distribution. However, the radioactive microsphere technique probably underestimates peak change in flow during short-lived interventions. The actual flow reduction after bolus phenylephrine may have been greater.

Coronary vasoconstriction following brief alpha-adrenergic stimulation has also been shown using norepinephrine and the carotid sinus reflex. In both anesthetized and conscious beta-blocked animals, brief administration of either i.v. or intracoronary norepinephrine elevates coronary vascular resistance.14 Furthermore, in the anesthetized closed-chest dog, carotid sinus hypotension (1.5-3 minutes) also increases coronary vascular resistance, an action judged independent of changes in myocardial metabolism or aortic blood pressure. Conversely, both electrical stimulation of the carotid sinus nerve and left stellectomy causes coronary vasodilatation, attributed to withdrawal of alpha-adrenergic tone.15, 16

The degree to which brief alpha-adrenergic stimulation can influence the coronary circulation is important. In the conscious dog, norepinephrine administered as an i.v. bolus not only increases coronary vascular resistance, but also reduces coronary sinus oxygen concentration. Furthermore, in the anesthetized dog, both intracoronary norepinephrine and carotid sinus reflex-induced coronary vasoconstriction is capable of restricting increases in coronary blood flow anticipated from augmented myocardial metabolism. Thus, brief alpha-adrenergic stimulation is capable of causing coronary vasoconstriction of

FIGURE 2. Effect of a sustained intracoronary infusion of phenylephrine (PHEN) during i.v. adenosine. Values are mean ± sd. LAD/LCF = ratio of simultaneous myocardial blood flow distribution of left anterior descending coronary artery and left circumflex artery.
sufficient magnitude to counteract metabolically mediated coronary vasodilatation.

In this investigation, the effect of sustained alpha-adrenergic stimulation on the coronary circulation contrasted sharply with that of brief stimulation. Myocardial blood flow in the distribution of the LAD was similar to LCF flow during sustained phenylephrine infusion. Thus, sustained alpha-adrenergic stimulation did not result in coronary vasoconstriction sufficient to decrease myocardial blood flow.

An alternative explanation is that phenylephrine, infused into the anterior descending coronary artery, recirculated and caused vasoconstriction of the circumflex vasculature. Systemic “spillover” may have occurred at the high (50–100 μg/min) dose because arterial blood pressure increased. However, this explanation requires a precisely balanced vasoconstrictive effect upon both the LAD and LCF vascular beds. Such an effect is unlikely in view of the great disparity in the concentrations of phenylephrine in the two vascular beds. Furthermore, phenylephrine administered at 5–10 μg/min was not associated with any systemic effect such that its coronary action could reasonably be considered limited to LAD vasculature. It is also unlikely that the absence of vasoconstriction after the sustained infusion was caused by receptor saturation because myocardial blood flow fell in each pig when a phenylephrine bolus was superimposed on the sustained infusion. Thus, responsiveness of the coronary circulation to brief vs sustained alpha-adrenergic stimulation differs. In the steady-state condition, myocardial blood flow is not decreased and indicates a potent ability of the coronary circulation to offset the vasoconstrictor influences of chronic alpha stimulation.

The ability of regional vascular beds, including the coronary circulation, to develop tolerance to vasoconstrictor agents has been observed by others. A sustained norepinephrine infusion into the superior mesenteric artery of the anesthetized cat initially reduces mesenteric flow, but by the fifth minute, flow returns to control values. In the anesthetized, perfused dog, intracoronary angiotensin initially increases resistance in both small and large vessels. Continued infusion, however, maintains constriction of large vessels, but small vessels demonstrate tachyphylaxis and resistance falls. Redistribution of blood flow has been postulated as one mechanism of vascular compensation for sustained vasoconstriction. Such a mechanism is an unlikely explanation for the observations reported in this investigation, because no change was observed in myocardial transmural flow distribution during the sustained infusion.

After the i.v. administration of adenosine, the vasoconstrictor potential of sustained alpha stimulation was unmasked. Intravenous adenosine, as expected, increased blood flow to myocardium in the distribution of both the LAD and LCF. Considering the large increase in myocardial blood flow, the small changes in heart rate and blood pressure (table 3) suggest that the increase in flow was most likely attributable to adenosine-induced coronary vasodilatation. In this setting, sustained phenylephrine infusion reduced myocardial blood flow in each pig in the perfused as compared with the nonperfused zones. Thus, sustained alpha stimulation caused coronary vasoconstriction in the setting of excessive myocardial oxygen supply.

Although the coronary circulation autoregulates flow in close relationship to myocardial oxygen need, this capability may be time-dependent and could account for the different effects of brief vs sustained alpha-adrenergic stimulation. Brief alpha stimulation acutely augments basal alpha-constrictor tone enough to reduce myocardial blood flow. During sustained stimulation, on the other hand, a steady state develops in which metabolically mediated vasodilatation can fully offset vasoconstrictive effects. When an additional pulse of alpha stimulation is superimposed on this background, transient disequilibrium again results and myocardial blood flow is transiently reduced. When myocardium is overperfused, the constrictive potential of sustained stimulation is unmasked. Understandably, autoregulation is less of a modifying factor when there is an excess of myocardial blood flow (oxygen supply). Moderate vasoconstriction in this circumstance does not jeopardize myocardial oxygenation and the defensive response is unnecessary.

This interaction between alpha-adrenergic vasoconstriction and metabolically regulated vasodilatation in modifying myocardial blood flow may have significant clinical implications. In patients with significant coronary artery disease, coronary vascular resistance increases during the cold pressor test. In some instances, coronary flow may fall. This response can be blocked by phentolamine. Normal persons show no change in coronary vascular resistance after the cold pressor test. Mudge et al. postulate that in patients with proximal coronary obstruction, vasodilatory reserve has been exhausted such that neurally mediated alpha vasoconstriction is unopposed and coronary resistance rises. In normal subjects, however, metabolic vasodilatory reserve is intact and is capable of resisting the vasoconstrictive stimulus.

Thus, the responsiveness of the coronary circulation to alpha-adrenergic stimulation may be variable. Changes in blood flow are a result of the opposing actions of alpha receptor-induced vasoconstriction and metabolic mediated vasodilatation. If stimulation is abrupt, vasoconstriction is evident. Sustained stimulation, on the other hand, does not reduce myocardial blood flow if vasodilatory reserve is functional. If vasodilatory reserve is exhausted or the coronary vasculature pharmacologically vasodilated, sustained alpha-adrenergic stimulation can result in myocardial blood flow reduction.

Acknowledgment

We gratefully acknowledge the technical assistance of Thomas DeVona, Lorraine Schofield, Luis Sousa and James O'Neil, and the secretarial assistance of Christine Abatiello and Katherine Seropian.
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Responsiveness of the coronary circulation to brief vs sustained alpha-adrenergic stimulation.
D O Williams and A S Most

Circulation. 1981;63:11-16
doi: 10.1161/01.CIR.63.1.11

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

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