Vagal Chemoreflex Coronary Vasodilation Evoked by Stimulating Pulmonary C-Fibers in Dogs

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SUMMARY. We performed experiments on anesthetized, open-chest dogs to determine whether the pulmonary chemoreflex (bradycardia and systemic hypotension) evoked by stimulating pulmonary C-fibers also involves reflex changes in coronary vascular resistance. We perfused the circumflex coronary artery at constant pressure (usually 100 mm Hg) and recorded mean circumflex blood flow. Stimulation of pulmonary C-fibers by right atrial injection of capsaicin (10 µg/kg) decreased arterial blood pressure and heart rate and increased circumflex blood flow by 32–109% (P < 0.001). Circumflex blood flow also increased, by 26–100% (P < 0.001), when heart rate was kept constant by pacing. Coronary vasodilation was not secondary to the reflex decrease in arterial blood pressure. Injecting capsaicin (10 µg/kg) into the left atrium did not increase circumflex blood flow. Reflex coronary vasodilation could still be evoked when myelinated nerve fibers were blocked selectively by cooling the cervical vagus nerves to 7–8°C but was abolished by cooling to 0°C, by cutting the pulmonary vagal branches, or by giving atropine. Reducing coronary perfusion pressure shifted the stimulus (dose of capsaicin)-response (increase in coronary blood flow) curve to the right, but, even at low perfusion pressures, significant reflex vasodilation still occurred. Regional (transmural) distribution of myocardial blood flow was measured by the microsphere technique at various perfusion pressures. The endocardial:epicardial blood flow ratio decreased significantly as perfusion pressure was reduced, but was not altered by right atrial injection of capsaicin at any perfusion pressure. Our results indicate that stimulation of pulmonary C-fibers triggers reflex cholinergic vasodilation in all layers of the myocardium.

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THE existence of a parasympathetic vasodilator nerve supply to the coronary vascular bed was first demonstrated conclusively in dogs (Feigl, 1969). Feigl found that, when heart rate was kept constant by pacing, electrical stimulation of the peripheral cut ends of the cervical vagus nerves caused an increase in coronary blood flow that was prevented by atropine. Subsequent studies established that this vasodilator pathway is engaged reflexly when carotid body chemoreceptors are stimulated by cyanide or nicotine (Hackett et al., 1972), when carotid baroreceptors are stimulated by distending the sinus (Feigl, 1984), and, also, as part of the Bezold-Jarisch reflex, when afferent vagal nerve endings in the heart are stimulated by veratridine injected into the coronary circulation (Feigl, 1975).

We undertook these experiments to determine whether the cholinergic coronary vasodilator pathway can also be activated by stimulating chemosensitive vagal endings in the lung. Pulmonary C-fibers are known to be the afferents responsible for triggering the pulmonary chemoreflex (bradycardia, systemic hypotension, and various respiratory effects) observed when small doses of certain chemicals are injected into the pulmonary circulation (Coleridge and Coleridge, 1984). Because the pulmonary chemoreflex has cardiovascular effects in common with the Bezold-Jarisch (coronary) chemoreflex, it seemed likely that the two chemoreflexes could have similar effects on the coronary circulation.

We investigated coronary vasomotor changes by perfusing the circumflex coronary artery from a constant pressure reservoir and measuring changes in circumflex blood flow. We stimulated pulmonary C-fibers by injecting small doses of capsaicin into the right atrium (Coleridge et al., 1965). In some experiments, heart rate was kept constant by atrioventricular pacing to eliminate effects secondary to the reflex bradycardia. We also attempted to determine whether coronary vascular responses to stimulation of pulmonary C-fibers were affected by changing coronary perfusion pressure. Finally, we injected radioactive microspheres into the circumflex artery to determine whether the pulmonary chemoreflex involved changes in the distribution of blood flow between endocardial and epicardial layers of the myocardium.

Methods

General

Experiments were performed on 23 mongrel dogs (20–43 kg). Eighteen of the dogs were given promazine hydrochloride (25 mg, im) and were anesthetized with thiopen-
and cannula and connected to a flowmeter (Narcomatic of compressed air, controlled by a solenoid (Fairchild, cannulating electromagnetic transducer (Howell, model HSH 3)), to measure the coronary blood flow. In some experiments, we also compared the reflex effects on coronary flow evoked by lung C-fibers in the perfusion circuit between vagus nerves and the circumflex artery with a Statham strain gauge (P23Gb). If afferent input from the lungs was blocked, coronary vascular reserve was assessed at perfusion pressures of 35, 50, and 100 mm Hg, in random sequence. Coronary flow was measured with an external electromagnetic flowmeter (Howell, model HSH 2.5) placed around the vessel, which received its normal aortic blood supply.

**Measurement of Coronary Blood Flow**

The circumflex coronary artery was cannulated via the right common carotid artery and perfused from a constant pressure reservoir, flow into the circumflex artery being measured by a flowmeter. The right common carotid artery was separated from the vagosympathetic trunk. Sodium heparin (75 U/kg) was injected iv. Four milliliters of sodium heparin (75 U/kg) was injected iv; supplemental doses of heparin (10 mg/kg) were given hourly to maintain anesthesia. The remaining five dogs were anesthetized with 0.5% halothane. Results obtained with the two methods of anesthesia were identical and have been combined.

The trachea was intubated low in the neck and the chest was opened in the midsternal line. The lungs were ventilated with 50% O_2 by a Harvard ventilator (model 607), operating with a positive end-expiratory pressure of 3-5 cm H_2O; tidal volume was 15 ml/kg and ventilator frequency 10-15/min. Arterial blood gases and pH were measured periodically, and metabolic acidosis was corrected by giving sodium bicarbonate, iv.

Blood pressure in the thoracic aorta was measured with a catheter-tip transducer (Gaeltec 167/7FL) introduced via a femoral artery. Heart rate was recorded by a cardiometer triggered by the aortic pressure. The signals representing blood pressure, heart rate, and other variables described below (coronary perfusion pressure, coronary blood flow, and vagal temperature) were recorded on an eight-channel Beckman physiologic recorder (model R612).

In some experiments, we used an external pacemaker to keep heart rate constant, pacing the right atrium and ventricle at a rate 5-10 beats/min higher than the sinus rate, with a delay of 90 msec between atrial and ventricular pulses. In different dogs, the paced rates ranged from 120-180 beats/min.

**Interruption of Reflex Pathways**

Conduction in the right and left cervical vagus nerves was blocked reversibly by cooling (Franz and Iggo, 1968; Coleridge and Coleridge, 1984). Each vagus nerve was freed for about 3-4 cm from the carotid sheath and was placed in a groove on the platform of a silver cooling device through which alcohol of different temperatures was circulated. To reduce thermal gradients, the nerve and adjacent surface of the platform were covered with a warm (40°C) solution of 4% agar in saline, which, upon cooling, gelled to form a semi-solid layer 1 cm thick. The temperature of each platform was measured with a thermistor (Yellow Springs, model 729). In some experiments, we abolished afferent input from the lungs by cutting the pulmonary branches of the right and left vagus nerves. In others we blocked vagal effenter pathways by injecting atropine (1 mg/kg, iv).

**Coronary Perfusion at Different Pressures**

In most of the experiments, we examined the effects of injecting capsaicin into the right atrium while coronary perfusion pressure was maintained at 100 mm Hg. In some experiments we also compared the reflex effects obtained at different coronary perfusion pressures (35, 50, 75, and 100 mm Hg, in random sequence).

**Evaluation of Coronary Vasodilator Reserve**

In three dogs, we attempted to assess the proportion of coronary vascular reserve utilized during reflex coronary vasodilation, coronary vascular reserve being defined as the difference between coronary flow in the fully dilated...
vascular bed and coronary flow in the autoregulating bed (Hoffman, 1984). We first obtained the autoregulating curve, examining the pressure-flow relationship over a range of coronary perfusion pressures between 35 and 120 mm Hg. We then examined the coronary response to capsaicin at two different coronary perfusion pressures (usually 50 and 100 mm Hg). We next injected carboxymethyloxirane (10 mg/kg in 100 ml 0.9% saline, iv) to dilate the circumflex coronary vascular bed maximally; the presence of maximal vasodilation was confirmed after an interval of 15 minutes by the absence of reactive hyperemia when coronary perfusion was interrupted for 15 seconds. Finally, we examined the pressure-flow relationship to determine coronary vasodilator reserve.

Changes in Transmural Coronary Blood Flow

In seven dogs, we injected radioactive microspheres into the circumflex artery to determine whether the coronary vasodilation of the pulmonary chemoreflex was accompanied by changes in the transmural distribution of coronary blood flow. After being mixed vigorously, about 10^6 microspheres (15 µm in diameter) contained in 0.5 ml of saline were injected into the perfusion circuit through a side port located 2 cm upstream to the cannula. We confirmed in preliminary experiments that mixing of microspheres was adequate. To ensure that the distribution of microspheres within the myocardium coincided with the reflex coronary vasodilation, we timed the onset of microsphere injection into the perfusion circuit to coincide with the onset of capsaicin injection into the right atrium, prolonging the effects of capsaicin by injecting 20 µg/kg over a period of 10 seconds. The injection of microspheres took 5 seconds, and Belloni and Sparks (1977) and Hoff- man and Grattan (unpublished observations) have determined that when microspheres are injected into the coronary cannula, a maximum of 3 seconds is required for distribution in the myocardium. A total delay of 8 seconds between the beginning of the microsphere injection and the final distribution of microspheres in the myocardium corresponded to the interval between the beginning of capsaicin injection and the maximum vasodilator response (see Results). We measured the effect of capsaicin on the transmural distribution of circumflex coronary blood flow at four different coronary perfusion pressures (35, 50, 75, and 100 mm Hg, in random sequence) while the heart was paced at a constant rate. Each of the eight injections (four during the control periods and four accompanying the injections of capsaicin) was labeled with one of eight different isotopes (^52Mn, ^57Co, ^95Nb, ^51Cr, ^53Gd, ^114In, ^85Sr, ^65Zn).

In each of two experiments in another dog, we injected four sets of microspheres at 4-second intervals during the period of 16 seconds after injection of capsaicin, in order to examine the possibility that reflex vasodilation in the various layers of myocardium followed different time courses.

At the end of the experiment, while the heart was still beating, methylene blue was injected into the cannula to delineate the vascular territory of the circumflex coronary artery. Immediately after this injection, the heart was arrested by injecting KCl, iv; it was then removed and fixed in 10% formalin for 5 days. A specimen (20 g) of the whole thickness of the left ventricular wall was taken from the center of the region of myocardium perfused by the circumflex coronary artery and was cut into four slices of equal thickness, from endocardium to epicardium. Radiactivities of these four specimens were counted in a well-type scintillation counter. Corrections for background counts and overlapping of the eight microspheres were made as described previously (Heymann et al., 1977; Baer et al., 1984). Coronary flow per gram of tissue was calculated by multiplying radioactivity per gram of tissue by the ratio of circumflex coronary flow (measured by the flowmeter) to the total radioactivity of the heart. Transmural flow was calculated by dividing the total flow to the sample of left ventricular wall by the weight of the sample.

Data Analysis

Data are expressed as means ± sd. Reflex changes in coronary flow before and during cardiac pacing were compared by two-tailed paired t-test. Reflex effects on blood flow in the different myocardial layers were compared at various coronary perfusion pressures by two-factor analysis of variance; means were compared by the Newman-Keuls multiple range test.

Results

In experiments on 23 dogs, we found that injecting capsaicin (10 µg/kg) into the right atrium evoked a prompt decrease in systemic arterial blood pressure, and, in dogs with normal (unpaced) sinus rhythm, caused a prompt decrease in heart rate. This combination of systemic hypotension and bradycardia, which represents the classical depressor component of the pulmonary chemoreflex, was invariably accompanied by dilation of the circumflex coronary vascular bed.

Preliminary Experiments

In a few preliminary experiments, we did not attempt to control coronary perfusion pressure or blood flow (Fig. 1). The circumflex artery was not cannulated, and it received its normal blood supply from the aorta via the left coronary artery, circumflex flow being measured by a flowmeter around the vessel. Calculation of the changes in circumflex coronary vascular resistance evoked by right atrial injection of capsaicin under these conditions revealed a vasodilation whose onset usually coincided with that of the reflex bradycardia, so that, in spite of the reduction in arterial blood pressure, coronary flow was well maintained for the first few seconds, although it decreased thereafter (Fig. 1). The coincidence of this decrease in coronary resistance with the reflex changes in heart rate and blood pressure suggested that the vasodilation represented a primary and integral component of the pulmonary chemoreflex. Nevertheless, in an uncontrolled preparation of this type, it was not possible to distinguish a primary reflex vasodilation from a secondary autoregulatory vasodilation brought into play by the reflex decrease in driving pressure in the coronary vascular circuit. Therefore, in subsequent experiments, we perfused the circumflex coronary artery at a constant pressure.
Effects at Constant Coronary Perfusion Pressure

When the circumflex coronary artery was perfused at a constant pressure of 100 mm Hg, the cardiac slowing and systemic hypotension evoked by right atrial injection of 10 μg/kg capsaicin were invariably accompanied by an increase in coronary blood flow and a decrease in calculated coronary vascular resistance (Fig. 2, A and B; Table 1). Right atrial injection of capsaicin vehicle had no effect. Injection of 10 μg/kg capsaicin into the left atrium was usually followed after several seconds by increases in heart rate and blood pressure, but there was never an increase in circumflex blood flow during the 20 seconds after injection. On the contrary, vasoconstriction was the usual immediate response of the circumflex vascular bed to left atrial injection.

In 11 dogs studied without cardiac pacing, right atrial injection of capsaicin increased circumflex coronary flow by 32–109% (mean, 71%; P < 0.001) (Fig. 2A; Table 1). Flow began to increase 1.9 ± 0.3 seconds after the injection of capsaicin and reached a peak 7.7 ± 2.6 seconds later, remaining above control for 19.0 ± 1.6 seconds. The bradycardia and systemic hypotension were of longer duration, usually persisting for 2–3 minutes. The initial period of coronary vasodilation was followed by a small but prolonged vasoconstriction (Fig. 2A).

The evoked increase in coronary blood flow was essentially unaltered when heart rate was kept constant. Thus, in 14 dogs in which the heart was paced, right atrial injection of capsaicin increased circumflex coronary flow by 26–100% (mean, 56%; P < 0.001) (Fig. 2B; Table 1). On the average, control coronary vascular resistance was lower in the paced than in the unpaced heart (Table 1). Control mean systemic arterial pressure was identical in the two groups of experiments, but, on the average, systemic arterial pressure decreased less when heart rate was kept constant (Table 1). In some experiments we compared the effects of capsaicin when heart rate was allowed to vary with those in the same dog when heart rate was kept constant. Thus, in five dogs, capsaicin increased circumflex blood flow from 59 ± 20 to 94 ± 34 ml/min when the heart was unpaced and from 61 ± 9 to 99 ± 20 ml/min when it was paced.

The coronary vasodilation evoked by right atrial injection of capsaicin did not appear to be caused by the decrease in systemic arterial pressure. In several experiments on each of two dogs, we briefly inflated a balloon in the abdominal inferior vena cava to produce a decrease in systemic arterial blood pressure matching that of the pulmonary chemoreflex. Injection of capsaicin increased circumflex coronary flow by 50% and 52% in these two dogs (Fig. 2C), whereas obstruction of vena caval flow to produce a corresponding reduction in blood pressure decreased coronary flow by 10% and 25% (Fig. 2D).

Interrupting Vagal Pathways

We examined the effects of cooling the cervical vagus nerves on the reflex response to right atrial injection of capsaicin in nine dogs: the heart was unpaced in seven dogs, and paced in two (Fig. 3; Table 2). The usual reflex effects of coronary vasodilation and systemic hypotension, accompanied by bradycardia when the heart was unpaced, could still be evoked when the vagus nerves were cooled to 7–8°C (Fig. 3B), although the responses usually were attenuated. Thus, injection of capsaicin decreased coronary resistance by an average of 45% when vagal temperature was 37°C and by 30% after the
nerves had been cooled to 7–8°C. Reflex effects were abolished by cooling the vagi to 0°C (Fig. 3C) and were restored by rewarming the nerves (Fig. 3D). In two dogs, we examined the effects of cooling the nerves to an intermediate temperature of 3°C. In both, small decreases (of 19% and 21%) in coronary vascular resistance still could be evoked at this temperature.

The reflex coronary vasodilation, systemic hypotension, and bradycardia evoked by right atrial injection of capsaicin were also abolished by cutting the pulmonary vagal branches (three dogs). In another three dogs, the reflex coronary vasodilation and bradycardia were abolished by atropine (1 mg/kg, iv). Atropine reduced, but did not abolish, the reflex systemic hypotension.

### Dose-Response Curve

In three dogs, we examined the relationship between the dose of capsaicin and the magnitude of

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**Table 1**

<table>
<thead>
<tr>
<th>Experimental variable</th>
<th>Circumflex artery</th>
<th>Arterial blood pressure (mm Hg)</th>
<th>Heart rate (beats/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Flow (ml/min)</td>
<td>Resistance (mm Hg/ml per min)</td>
<td>Systolic</td>
</tr>
<tr>
<td>Heart unpaced</td>
<td>60 ± 19</td>
<td>1.83 ± 0.53</td>
<td>102 ± 24</td>
</tr>
<tr>
<td>Heart paced</td>
<td>77 ± 27</td>
<td>1.49 ± 0.36</td>
<td>108 ± 24</td>
</tr>
</tbody>
</table>

Data (means ± so) represent values during control period and at peak of reflex response to right atrial injection of 10 µg/kg capsaicin. Numbers in parentheses indicate number of dogs. All changes were statistically significant (P < 0.001).
FIGURE 3. Effect of cooling both cervical vagus nerves on the circumflex coronary vasodilation and systemic hypotension evoked by injecting capsaicin, 10 μg/kg, into the right atrium (at the signal in parts A–D). Coronary perfusion pressure maintained at 100 mm Hg; heart paced at 180 beats/min. Temperature of vagus nerves: part A, 37°C; part B, 7–8°C; part C, 0°C; part D, 37°C. Abbreviations as in Figures 1 and 2.

the coronary vasodilator response. Doses of capsaicin ranged from 1–20 μg/kg (Fig. 4) and were injected into the right atrium in random order. Effects of larger doses (e.g., 40 μg/kg) were often complicated by irregular changes in arterial blood pressure and spontaneous respiratory movements of the chest wall, and were not examined systematically.] When the dose-response curve was examined at the standard coronary perfusion pressure of 100 mm Hg, coronary vasodilation was first evoked by a dose of 2.5 μg/kg and reached a maximum at a dose of 10 μg/kg. When coronary perfusion pressure was reduced to 50 mm Hg, the dose-response curve was shifted to the right. Vasodilation was first observed at 10 μg/kg in one dog and at 20 μg/kg in the other two (Fig. 4).

Effect of Varying Coronary Perfusion Pressure

In some experiments, we paced the heart and examined the coronary vasodilator reflex response

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Effect of Vagal Cooling on Reflex Responses to Right Atrial Injection of Capsaicin</th>
</tr>
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<tbody>
<tr>
<td>Experimental variable</td>
<td>Circumflex artery</td>
</tr>
<tr>
<td>Temperature*</td>
<td>Capsaicin</td>
</tr>
<tr>
<td>37°C</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Capsaicin</td>
</tr>
<tr>
<td>7–8°C</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Capsaicin</td>
</tr>
<tr>
<td>0°C</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Capsaicin</td>
</tr>
<tr>
<td>37°C†</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>Capsaicin</td>
</tr>
</tbody>
</table>

Data (mean ± SD) represent values during control period and at peak of reflex response to right atrial injection of capsaicin 10 μg/kg. Results in seven dogs; heart un paced.

* Temperature (°C) of cervical vagus nerves on cooling platforms. At vagal temperatures of 37°C and 7–8°C, all changes evoked by capsaicin were statistically significant.

† After rewarming the nerves.
Utilization of Coronary Vasodilator Reserve

In three dogs, we attempted to estimate the proportion of coronary vascular reserve utilized during the pulmonary chemoreflex vasodilation. After obtaining an autoregulating pressure-flow curve over a range of coronary perfusion pressures, we injected capsaicin while coronary perfusion pressure was held in turn near the upper (100 mm Hg) and lower (50 mm Hg) ends of the autoregulating range; we then obtained a pressure-flow curve at maximum vasodilation (Fig. 6). At a coronary perfusion pressure of 100 mm Hg, chemoreflex coronary vasodilation in the three dogs amounted to 20%, 14%, and 9%, respectively, of the coronary vascular reserve. At a coronary perfusion pressure of 50 mm Hg, the corresponding values were 53%, 24%, and 8%.

Transmural Distribution of Blood Flow

In seven dogs, we injected radioactive microspheres into the circumflex coronary artery to determine whether the chemoreflex coronary vasodilation was accompanied by changes in transmural distribution of coronary blood flow. The heart was paced and microspheres were injected at four different coronary perfusion pressures (100, 75, 50, and 35 mm Hg) (Fig. 7; Table 4). As coronary perfusion pressure was reduced and coronary blood flow decreased, the endocardial:epicardial (endo:epi) blood flow ratio decreased significantly (from 0.98 at 100 mm Hg to 0.49 at 35 mm Hg). Right atrial injection of capsaicin increased transmural blood flow significantly at the two higher perfusion pressures, but the relative distribution of flow between endocardium and epicardium was not significantly altered by the reflex at any perfusion pressure (Fig. 7).

In the two experiments in which serial injections of microspheres were made during the reflex to determine whether vasodilation followed a different...
TABLE 3
Coronary Vascular Changes Evoked by Right Atrial Injection of Capsaicin at Different Coronary Perfusion Pressures

<table>
<thead>
<tr>
<th>Experimental variable</th>
<th>Circumflex artery</th>
<th>Arterial blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MPP (mm Hg)</td>
<td>Capsaicin</td>
</tr>
<tr>
<td>100 (10)</td>
<td>Control</td>
<td>85 ± 28</td>
</tr>
<tr>
<td>75 (6)</td>
<td>Capsaicin</td>
<td>128 ± 40</td>
</tr>
<tr>
<td>50 (10)</td>
<td>Control</td>
<td>81 ± 32</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>104 ± 29</td>
<td>0.77 ± 0.20</td>
</tr>
<tr>
<td>35 (5)</td>
<td>Control</td>
<td>52 ± 13</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>59 ± 13</td>
<td>0.88 ± 0.32</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>20 ± 9</td>
</tr>
<tr>
<td>Capsaicin</td>
<td>24 ± 13</td>
<td>1.43 ± 1.00</td>
</tr>
</tbody>
</table>

Data (means ± sd) represent values during control period and at peak of reflex response to right atrial injection of 20 μg/kg capsaicin; heart paced. Numbers in parentheses indicate numbers of dogs. Reflex changes in coronary blood flow and resistance were significant at perfusion pressures of 100 mm Hg (P < 0.001), 75 mm Hg (P < 0.001), and 50 mm Hg (P < 0.02). MPP = mean perfusion pressure.

discussion

The present results show clearly that the vagally mediated pulmonary chemoreflex in dogs includes a cholinergic, muscarinic coronary vasodilator component with a latency of onset similar to that of the bradycardia and hypotension. The rapid onset of the coronary vasodilation evoked by injecting a small dose of capsaicin into the right atrium, and the lack of response to injection of a similar dose into the left atrium, was consistent with the operation of a reflex triggered by stimulation of pulmonary C-fibers as capsaicin passed through the pul-

**Figure 6.** Pressure-flow relationships in circumflex coronary artery during autoregulation (closed circles) and maximum coronary vasodilation (open circles). Results obtained in three dogs (parts A–C). Vertical lines at coronary perfusion pressures of 50 and 100 mm Hg indicate the extent to which reflex coronary vasodilation evoked by capsaicin utilized coronary vascular reserve.
Coronary vascular bed. The identity of the afferent pathway was confirmed by the persistence of the coronary vasodilator reflex after myelinated vagal fibers had been blocked selectively by cooling (Coleridge and Coleridge, 1984), and by its absence after the lungs had been denervated. The possibility that coronary vasodilation was secondary to the depressor components of the pulmonary chemoreflex can be discounted, because the response was unaltered when heart rate was kept constant, and because a reduction in systemic arterial pressure per se caused, if anything, a decrease in coronary blood flow, probably as a result of reduced cardiac afterload.

Our results confirm those briefly reported by Piteti and Ordway (1984). These investigators, who described a coronary vasodilator component of the pulmonary chemoreflex in dogs, used a preparation in which coronary blood flow was kept constant and vasomotor effects were assessed from the changes in coronary perfusion pressure. However, changes in transmural pressure in coronary resistance vessels are thought to have direct (myogenic) effects on vascular smooth muscle tone (Feigl, 1983)—effects whose contribution to vasomotor...
changes cannot be assessed quantitatively if flow is kept constant and pressure is allowed to vary. By keeping coronary perfusion pressure constant and recording the evoked changes in coronary blood flow, we not only were able to make a more precise estimate of the reflex component of the vasodilation, but, also, were able to examine the reflex vasodilation at various points on the autoregulatory pressure-flow curve and to relate it to coronary vascular reserve. Moreover, in constant flow preparations, an evoked reduction in perfusion pressure may secondarily modify the intramyocardial distribution of blood flow (Feigl, 1983). By keeping coronary perfusion pressure constant, we were able to use radioactive microspheres to examine possible reflex changes in the intramyocardial distribution of blood flow in the absence of this secondary complication.

The magnitude of the pulmonary chemoreflex increase in coronary blood flow was related directly to coronary perfusion pressure, and, as perfusion pressure was reduced, the dose-response curve shifted to the right and the effect on flow diminished. However, appreciable coronary reserve was still present at low perfusion pressures, as noted by other investigators (Aversano and Becker, 1985; Canty and Klocke, 1985), and, in most dogs, reflex coronary vasodilation could still be evoked when perfusion pressure was as low as 50 mm Hg. Indeed, in one dog, the reflex was present at a perfusion pressure of 35 mm Hg.

Intracoronary infusion of acetylcholine has been shown to produce redistribution of myocardial blood flow toward the endocardium (Gross et al., 1981). However, although the results of microsphere injection in our experiments showed that endo:epi flow ratios decreased significantly as perfusion pressure was reduced, flow distribution was not further modified by cholinergic reflex vasodilation. We do not think our failure to detect any reflex influence on endo:epi flow distribution was due to deficiencies in our experimental method, although this could be criticized on the grounds that injection of microspheres directly into the coronary cannula gives a virtually instantaneous estimate of flow. However, we timed the injection of microspheres so that their distribution in the myocardium corresponded fairly closely to the maximum reflex increase in flow, measured by the flowmeter. The variation in coronary flow as the microspheres were injected might lead to an underestimate of the maximum reflex increase in flow in the different myocardial layers, but it would not modify the relative distribution of microspheres in the different layers. Moreover, the absence of change of microsphere distribution during the reflex indicates not only that the different layers had the same degree of vasodilation, but also that vasodilation occurred simultaneously in the different layers. The latter was confirmed by the results of the serial injections of microspheres.

It is unlikely that collateral flow between anterior descending and circumflex coronary arteries influences flow distribution, since collateral flow is negligible when the gradient of pressure between the two vascular beds is less than 50–75 mm Hg (Messina et al., 1985; Canty and Klocke, 1985). Larger gradients would be achieved in our experiments only at coronary perfusion pressures of 35 mm Hg, and then only during the control state. We conclude that reflex cholinergic vasodilation affects the coronary vascular bed in a uniform manner.

A similar cholinergic coronary vasodilation has been evoked by intracoronary injection of veratridine (Feigl, 1975) and by pharmacological stimulation of carotid body chemoreceptors (Hackett et al., 1972). However, in spontaneously breathing, conscious dogs, the reflex stimulation of breathing triggered by carotid body chemoreceptors appears to evoke a secondary coronary reflex vasodilation which differs from the reflex vasodilation we have described, in that it is prevented by phentolamine, but not by atropine (Vatner and McRitchie, 1975). Hence, the coronary circulation appears to be influenced by two reflexes from the lungs, one triggered by chemical stimulation of pulmonary C-fibers and producing coronary vasodilation by engaging the parasympathetic vasodilator pathway and one triggered by mechanical stimulation of lung afferents, producing vasodilation mainly by withdrawal of sympathetic α-adrenergic vasoconstrictor tone.

Injection of chemicals at appropriate points in the circulation is a convenient experimental method for stimulating afferent fibers, and has often been used in studies of coronary reflexes. Right atrial injection of capsaicin is another example of this approach. However, the functional significance of the reflex mechanisms demonstrated by pharmacological stimuli must depend on the physiological or pathological circumstances in which the reflex mechanisms are brought into play naturally. Pulmonary C-fibers are known to be stimulated in a variety of pathophysiological conditions, including embolization, inflammation, congestion, or edema of the lung, and inhalation of irritant gases (Coleridge and Coleridge, 1984). Reflex effects identical to the pulmonary chemoreflex have been induced in experimental animals by pulmonary embolization (Whitteridge, 1950), by acute, severe pulmonary congestion (Churchill and Cope, 1929; Downing, 1957), and by inhalation of irritant gases (Brodie and Russell, 1900). In the presence of lung damage, and with the possibility of impaired gas exchange, a coronary vasodilator component of the reflex response would have obvious protective value.

Stimulation of pulmonary C-fibers decreases cardiac output and peripheral resistance, sympathetic vasoconstrictor tone being withdrawn from both skeletal muscle and visceral vascular beds (Barer and Nusser, 1958; Brender and Webb-Peploe, 1969). If this widespread reflex vasodilation were not accompanied by equally rapid coronary reflex vasodilation,
the myocardial share of the reduced cardiac output would fall, at least initially. In the event, the neural response appears to be sufficiently rapid to forestall an appreciable decrease in myocardial blood flow (Fig. 1). The same arguments apply to other reflexes involving a decrease in peripheral resistance, and in which reflex coronary vasodilation appears to play an integral part.

Autoregulatory vasodilation is undoubtedly the basic mechanism for maintaining coronary blood flow in the face of a decrease in perfusion pressure under both physiological and pathological circumstances. Our results show that, even under these conditions, neurally induced vasodilation can provide additional protection to the myocardium.

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Barer GR, Nusser E (1958) Cardiac output during excitation of coronary cannula used in these experiments.

Dr. Clozel was a Research Fellow of the American Heart Association, California Affiliate.

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