**α-Adrenergic-Mediated Reduction in Coronary Blood Flow Secondary to Carotid Chemoreceptor Reflex Activation in Conscious Dogs**

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SUMMARY. We examined the late coronary vascular response to carotid chemoreceptor reflex activation in normal, conscious dogs instrumented for the measurement of right main and left circumflex coronary artery blood flows, arterial and right ventricular pressures, and arterial and coronary sinus blood gases and O₂ contents. With heart rate held constant by electrical stimulation, and with respiration controlled or allowed to vary spontaneously, carotid chemoreceptor reflex activation (induced by intracarotid nicotine) elicited a striking biphasic coronary vascular response characterized by an early dilation (previously described) and a late constriction. For example, with respiration controlled and with the autonomic nervous system intact, carotid chemoreceptor reflex activation resulted in a late increase in arterial pressure (19 ± 4%; \( P < 0.002 \)), absolute reductions in right main (24 ± 4%; \( P < 0.002 \)), and left circumflex (12 ± 2%; \( P < 0.004 \)) coronary blood flows, and increases in right (62 ± 13%; \( P < 0.002 \)) and left (26 ± 3%; \( P < 0.0001 \)) coronary resistances. This carotid chemoreceptor reflex activation-induced late coronary constriction was also associated with a concomitant increase in myocardial oxygen extraction, i.e., arterial oxygen content remained constant, while coronary sinus oxygen content decreased (19 ± 6%; \( P < 0.04 \)). Neither propranolol nor atropine had any significant effect on the magnitude of the right coronary constriction. However, both the absolute reduction in right coronary blood flow and increase in right coronary resistance were abolished by phentolamine. Furthermore, either total cardiac denervation or adrenalectomy significantly attenuated (\( P < 0.01 \)) carotid chemoreceptor reflex activation-induced reductions in right coronary blood flow and increase in right coronary resistance. We conclude that, with autonomic nervous system activity intact, carotid chemoreceptor reflex activation can elicit an absolute reflexly mediated reduction in coronary blood flow in the normal, conscious dog, despite an increase in arterial pressure. The mechanism of this vasoconstriction involves α-adrenergic receptor stimulation mediated by both cardiac sympathetic nerves and circulating catecholamines. (Circ Res 54: 96–106, 1984)

THERE NOW exists a relatively large body of experimental evidence which supports the concept that sympathetic activation can result in α-adrenergic coronary vasoconstriction. This concept is based primarily on experiments in which sympathetic activation has resulted in increases in arterial pressure which have been greater than concomitant increases in coronary blood flow, with a consequent increase in coronary resistance. It is somewhat surprising that despite recent interest in the role of coronary vasoconstriction in the pathogenesis of coronary artery vasospasm (Hillis and Braunwald, 1978; Maseri et al., 1978), there is little compelling evidence that α-adrenergic vasoconstriction can mediate an absolute reduction in coronary blood flow in the presence of an intact autonomic nervous system.

In the present investigation, our goal was to assess the reflex sensitivity of the coronary circulation to carotid chemoreceptor activation. Whereas this stimulus has been shown to result in profound reflex α-adrenergic constriction of peripheral vascular beds (Heistad et al., 1974; Rutherford and Vatner, 1978), it results in substantial left coronary vasodilation (Hackett et al., 1972; Vatner and McRitchie, 1975). However, we tested the hypothesis that—in addition to the early period of coronary dilation—this stimulus also results in a later period of coronary artery vasoconstriction, as has been demonstrated recently in the cerebral circulation (Vatner et al., 1980b). Because the canine right coronary circulation normally supplies only the right ventricle (Murray and Vatner, 1980), this vascular bed provides a useful experimental model for the direct assessment of reflex sensitivity of the coronary circulation without the potentially confounding metabolic vasodilator influences associated with sympathetic activation (Murray and Vatner, 1981b). Specifically, increases in preload and afterload, which characterize the left ventricular response to carotid chemoreceptor stimulation (Vatner and Rutherford, 1978) and result in metabolically induced left coronary vasodilation, would be expected to be less prominent in the right ventricular response to carotid chemoreceptor reflex stimulation. This should allow clearer
expression of reflex vasoconstrictor action on the right coronary circulation, since competing metabolic vasodilator influences would play a less prominent role.

Methods

Surgical Preparation and Instrumentation

Twenty-eight conditioned, mongrel dogs of either sex (free of microfilaria) were tranquilized (propiomazine HCl, 0.1 mg/kg, im), anesthetized (sodium pentobarbital, 30 mg/kg, iv), and, after intubation, were artificially ventilated and prepared for sterile surgery. Through a right thoracotomy in the 4th intercostal space, heparin-filled Tygon catheters (Norton Co.) were implanted in the aorta and right ventricle. A 2-cm segment of the right main coronary artery was dissected in a retrograde direction from the right marginal artery branch to the aortic origin for placement of a Doppler ultrasonic flow transducer and a distal inflatable hydraulic occluder [4 mm inside diameter (Jones Co.)]. Pacing electrodes were sutured to the surface of the right atrium and right ventricle. In nine dogs, a solid state pressure transducer (Köningsberg Instruments, Inc.) was inserted into the right ventricular cavity via a stab wound in the mid- anterior free wall and secured with a purse-string suture. A second thoracotomy was performed at a later date through the 5th left intercostal space in six dogs for placement of a Doppler ultrasonic flow transducer and hydraulic occluder on the left circumflex coronary artery (approximately 2 cm distal to the bifurcation of the left main coronary artery), and a catheter in the coronary sinus (five dogs). A second thoracotomy was performed at a later date in six additional dogs to perform an intrapericardial denervation (Randall et al., 1980). In brief, this technique consists of stripping the adventitia from the main pulmonary artery, left superior pulmonary vein, right pulmonary artery, resection of pericardial reflections in the transverse sinus, and around the superior vena cava and section of the left ventrolateral cardiac nerve. The adequacy of denervation was tested at operation by establishing no response to stellate ganglion stimulation and, later, in the conscious dog, by finding no tachycardia in response to iv nitroglycerin, 25 μg/kg. Finally, measurement of norepinephrine in the left ventricular cavity demonstrated extremely low levels of norepinephrine, i.e., 3.38 ± 0.57 ng/g. Bilateral adrenalectomy followed this procedure and was also performed in four other intact animals. Replacement therapy following adrenalectomy was instituted with daily injections of deoxycorticosterone acetate (0.1 mg/kg) and hydrocortisone sodium acetate (1.0 mg/kg).

The distal ends of the catheters, hydraulic occluders, and implanted transducers were exteriorized via the lateral chest wall and tunneled subcutaneously to positions between the scapulae. All dogs were placed on a 10-day post-surgical regimen of antibiotics. Two to 4 weeks were allowed for recovery from the effects of the surgery.

Three days prior to actual experimentation, all dogs were reanesthetized with a short-acting barbiturate (sodium thiamyyl: 10 mg/kg, iv). Through a 5-cm cervical incision a heparin-filled Tygon catheter was inserted into one of the main carotid arteries via the thyroid artery such that the tip of the catheter was positioned just proximal to the carotid sinus. Utilizing this technique, both main carotid arteries remain patent (Vatner and McRitchie, 1975; Vatner and Rutherford, 1978; Rutherford and Vatner, 1978; Vatner et al., 1980b).

Experimental Measurements

Right main and left circumflex coronary artery blood flows were measured with a continuous wave Doppler ultrasonic flowmeter (Franklin et al., 1966). The accuracy and reliability of this method has been described previously in detail (Vatner et al., 1970). Right coronary artery flow probe calibration was performed at autopsy by pump-perfusing blood at a known rate through a catheter inserted into the right main coronary artery via the ostium with its tip proximal to the implanted flow probe. Aortic and right ventricular pressures were measured from the implanted catheters attached to Statham P23Db strain gauge manometers. High fidelity right ventricular pressure was measured from the implanted solid state transducers (Patrick et al., 1974; Baig et al., 1977), which were calibrated in vitro, and in vivo using the implanted right ventricular catheter. Arterial and coronary sinus pH, P02, and PCO2 were measured with a Radiometer acid base analyzer (PHM 71 MK 2) and blood microsystem (BMS 3 MK 2), respectively. Arterial and coronary sinus O2 contents were measured with a Lex-O2-Con-K oximeter (Lexington Instruments Corp.)

Experimental Protocols

Response to Carotid Chemoreceptor Reflex Activation (CCRA): Spontaneous Respiration

All experiments were performed in a dimly illuminated, quiet room with the unsedated conscious dog lying on its right side. The right (16 dogs) and left (five dogs) coronary responses to CCRA with an intact autonomic nervous system were assessed in this portion of the study. Heart rate was held constant (ventricular pacing) by electrical stimulation from an external pacemaker (Medtronic, Inc.) in all experiments. Following control measurements of all variables, CCRA was achieved by a bolus (1 ml total volume) injection of nicotine into the catheter chronically implanted in one of the main carotid arteries. Increasing doses of nicotine (range from 1 to 10 μg) were administered to determine the dose of nicotine required to achieve peak coronary vascular effects in each dog. This dose was subsequently used throughout the remainder of the study. Triplicate responses of the measured variables to CCRA (which in the conscious, spontaneously respiring dog also elicits the pulmonary inflation reflex) were then obtained. It has been determined previously (Vatner and McRitchie, 1975; Vatner and Rutherford, 1978; Vatner et al., 1980b) that the cardiovascular effects elicited by the intracarotid injection of nicotine in this dose range are entirely reflex in nature, because the nicotine-induced effects are abolished by ipsilateral carotid sinus nerve section. The integrated right coronary vascular response to combined carotid chemoreceptor and pulmonary inflation reflex activation was further assessed following the sequential intravenous administration of the β-adrenergic antagonist, propranolol HCl (1.0 mg/kg; 14 dogs), the cholinergic antagonists, atropine sulfate or atropine methyl bromide (0.1 mg/kg; 13 dogs), and the α-adrenergic antagonist, phentolamine HCl (2.0 mg/kg; 13 dogs). The adequacy of β-adrenergic blockade was tested with isoproterenol (1.0 μg/kg, iv), that of cholinergic blockade with acetylcholine (40 μg/kg, iv), and that of α-adrenergic blockade with norepinephrine (1.0 μg/kg, iv).
Response to Carotid Chemoreceptor Activation: Controlled Respiration

To assess the selective effects of CCRA on the measured variables and to avoid the potentially confounding influences of changes in intrathoracic pressure and arterial blood gases associated with pulmonary inflation reflex activation, the effects of intracarotid nicotine were assessed on a separate day when ventilation was controlled by a respirator during succinylcholine chloride infusion (0.1 mg/kg per min, iv). Prior to these experiments, this protocol was reviewed by the Animal Care Committee of the institution and found to conform to the guidelines for research in experimental animals. All dogs were lightly anesthetized with a short-acting barbiturate (sodium thiopental: 2.0 mg/kg, iv) before intubation and succinylcholine administration. The larynx was sprayed with a topical anesthetic (Cetacaine; Cetylite Industries) and the endotracheal tube was coated with a lidocaine paste. No intervention was performed which would not be fully tolerated by the conscious dog in the absence of succinylcholine. At the end of each experiment, the dogs were given an intramuscular injection of morphine sulfate (10 mg) as an analgesic.

The right (11 dogs) and left (six dogs) coronary response to selective CCRA, as well as changes in arterial and coronary sinus blood gases and O₂ contents, were first assessed with the autonomic nervous system intact. The right coronary response to intracarotid nicotine was further examined after the sequential intravenous administration (doses noted above) of propranolol (seven dogs), atropine (seven dogs), and phentolamine (six dogs). On a separate day, the right coronary response to intracarotid nicotine was examined again in eight dogs, but the order of the pharmacological antagonists was reversed, i.e., the response to intracarotid nicotine was assessed following the sequential intravenous administration of propranolol (six dogs) and phentolamine (six dogs). The right coronary response to intracarotid nicotine was examined in two dogs both before and after the administration of phentolamine alone. In a separate group of dogs, right coronary artery responses to intracarotid injections of nicotine were also examined in dogs with controlled respiration, before and after recovery from the cardiac denervation operation (n = 6) or bilateral adrenalectomy (n = 4). The six dogs with cardiac denervation were also evaluated after bilateral adrenalectomy.

Data Analysis

The experimental data (except arterial and coronary sinus blood gases and O₂ contents) were recorded on magnetic tape with a multichannel tape recorder (Honeywell model 5600 C) and played back onto a multichannel direct writing oscillograph (Gould-Brush). The maximal rate of change of right ventricular pressure (dp/dt max) was derived from the pressure signal with an operational amplifier (National Semiconductor, Inc.) connected as a differentiator. A triangular wave signal with known slope (rate of change) was substituted for the pressure signal for direct calibration of the differentiator. Mean aortic pressure, mean right coronary blood flow, and mean left circumflex coronary blood flow were derived using passive electronic filters with a 2-second time constant. Mean right coronary and left circumflex coronary resistances were calculated as the quotient of mean aortic pressure and mean right coronary or left circumflex coronary blood flow. A cardiotachometer triggered by the electrical signal from the aortic or ventricular pressure pulse provided instantaneous and continuous measurements of heart rate.

While measured variables were assessed continuously, data were collected—during the steady state, over at least a 30-second period prior to nicotine administration, and during the late nicotine-induced peak decrease in coronary blood flow. As described in the experimental protocols, the response to intracarotid nicotine was assessed (1) with the conscious dog breathing spontaneously and with autonomic nervous system activity intact, and after administration of propranolol, atropine and phentolamine, and (2) during controlled respiration with autonomic nervous system activity intact, and after administration of the various pharmacological antagonists and before and after cardiac denervation and bilateral adrenalectomy. Triplet responses to CCRA under each experimental condition were averaged so that the responses of all dogs and for each experimental condition were weighted equally. The data were stored and statistically analyzed with a PDP 11/34 computer (Digital Equipment Corp.). Student’s t-test for paired comparisons was utilized to assess the effects of CCRA on the measured variables (Snedecor and Cochran, 1969). Three-way analysis of variance (with the three-way interaction equal to zero) was utilized to assess...
sequential differences in the responses of the measured variables to intracarotid nicotine with autonomic nervous system activity intact, and following the various pharmacological blockades and following surgical denervation (Armitage, 1974). Values presented represent mean ± 1 SEM. Values of n throughout the text refer to the number of dogs.

**Results**

CCRA induced by the intracarotid injection of nicotine elicited a biphasic right coronary vascular response characterized by an early, rapid dilation, followed by a late, prolonged constriction (refer to Fig. 1). Because a similar early dilation in the left coronary circulation has been described previously (Hackett et al., 1972; Vatner and McRitchie, 1975), it will not be discussed in detail in the present study. Rather, the focus of the present study is on the later period of coronary constriction induced by CCRA.

**Late Right Coronary Vascular Response to Carotid Chemoreceptor Reflex Activation (CCRA)**

**Spontaneous Respiration**

*Autonomic Activity Intact.* When the conscious dog is allowed to change its respiration spontaneously, intracarotid nicotine activates both the carotid chemoreceptor and pulmonary inflation reflexes. The integrated right coronary vascular response to these reflex stimuli is illustrated in Figure 1 and summarized in Table 1. With heart rate held constant by electrical pacing (140 ± 5 beats/min), CCRA elicited a marked biphasic right coronary vascular response. The late response was characterized by a decrease ($P < 0.0001$) in right coronary blood flow (20 ± 3%) and an increase ($P < 0.0001$) in right coronary resistance (32 ± 6%). The decrease in right coronary blood flow occurred in all 16 dogs studied. During this late phase, arterial pressure was maintained, and CCRA had no significant effect on right ventricular hemodynamics when respiration was allowed to vary spontaneously (Table 2).

**$\beta$-Adrenergic Receptor Blockade.** With heart rate held constant at 136 ± 5 beats/min, $\beta$-adrenergic receptor blockade had no significant effect on baseline values of arterial pressure, right coronary blood flow, or right coronary resistance (Table 1). Moreover, the magnitude of both the CCRA-induced reduction ($P < 0.0001$) in right coronary blood flow (18 ± 3%) and increase ($P < 0.0009$) in right coronary resistance (34 ± 8%) was similar to that observed with autonomic neural activity intact (Table 1).

**$\beta$-Adrenergic and Cholinergic Receptor Blockades.** In the presence of atropine, it was necessary to hold heart rate constant at a higher level (176 ± 6 beats/min), compared with $\beta$-adrenergic receptor blockade alone, which probably accounts for the increase ($P < 0.01$) in baseline right coronary blood flow and decrease ($P < 0.05$) in baseline right coronary resistance (Table 1). However, CCRA still elicited a significant reduction ($P < 0.02$) in right coronary blood flow (10 ± 3%) and an increase ($P < 0.004$) in right coronary resistance (21 ± 6%), values which were slightly but not significantly less than those observed during $\beta$-adrenergic receptor blockade alone (Table 1).

**$\alpha$-Adrenergic Receptor Blockades.** Following $\alpha$-adrenergic receptor blockade and with heart rate constant at 163 ± 4 beats/min, baseline values for arterial pressure and right coronary blood flow were reduced ($P < 0.01$), and right coronary resistance was elevated ($P < 0.01$) compared with combined $\beta$-adrenergic and cholinergic blockades; i.e., these values returned to preatropine levels (Table 1). Moreover, after $\alpha$-adrenergic receptor blockade, CCRA failed to elicit a significant change in right coronary blood flow (1 ± 2%) or right coronary resistance (4 ± 3%; Table 1).

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Response</th>
<th>$\Delta$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
<td>109 ± 3</td>
<td>113 ± 4</td>
<td>4 ± 2</td>
<td>&lt;0.08</td>
</tr>
<tr>
<td>Mean right coronary blood flow (ml/min)</td>
<td>18.7 ± 0.8</td>
<td>14.9 ± 0.7</td>
<td>-3.8 ± 0.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean right coronary resistance (mm Hg/ml per min)</td>
<td>5.97 ± 0.34</td>
<td>7.84 ± 0.54</td>
<td>1.87 ± 0.36</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Symbols (*$P < 0.01$; †$P < 0.05$) indicate significant differences in measured variables before and after administration of each subsequent pharmacological antagonist. $P$ value represents probability that effects of carotid chemoreceptor reflex activation on the measured variables occurred by chance. NS is not significant ($P > 0.1$). Values in parentheses represent the number of dogs.
Late Right Ventricular Hemodynamic Response to Carotid Chemoreceptor Reflex Activation: Spontaneous and Controlled Respiration

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Response</th>
<th>Δ</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>Spontaneous respiration</strong></td>
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<td></td>
</tr>
<tr>
<td>Right ventricular systolic pressure (mm Hg)</td>
<td>Intact (8)</td>
<td>28.4 ± 1.0</td>
<td>29.7 ± 0.9</td>
<td>1.3 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>β-Block (7)</td>
<td>26.4 ± 1.0†</td>
<td>27.2 ± 1.5*</td>
<td>0.8 ± 0.6</td>
</tr>
<tr>
<td>Right ventricular end-diastolic pressure (mm Hg)</td>
<td>Intact</td>
<td>1.5 ± 0.5</td>
<td>1.8 ± 0.5</td>
<td>0.3 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>β-Block</td>
<td>2.4 ± 0.7*</td>
<td>2.8 ± 0.8*</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td>Right ventricular dP/dtmax (mm Hg/sec)</td>
<td>Intact</td>
<td>566 ± 39</td>
<td>601 ± 35</td>
<td>35 ± 26</td>
</tr>
<tr>
<td></td>
<td>β-Block</td>
<td>454 ± 31*</td>
<td>476 ± 30*</td>
<td>22 ± 13</td>
</tr>
<tr>
<td><strong>Controlled respiration</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Right ventricular systolic pressure (mm Hg)</td>
<td>Intact (9)</td>
<td>28.9 ± 0.9</td>
<td>32.1 ± 1.0</td>
<td>3.2 ± 0.9</td>
</tr>
<tr>
<td></td>
<td>β-Block (8)</td>
<td>27.3 ± 0.8</td>
<td>30.5 ± 1.4</td>
<td>3.2 ± 0.8</td>
</tr>
<tr>
<td>Right ventricular end-diastolic pressure (mm Hg)</td>
<td>Intact</td>
<td>2.6 ± 0.7</td>
<td>3.7 ± 0.7</td>
<td>1.1 ± 0.3</td>
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<tr>
<td></td>
<td>β-Block</td>
<td>3.4 ± 0.8†</td>
<td>4.5 ± 0.8*</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>Right ventricular dP/dtmax (mm Hg/sec)</td>
<td>Intact</td>
<td>599 ± 23</td>
<td>676 ± 40</td>
<td>77 ± 22</td>
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<tr>
<td></td>
<td>β-Block</td>
<td>525 ± 26*</td>
<td>552 ± 36*</td>
<td>24 ± 13</td>
</tr>
</tbody>
</table>

Symbols (* P < 0.01; † P < 0.05) indicate significant differences in measured variables between intact and β-block groups. P value represents probability that effects of carotid chemoreceptor reflex activation on the measured variables occurred by chance. NS is not significant (P > 0.1). Values in parentheses represent the number of dogs.

**Controlled Respiration**

*Autonomic Activity Intact.* With respiration controlled, intracarotid nicotine elicits selective CCRA; i.e., pulmonary inflation reflex activation is prevented. The right coronary vascular response to selective CCRA is illustrated in Figure 2, and the data are summarized in Table 3. Heart rate was held constant at 135 ± 6 beats/min. Despite a significant increase (P < 0.002) in arterial pressure (19 ± 4%), selective CCRA elicited a significant reduction (P < 0.002) in right coronary blood flow (24 ± 4%), resulting in a concomitant increase (P < 0.002) in right coronary resistance (62 ± 13% Table 3). Right ventricular systolic and end-diastolic pressures and right ventricular dP/dtmax all increased (P < 0.003) slightly in response to CCRA during controlled respiration (Table 2).

**β-Adrenergic Receptor Blockade.** With heart rate constant at 128 ± 5 beats/min, propranolol administration slightly increased (P < 0.05) baseline right coronary resistance, but had no significant effect on the magnitude of the selective CCRA-induced decrease (P < 0.04) in right coronary blood flow (19 ± 5%) or increase (P < 0.01) in right coronary resistance (54 ± 12%) compared with autonomic activity intact (Table 3).

**α- and β-Adrenergic Receptor Blockades.** With heart rate constant at 133 ± 6 beats/min, α-adrenergic receptor blockade completely abolished the selective CCRA-induced increase in arterial pressure (4 ± 3%), decrease in right coronary blood flow (1 ± 1%), and increase in right coronary resistance (6 ± 4%; Table 3).

When the experiments were repeated on a separate day, cholinergic receptor blockade also had no significant effect on the magnitude of the selective CCRA-induced right coronary constriction, whereas this response was once again abolished following α-adrenergic receptor blockade (Fig. 3). In two additional dogs right coronary blood flow decreased 17 and 20%, and right coronary resistance increased 41 and 45%, respectively, during the late response to CCRA. After selective α-adrenergic receptor blockade, both the CCRA-induced reduction in right coronary blood flow and increase in right coronary resistance were abolished.

**Cardiac Denervation and Bilateral Adrenalectomy.** In a separate group of dogs, cardiac denervation alone or in combination with bilateral adrenalectomy also reduced (P < 0.05) the late right coronary vasoconstrictor response to CCRA (Table 4). Cardiac denervation alone diminished both the decrease in right coronary blood flow (36 ± 4% to 14 ± 4%, P < 0.01) and the increase in right coronary resistance (66 ± 11% to 29 ± 8%, P < 0.05) in response to CCRA. Cardiac denervation in combination with bilateral adrenalectomy abolished the CCRA-induced decrease in right coronary blood flow (~5 ± 2%) and further attenuated the increase in right coronary resistance to 21 ± 3%.

Bilateral adrenalectomy alone also diminished the right coronary vasoconstrictor response to CCRA in a separate group of dogs. Before adrenalectomy, CCRA reduced right coronary blood flow (32 ± 6% from 18 ± 3 ml/min; P < 0.01) and increased right coronary resistance (73 ± 23% from 7.58 ± 0.77 mm Hg/ml per min, P < 0.01). After adrenalectomy, both the CCRA-induced decrease in right coronary blood flow (20 ± 6% from 14 ± 2 ml/min) and
increase in right coronary resistance (44 ± 16% from 8.98 ± 0.99 mm Hg/ml per min) were attenuated significantly (P < 0.05).

Late Left Coronary Vascular Response to CCRA

As summarized in Table 5, in contrast to the right coronary circulation, when respiration was allowed to vary, CCRA elicited only a slight reduction (P < 0.004) in left circumflex coronary blood flow (6 ± 1%), but no change in left circumflex coronary resistance (2 ± 6%). However, with respiration controlled (i.e., no pulmonary inflation reflex), selective CCRA induced a significant increase (P < 0.02) in arterial pressure (11 ± 3%), a decrease (P < 0.004) in left circumflex blood flow (12 ± 2%), and an increase (P < 0.0001) in left circumflex coronary resistance (26 ± 3%) (Fig. 4).

Late Effects of Selective CCRA on Arterial and Coronary Sinus Blood Gases and O2 Content

As summarized in Table 6, with respiration controlled, selective CCRA had no detectable effect on arterial or coronary sinus blood gases except for a slight decrease (13 ± 5%, P < 0.06) in coronary sinus Po2 during the period of peak right and left coronary

<table>
<thead>
<tr>
<th>Table 3 Late Right Coronary Vascular Response to Carotid Chemoreceptor Reflex Activation: Controlled Respiration</th>
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<tbody>
<tr>
<td><strong>Control</strong></td>
</tr>
<tr>
<td>Mean aortic pressure (mm Hg)</td>
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<tr>
<td>Mean right coronary blood flow (ml/min)</td>
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<td>Mean right coronary resistance (mm Hg/ml per min)</td>
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Symbols (*P < 0.01; †P < 0.05) indicate significant differences in measured variables before and after administration of each subsequent pharmacological antagonist. P value represents probability that effects of carotid chemoreceptor reflex activation on the measured variables occurred by chance. NS is not significant (P > 0.1). Values in parentheses represent number of dogs.
Late Right Coronary Vascular Response to Carotid Chemoreceptor Reflex Activation: Effects of Cardiac Denervation and Bilateral Adrenalectomy

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
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<tbody>
<tr>
<td>Right coronary flow</td>
<td></td>
<td></td>
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<tr>
<td>(ml/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>17.2 ± 1.1</td>
<td>-35.7 ± 3.5</td>
</tr>
<tr>
<td>Cardiac denervation</td>
<td>16.0 ± 1.4</td>
<td>-13.5 ± 4.3*</td>
</tr>
<tr>
<td>Cardiac denervation and adrenalectomy</td>
<td>13.9 ± 1.9</td>
<td>-4.6 ± 1.5*</td>
</tr>
<tr>
<td>Right coronary resistance (mm Hg/ml per min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>7.34 ± 0.69</td>
<td>+66.4 ± 10.7</td>
</tr>
<tr>
<td>Cardiac denervation</td>
<td>7.02 ± 0.57</td>
<td>+29.2 ± 7.7†</td>
</tr>
<tr>
<td>Cardiac denervation and adrenalectomy</td>
<td>7.84 ± 1.13</td>
<td>+21.3 ± 2.5*</td>
</tr>
</tbody>
</table>

Different from intact: * (P < 0.01); † (P < 0.05).

Discussion

Our most important finding was that carotid chemoreceptor reflex activation (CCRA) resulted in a significant, late, absolute reduction in coronary blood flow despite the presence of an intact autonomic nervous system. The reduction in right coronary blood flow was observed in the presence or absence of a CCRA-induced pulmonary inflation reflex. An absolute reduction in coronary blood flow also occurred despite a concomitant increase in arterial pressure during selective CCRA. Moreover, this CCRA-induced coronary constriction was temporally related to a significant reduction in both coronary sinus O₂ content and O₂ tension. Finally, both the decrease in right coronary blood flow and increase in right coronary resistance induced by CCRA were attenuated by either cardiac denervation or bilateral adrenalectomy and entirely abolished by α-adrenergic blockade.

Despite the striking attenuation by α-adrenergic receptor blockade on the magnitude of the right coronary constrictor response to CCRA, it is important to assess other possible mechanisms which alternatively could be responsible for the observed response. The decrease in right coronary blood flow was clearly not the result of a decrease in coronary perfusion pressure, since perfusion pressure was actually increased relative to control during the late response to selective CCRA with respiration controlled. Heart rate was held constant by ventricular pacing. Control values are at the base of the bars. Symbols represent significant changes in the measured variables from control levels. With autonomic nervous system activity intact, selective CCRA resulted in a late absolute reduction in left circumflex coronary blood flow and an increase in resistance, and a concomitant increase in myocardial O₂ extraction and decrease in coronary sinus O₂ content. Values are mean ± SEM.

Late Left Circumflex Coronary Vascular Response to Carotid Chemoreceptor Reflex Activation: Spontaneous and Controlled Respiration

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Response</th>
<th>Δ</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean aortic pressure</td>
<td>Spontaneous respiration (5)</td>
<td>103 ± 2</td>
<td>103 ± 3</td>
<td>0 ± 2</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>Controlled respiration (6)</td>
<td>112 ± 6</td>
<td>123 ± 4</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>Mean left circumflex coronary blood flow (ml/min)</td>
<td>Spontaneous respiration</td>
<td>39.5 ± 3.3</td>
<td>37.3 ± 3.2</td>
<td>-2.2 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>Controlled respiration</td>
<td>40.3 ± 2.6</td>
<td>35.4 ± 2.0</td>
<td>-4.9 ± 0.9</td>
</tr>
<tr>
<td>Mean left circumflex coronary resistance (mm Hg/ml per min)</td>
<td>Spontaneous respiration</td>
<td>2.61 ± 0.28</td>
<td>2.60 ± 0.12</td>
<td>-0.01 ± 0.21</td>
</tr>
<tr>
<td></td>
<td>Controlled respiration</td>
<td>2.77 ± 0.20</td>
<td>3.46 ± 0.20</td>
<td>0.69 ± 0.05</td>
</tr>
</tbody>
</table>

P value represents probability that effects of carotid chemoreceptor reflex activation on the measured variables occurred by chance. NS is not significant (P > 0.1). Values in parentheses represent number of dogs.
response to CCRA with respiration controlled. It is also unlikely that the CCRA-induced decrease in right coronary blood flow was the result of an increase in systolic extravascular compressive forces (Sabiston and Gregg, 1957). Unlike the left coronary circulation, significant perfusion of the normal right coronary artery occurs during both diastole and systole (Lowensohn et al., 1976; Murray and Vatner, 1981a), indicating that the effects of systolic extravascular compression are less prominent in the right coronary circulation. Moreover, the degree of systolic extravascular compression is largely dependent on levels of heart rate, ventricular inotropy, and afterload. In this regard, heart rate was held constant throughout these experiments, and the reduction in right coronary blood flow was observed during spontaneous respiration, when the small CCRA-induced increases in right ventricular afterload (as reflected by right ventricular systolic pressure) and contractility (right ventricular dP/dtmax) observed during controlled respiration were not apparent. Certainly the fall in right coronary blood flow was not the result of a decrease in diastolic perfusion time, since heart rate remained constant.

It could be argued that a decrease in O2 demand secondary to the early, marked increase in coronary blood flow in response to CCRA was responsible for the late reduction in coronary blood flow. However, this appears to be an unlikely explanation in view of the late reduction in coronary sinus O2 content and PO2 concomitant with the decreased level of blood flow. It is also clear that neither direct nor indirect sympathetic (β1 or β2) nor parasympathetic influences on the coronary vasculature were responsible for the right coronary constriction, because the response was observed following propranolol and atropine administration. Propranolol administration also did not have the effect of potentiating the CCRA-induced right coronary vasoconstriction. This is likely due to the fact that, with heart rate held constant and with only minor changes in right ventricular hemodynamics occurring during the late response to CCRA (Table 2), β-adrenergic-mediated coronary vasodilator influences were minimal, and no further enhancement in the magnitude of the right coronary constriction would be predicted following β-adrenergic receptor blockade.

Thus, it appears that the CCRA-induced reflex decrease in right coronary blood flow is the result of either neurally or humorally mediated α-adrenergic coronary vasoconstriction. Humoral mechanisms potentially responsible for the coronary vasoconstriction include high levels of circulating norepinephrine of adrenal origin or due to spillover from neurally released norepinephrine in peripheral vascular beds. Based upon the observations made in dogs with either total cardiac denervation or adrenalectomy, the present study clearly indicates that neurally released as well as circulating catecholamines derived from the adrenals are responsible for the right coronary vasoconstriction following CCRA. Both procedures were demonstrated to attenuate significantly the late reductions in right coronary blood flow and increases in resistance induced by CCRA. Since, after cardiac denervation and adrenalectomy, reductions in right coronary blood flow were trivial, and since phentolamine abolished right coronary vasoconstriction, the present findings strongly support the concept that coronary vasoconstriction can be elicited through endogenous release of catecholamines activating coronary α-adrenergic receptors.

Carotid chemoreceptor-induced reflex vasoconstriction of peripheral vascular beds achieved either by the intracarotid injection of nicotine (Heistad et al., 1974) or by perfusion with hypoxic, hypercapnic blood (Mancia, 1975) has been shown to be inhibited by an increase in arterial baroreceptor activity. This attenuating influence of arterial hypertension was not apparent in the present study, in that the magnitude of the CCRA-induced reduction in right coronary blood flow was well-maintained during con-
controlled respiration, despite a significant CCRA-induced increase in arterial pressure. However, when respiration is controlled, the coronary vasodilator influence associated with pulmonary inflation reflex activation is abolished. Thus, the failure of arterial hypertension to attenuate the magnitude of the absolute reduction in right coronary blood flow in response to CCRA during controlled respiration is most likely due to the elimination of the vasodilator influence associated with pulmonary inflation reflex activation (Vatner and McRitchie, 1975; Daly and Hazzledine, 1963; Daly et al., 1967; Daly and Robinson, 1968).

The pulmonary inflation reflex appears to have completely masked the late period of CCRA-induced left coronary vasoconstriction. However, with respiration controlled, CCRA elicited a significant, late decrease in left circumflex coronary blood flow and an increase in left circumflex coronary vascular resistance. This left coronary constriction was associated with a concomitant decrease in coronary sinus O₂ content and O₂ tension. Hashimoto et al. (1964) also reported a slight (7%) reduction in left coronary blood flow in response to large doses (20–100 μg) of intracarotid nicotine in a fibrillating, isolated dog heart preparation. However, neither the significance nor the mechanism of action responsible for this change in left coronary blood flow was identified in that study.

The concept that the coronary vasculature has the capacity to respond to sympathetic α-adrenergic activation elicited by direct electrical stimulation of sympathetic nerves to the heart (Berne et al., 1965; Granata et al., 1965; Feigl, 1967; Ross and Mulder, 1969; McRaven et al., 1971; Nayler and Carson, 1973; Feigl, 1975) or by the exogenous administration of α-adrenergic agonists (Vatner et al., 1974; Mohrman and Feigl, 1978) is firmly established. Recent evidence also indicates that α-adrenergic activation can reduce the diameter of large coronary arteries (Gerova et al., 1979; Vatner et al., 1980a). Carotid sinus hypotension (Feigl, 1968; Bond and Green, 1969; DiSalvo et al., 1971; Mohrman and Feigl, 1978; Powell and Feigl, 1979) has also been shown to result in sympathetic α-adrenergic-mediated changes in left coronary resistance in the presence of β-adrenergic receptor blockade. Whereas reflex α-adrenergic constriction of the right coronary circulation in conscious dogs has been demonstrated with autonomic nervous system activity intact (Murray and Vatner, 1981b), an absolute reduction in right coronary blood flow was not observed during carotid sinus hypotension. Reflex sympathetic α-adrenergic activation has also been shown to play a significant role in the coronary vascular response to free-ranging, maximal exercise (Murray and Vatner, 1979), as well as static exercise (Aung-Din et al., 1981). Initial, transient reductions in either mean or stroke left coronary blood flow followed by pronounced coronary vasodilation have been reported in intact, conscious dogs in response to electrical stimulation of the stellate ganglion (Granata et al., 1965), noise and excitement (Rayford et al., 1965), and behavioral stress (Bergamaschi et al., 1973; Billman and Randall, 1981). However, the mechanisms responsible for the transient decrease in coronary blood flow were not investigated in those earlier studies (Granata et al., 1965; Rayford et al., 1965), and concomitant changes in heart rate and arterial pressure make it difficult to ascertain the extent to which sympathetic α-adrenergic constriction was involved in the coronary vascular response. Significant decreases in left coronary blood flow in response to behavioral stress were observed only in the presence of β-adrenergic receptor blockade (Billman and Randall, 1981).

The concept of coronary artery vasoconstriction is attracting increasing clinical interest as a possible mechanism, not only for Prinzmetal's variant angina (Prinzmetal et al., 1959; Hillis and Braunwald, 1978; Maseri et al., 1978), but, also, for typical angina pectoris and myocardial infarction (Hillis and Braunwald, 1978; Maseri et al., 1978). One possible mechanism for coronary vasoconstriction is activation of α-adrenergic receptors. In this regard, patients with ischemic heart disease have been shown to be more susceptible to α-adrenergic-mediated increases in coronary resistance in response to the cold pressor test (Mudge et al., 1976), even in the presence of a superimposed increase in myocardial metabolic demand induced by atrial pacing (Mudge et al., 1979).

However, the results of the present study provide compelling evidence that sympathetic α-adrenergic activation can result in an absolute reflex reduction in coronary blood flow in the presence of an intact autonomic nervous system.

Several recent studies (Bellamy, 1978; Ellis and Klocke, 1980) which have examined instantaneous diastolic coronary artery pressure-flow relationships indicate that the zero-flow pressure, i.e., the back pressure to flow through the coronary circulation, may be variable and significantly greater than coronary venous or right atrial pressure. Although interpretation of these instantaneous coronary artery pressure-flow curves may be confounded by changes in coronary resistance (Dole and Bishop, 1982) and coronary capacitance (Eng et al., 1982) during diastole, it is apparent that interpretation of changes in coronary arteriolar caliber for calculations of coronary resistance as the quotient of aortic pressure and coronary blood flow are subject to limitation. However, it must be emphasized that the major finding of this study was that CCRA elicited a late, absolute reduction in coronary blood flow despite a concomitant increase in arterial pressure and only minor changes in right ventricular hemodynamics with autonomic nervous system activity intact, and this coronary response was markedly reduced by both cardiac denervation and bilateral adrenalectomy and was entirely abolished by α-adrenergic blockade.

In conclusion, CCRA, which classically has been
thought to redistribute blood flow from peripheral vascular beds to vital organs like the heart, has been shown to result not only in an early period of coronary dilation (previously described) but, also, in a later period of coronary constriction. The late period of CCRA-induced coronary constriction is evidence that α-adrenergic activation by both sympathetic nerves and circulating catecholamines is sufficiently powerful to result in absolute reductions in coronary blood flow and coronary sinus O₂ content in the presence of an intact autonomic nervous system, and despite a concomitant increase in arterial pressure.

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