Carotid Baroreceptor Reflex Coronary Vasodilation in the Dog

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SUMMARY. The hypothesis that neurally mediated coronary vasodilation occurs as part of the carotid baroreceptor reflex was investigated. The left main coronary artery was cannulated and perfused at constant pressure (100 mm Hg) in closed-chest, chloralose-anesthetized dogs. The heart was paced at a constant rate between 60 and 70 beats/min after atrioventricular heart block. Propranolol (1 mg/kg) was given to prevent β-receptor-mediated alterations in contractility. Aortic blood pressure was stabilized with a blood reservoir. The aortic depressor nerves were cut bilaterally to prevent the buffering influence of aortic arch baroreceptors on the carotid baroreceptor reflex. The carotid sinuses were vascularly isolated and perfused with arterial blood at controlled pressures. Under these conditions, a step change in carotid sinus pressure from 70 to 210 mm Hg produced a 0.29 ml/min per g increase in coronary flow above control and a 10 mm Hg increase in coronary sinus blood oxygen tension. A step in carotid sinus pressure from 70 to 150 mm Hg resulted in a flow increase of 0.13 ml/min per g and a coronary sinus oxygen tension increase of 5.3 mm Hg relative to prestimulation values. Atropine (0.5 mg/kg, iv) blocked most of the reflex coronary vasodilation, indicating a parasympathetic component, and the addition of adrenergic α-receptor blockade with phenoxybenzamine (0.25 mg/kg, ic) abolished the remaining response, demonstrating sympathetic participation. The reflex nature of the coronary response was confirmed with carotid sinus denervation and vagotomy. It is concluded that carotid sinus hypertension results in a graded reflex neural coronary vasodilation independent of myocardial metabolic factors. The major component is due to activation of parasympathetic coronary vasodilator fibers, but there is also inhibition of sympathetic vasoconstrictor fibers. (Circ Res 56: 486-495, 1985)

PREVIOUS studies have demonstrated that adrenergic α-receptor coronary vasoconstriction can be reflexly elicited by carotid sinus hypotension (Feigl, 1968, 1983; DiSalvo et al., 1971; Limet et al., 1975; Powell and Feigl, 1979; Ely et al., 1981). However, the reflex response to carotid sinus hypertension is less clear. Both coronary vasoconostriction (DiSalvo et al., 1971) and coronary vasodilation (Limet et al., 1975) have been observed during acute elevations in carotid sinus pressure. Coronary vasodilation during the elevation of aortic pressure has also been attributed to the carotid baroreflex (White et al., 1976). Electrical stimulation of the afferent carotid sinus nerve has been employed to mimic carotid sinus hypertension, and either coronary vasoconstriction (Falico et al., 1970) or vasodilation (Vatner et al., 1970; Hackett et al., 1972; Religa et al., 1972; Solti et al., 1975) has been observed. However, it is difficult to equate a given nerve stimulation frequency with a carotid sinus pressure stimulus that physiologically activates baroreceptors. Furthermore, electrical stimulation of carotid sinus baroreceptor afferent fibers produces both excitatory and inhibitory reflex effects on cardiac vagal efferent fibers (McCloskey and Potter, 1981). In contrast to only excitatory effects reported with functional pressure stimulation of baroreceptors (Potter, 1981). It is also possible that much of the conflicting coronary flow data can be explained by alterations in myocardial metabolism, secondary to changes in heart rate and aortic pressure, in response to activation of the baroreceptor reflex. Large changes in myocardial metabolism would tend to mask the reflexly activated direct neural effect on coronary vascular resistance.

The present study was designed to determine the reflex response of the coronary vascular bed to carotid sinus hypertension and to identify the neural mechanisms involved. Large changes in myocardial metabolism were prevented by a combination of cardiac pacing, adrenergic β-receptor blockade, and stabilization of aortic pressure. Coronary blood flow was measured during constant perfusion pressure during acute pressure elevations in the isolated carotid sinuses, before and after interruption of various components of the baroreflex arc. Carotid sinus hypertension resulted in reflex coronary vasodilation primarily mediated by activation of parasympathetic vasodilator fibers, but also by inhibition of sympathetic vasoconstrictor fibers.

Methods

General Preparation

Adult mongrel dogs (23-30 kg) of either sex were premedicated with morphine sulfate (2.5 mg/kg, sc) and
anesthetized with α-chloralose (100 mg/kg, iv). The dogs were intubated with a cuffed endotracheal tube and ventilated with a positive displacement respiration pump (Harvard 607) with an end-expiratory pressure of 3 cm H₂O. Ventilatory rate was adjusted to give an end-expiratory carbon dioxide content of 4.5%-5%, as continuously measured with an infrared analyzer (Beckman LB-2). Rectal temperature was held at 37°C with a heating pad and temperature controller (Yellow Springs 73A). A continuous intravenous drip (5 ml/kg per hr) of a sodium bicarbonate solution (1.5%) reduced the metabolic acidosis common with chloralose anesthesia (Arfors et al., 1971). Anesthesia was maintained with a continuous α-chloralose infusion (10 mg/kg per hr) plus 0.5 g supplements, as needed. Arterial blood pressure was measured with a strain gauge manometer (Statham P23Dd) through a polyethylene catheter (PE 160) inserted in the aorta via the left brachial artery. Anticoagulation was achieved with sodium heparin (750 U/kg, iv) followed by a continuous intravenous drip of 250 U/kg per hr. Three extracorporeal circuits were utilized, as described in separate sections below (Fig. 1).

**Aortic Baroreceptor Denervation**

To prevent the buffering influence of aortic arch baroreceptors on carotid sinus baroreceptor-mediated reflexes, the cervical aortic depressor nerves were cut bilaterally (Edis and Shepherd, 1971; Ito and Scher, 1973). Anesthesia was maintained with a continuous α-chloralose infusion (10 mg/kg per hr) plus 0.5 g supplements, as needed. Arterial blood pressure was measured with a strain gauge manometer (Statham P23Dd) through a polyethylene catheter (PE 160) inserted in the aorta via the left brachial artery. Anticoagulation was achieved with sodium heparin (750 U/kg, iv) followed by a continuous intravenous drip of 250 U/kg per hr. Three extracorporeal circuits were utilized, as described in separate sections below (Fig. 1).

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To prevent the buffering influence of aortic arch baroreceptors on carotid sinus baroreceptor-mediated reflexes, the cervical aortic depressor nerves were cut bilaterally (Edis and Shepherd, 1971; Ito and Scher, 1973). The vagosympathetic trunks were dissected free from the common carotid arteries. With the aid of a dissecting microscope, the cervical aortic depressor nerves were located within the sheath of the vagosympathetic trunks just

**Figure 1.** Schematic of the closed-chest experimental preparation. The ventricles were paced at a constant rate while reflex changes in the atrial rate were recorded with an atrial electrocardiogram. The aortic pressure was stabilized with a pressurized reservoir. The left main coronary artery was perfused through a cannula inserted via the right carotid artery. Pressure at the cannula tip was maintained at 100 mm Hg with the servo-controlled pump while coronary flow was measured with an electromagnetic flowmeter in the perfusion line. A coronary sinus blood sample was continuously withdrawn for determination of myocardial venous oxygen tension. The isolated carotid sinuses were presented with step increases in distending pressure with a nonpulsatile roller pump.
below the bifurcation of the common carotid arteries (Hasimoto and Hirohata, 1936). Identification of the aortic depressor nerve was verified by extracelluar nerve recording with bipolar silver electrodes and a differential amplifier (Grass P15) prior to cutting.

Heart Block and Ventricular Pacing

Complete atrioventricular heart block was produced closed-chest by the injection of formalin into the AV node region with a fluoroscope (Ito and Feigl, 1983). A pacing catheter (USC #5651) was placed in the right ventricle via the right external jugular vein. The ventricles were paced at a constant rate (between 60 and 70 beats/min in different experimental animals) with 3- to 5-V, 0.3-msec pulses (Grass SD9 stimulator). An electrode placed in the right atrium via the left external jugular vein allowed recording of cardiac potentials relative to an indifferent electrode positioned subcutaneously in the neck. Analog filtering of this signal (Hewlett-Packard 8811A) resulted in an electrocardiogram with enhanced atrial depolarizations relative to the paced ventricular depolarizations. This atrial electrocardiogram was also used to confirm that the baroreceptor reflex was intact, as indicated by atrial bradycardia during carotid sinus hypertension.

Aortic Pressure Stabilization

To minimize changes in aortic pressure during carotid sinus hypertension, the arterial system was connected to an external pressurized reservoir via both femoral arteries. The reservoir consisted of a 1-liter intravenous solution bag within an acrylic chamber connected to a pressurized air source. Pressure within the chamber was monitored during baroreceptor reflex peripheral vasodilation. To avoid right atrial venous admixture (Koberstein et al., 1969), blood was withdrawn at a rate of less than 10 ml/min to avoid stagnant blood accumulating in the reservoir bag. Blood was continuously circulated through the bag via a small catheter in the right femoral vein.

Isolated Carotid Sinus Perfusion

Both carotid sinus regions were vascularly isolated by ligation of the major branches (internal carotid, external carotid, lingual, occipital, superior laryngeal, and ascending pharyngeal arteries) of the common carotid arteries downstream from the carotid bifurcation. Care was taken to avoid damage to the carotid sinus nerves and the venous drainage from the carotid bodies (Chungcharoen et al., 1952). The carotid sinus regions were perfused through a Y-shaped cannula inserted into the common carotid arteries (Fig. 1). Carotid sinus pressure was measured from a side port in the cannula (Statham P231D) and was controlled by a non-pulsatile perfusion pump (Mohrman, 1980) in a servo feedback configuration. Rapid programmed changes in carotid sinus pressure were achieved by externally offsetting the control signal to the pump with a voltage source. A 30-ml Windkessel in the perfusion line served to damp out excessive pressure overshoots. Arterial blood from the femoral arteries was used as the perfusion source.

Left Coronary Artery Perfusion

The left main coronary artery was cannulated with a balloon-tipped stainless steel cannula (Smith et al., 1974; Mohrman and Feigl, 1978) via the right common carotid artery, without opening the chest. Coronary artery pressure was measured at the tip of the cannula via an inner steel tube and strain gauge manometer (Statham P231D). Coronary pressure was held constant at 100 mm Hg with a servo-controlled roller pump (Sarns 3500). The seal between the balloon and the coronary ostium was checked by stopping inflow and measuring distal pressure. The seal was considered satisfactory if coronary pressure fell to 20-25 mm Hg. The cannula seal was further tested at the termination of the experiment with the pump running and the heart beating. Coronary pressure was set to 50 mm Hg above mean aortic pressure, and crystal violet dye was injected into the perfusion line. Leaks were readily demonstrated by dye stains in the aorta. Experiments with evidence of leaks were discarded. The crystal violet dye injection was also used to demarcate the region of perfused myocardium, which was excised and weighed postmortem.

Coronary Sinus Cannulation

In 14 dogs, the coronary sinus was cannulated with a Sones catheter (USC #5423) using fluoroscopy (Goodale et al., 1948). Myocardial venous blood was continuously sampled by withdrawal at constant flow (Cole-Farmer pump 4420). Blood was returned to the dog via a femoral vein. In four dogs, the coronary sinus was cannulated with a double-lumen, balloon-tipped cannula that allowed the collection of coronary sinus effluent. A flexible polyethylene tube down the center of the cannula was extended beyond the tip of the cannula for continuous coronary venous sampling. This cannula allowed collection of coronary sinus blood during the intracoronary infusion of phenoxymenzamine, thus diminishing systemic α-receptor blockade. When phenoxymenzamine was not being infused, blood was shunted into the right atrium.

With both techniques, verification was made postmortem that the tip of the sampling catheter was more than 20 mm into the coronary sinus measured from the ostium. Blood was withdrawn at a rate of less than 10 ml/min to avoid right atrial venous admixture (Koberstein et al., 1969).

Oxygen Tension Measurement

Coronary sinus blood oxygen tension was continuously measured with an in-line oxygen electrode (Feigl and D'Aleyc, 1971) and meter (Instrumentation Labs 125A). The tubing transit time was determined at the end of each experiment. This value varied between 13 and 19 seconds in the different dogs. The appropriate time delay has been subtracted from all reported oxygen tension values. The oxygen tension measurements shown as original records have also been corrected by an appropriate shift of the time axis. The oxygen electrode was calibrated with pure nitrogen and a known nitrogen-oxygen mixture at the beginning and end of each experimental run.

Experimental Design

All animals were given propranolol, 1 mg/kg, iv, plus 0.5 mg/kg per hour, iv, to minimize adrenergic β-receptor-mediated changes in cardiac contractility. Activation of the carotid sinus baroreceptor reflex was achieved by presenting step changes in pressure to the carotid sinus. After propranolol control runs, animals were subjected to
one of four treatment protocols to determine the afferent and efferent reflex mechanisms involved in mediating the observed coronary response. (1) In the 'atropine-first' group (six dogs), atropine (0.5 mg/kg, iv) was administered to block the parasympathetic cholinergic pathway to coronary vessels. Phenoxybenzamine (0.25 mg/kg, intracoronary (ic)) was then administered to block the sympathetic \( \alpha \)-receptor pathway to coronary vessels. This intracoronary dose of phenoxybenzamine was chosen because it effectively blocks \( \alpha \)-receptor-mediated coronary effects of the carotid sinus reflex (Mohrman and Feigl, 1978) and infused norepinephrine (Buffington and Feigl, 1983). (2) In the 'phenoxybenzamine-first' group (seven dogs), the phenoxybenzamine (0.25 mg/kg, ic) was given first, followed by atropine (0.5 mg/kg, iv). (3) In the 'vagotomy-first' group (two dogs), both vagi were sectioned in the neck, and the baroreceptor stimulus was repeated. Phenoxybenzamine (0.25 mg/kg, ic) was then administered and the stimulus repeated. (4) In the 'carotid denervation' group (three dogs), deaferentation of the carotid sinus regions was produced by stripping the adventitia of the sinus regions, followed by topical application of phenol (10%). The carotid pressure stimulus was then repeated.

Experimental Protocol

Control experimental runs were obtained following propranolol but before additional autonomic blockade. Prior to the beginning of an experimental run, the external reservoir air pressure was adjusted to allow the accumulation of 100–150 ml of blood in the reservoir bag to provide sufficient volume for buffering the reflex peripheral vasodilation during carotid baroreceptor stimulation. Each experimental animal was presented with a 140 mm Hg step in carotid sinus pressure from 70 to 210 mm Hg. In 14 animals, an 80 mm Hg step from 70 to 150 mm Hg was also given.

The protocol for an experimental run consisted of an oxygen electrode calibration, a 20-second control period, 30 seconds of carotid hypertension, and 2 minutes of recovery, followed by an oxygen electrode calibration. The experimental period was limited to 30 seconds, because it was not possible to sequester sufficient blood in the reservoir for longer runs without inducing hypotension. When practicable, runs were repeated for each experimental condition.

Data Analysis

Analog records were digitized (Numonics 2400) at 5-second intervals for a 20-second period preceding the start of carotid sinus pressure elevation, and then every second for the duration of the stimulus (30 sec) and the post-stimulus recovery period (45 sec). At each time point, mean coronary blood flow, carotid sinus pressure, mean aortic pressure, and coronary sinus oxygen tension were read.

The experiment was designed to have each dog serve as its own control. The prestimulus control value for an individual dog for each experimental condition was obtained by taking the average of the values 20, 15, 10, and 5 seconds before the onset of the carotid pressure stimulus. For the coronary blood flow, coronary sinus oxygen tension and aortic pressure data, all measurements are expressed as the difference from the average prestimulus control value. The averages of these values for all dogs in each experimental group are shown in the figures. The standard error of the mean values given in the figures and text are measures of the variability between dogs and were derived from data sets containing one value from each dog studied in any given experimental group (n = 18). When multiple runs were obtained under the same experimental conditions, the average of these gave a single value for that dog in the overall data analysis.

Two-tailed paired t-tests were used to determine the statistical significance of the differences in the responses following each intervention in all experimental groups.

Results

Under control conditions (propranolol only), step increases in carotid sinus pressure resulted in atrial bradycardia and increases in left main coronary artery blood flow and coronary sinus blood oxygen tension (Fig. 2). With step elevations in carotid sinus pressure from 70 to 210 mm Hg \((n = 18)\), average coronary flow increased 0.29 ± 0.04 (SEM) ml/min per g above the prestimulation value of 0.36 ± 0.03 ml/min per g (Fig. 3). Average oxygen tension in the coronary sinus rose by 10.0 ± 0.9 mm Hg above the prestimulation value of 20.5 ± 0.8 mm Hg. Step elevations in pressure from 70 to 150 mm Hg \((n = 14)\) resulted in an average coronary flow increase of 0.13 ± 0.03 ml/min per g above the prestimulation value of 0.38 ± 0.03 ml/min per g and a coronary sinus oxygen tension increase of 5.3 ± 0.6 mm Hg above the prestimulation value of 20.4 ± 0.9 mm Hg.

Atropine-First Group

Average values for six dogs that were subjected to the atropine-first protocol are shown in Figure 4. In the propranolol control condition, coronary flow increased 0.28 ± 0.03 ml/min per g above the prestimulation value of 0.39 ± 0.06 ml/min per g, and coronary sinus oxygen tension increased by 9.6 ± 1.6 mm Hg from the prestimulation value of 22.6 ± 1.9 mm Hg following the step elevation in carotid sinus pressure from 70 to 210 mm Hg. After cholinergic blockade with atropine, the same step change in carotid sinus pressure resulted in a reduced coronary response \((P < 0.01)\). Coronary flow increased 0.08 ± 0.01 ml/min per g above the prestimulation value of 0.44 ± 0.06 ml/min per g, and coronary sinus oxygen tension rose by 2.6 ± 0.6 mm Hg above the prestimulation value of 26.1 ± 2.6 mm Hg. The addition of \( \alpha \)-receptor blockade with phenoxybenzamine further decreased the remaining changes in coronary flow and coronary sinus oxygen tension \((P < 0.01)\) from the prestimulation values of 0.57 ± 0.10 ml/min per g and 31.3 ± 2.1 mm Hg (Fig. 4). The increase in prestimulation coronary blood flow from 0.44 to 0.57 ml/min per g following phenoxybenzamine indicates there was sympathetic vasoconstrictor coronary tone. In all three conditions, reflex changes in mean aortic pressure during the carotid sinus stimulus were less than 15 mm Hg (Fig. 4).
CONTROL

CORONARY FLOW (ml/min per g)

1.0

0.5

0

CORONARY SINUS PO₂ (mm Hg)

50

25

0

AORTIC PRESSURE (mm Hg)

200

100

0

ATRIAL ECG

paced ventricular potentials

atrial potentials

CAROTID SINUS PRESSURE (mm Hg)

250

125

0

FIGURE 2. Effects of carotid sinus hypertension after β-receptor blockade, with the heart paced at constant rate and the coronary artery perfused at constant pressure. A step change in carotid sinus pressure produced reflex coronary vasodilation and atrial bradycardia.

Phenoxybenzamine-First Group

Average values for seven dogs that were subjected to the phenoxybenzamine-first protocol are shown in Figure 5. In the propranolol control condition for these animals, coronary flow increased 0.36 ± 0.09 ml/min per g above the prestimulation value of 0.39 ± 0.03 ml/min per g, and coronary sinus oxygen tension rose by 10.0 ± 2.0 mm Hg from the prestimulation value of 19.1 ± 0.6 mm Hg. After α-receptor blockade, the same step stimulus resulted in a coronary flow increase of 0.34 ± 0.09 ml/min per g above the prestimulation value of 0.61 ± 0.06 ml/min per g and an increase in coronary sinus oxygen tension of 6.4 ± 1.5 mm Hg above the prestimulation value of 28.1 ± 2.2 mm Hg. The increase in prestimulation coronary blood flow from 0.39 to 0.61 ml/min per g by phenoxybenzamine indicates there was sympathetic vasoconstrictor coronary tone. The response in coronary flow and coronary sinus oxygen tension were not different compared to the propranolol control condition (P > 0.10). After the addition of atropine, reflex changes in coronary flow and coronary sinus oxygen tension from the prestimulation values of 0.59 ± 0.05 ml/min per g and 26.6 ± 2.0 mm Hg were significantly reduced (P < 0.01) (Fig. 5).

Vagotomy-First Group

The parasympathetic role in the coronary response to carotid sinus hypertension was verified in two animals by cutting the vagus nerves in the neck. Vagotomy gave results similar to those achieved with atropine. Before vagotomy, a step change in carotid sinus pressure from 70 to 210 mm Hg resulted in a 0.17 ml/min per g increase in coronary flow above the prestimulation value of 0.25 ml/min per g. Average oxygen tension in the coronary sinus rose 11.4 mm Hg from the prestimulation value of 19.0 mm Hg. Vagotomy reduced this vasodilator response in coronary flow to 0.07 ml/min per g above the prestimulation value of 0.27 ml/min per g, and the response in coronary sinus oxygen tension to 4.1 mm Hg above the prestimulation value of 22.4 mm Hg. Completion of autonomic blockade with phenoxybenzamine further attenuated these responses in coronary flow and oxygen tension.
FIGURE 3. Average responses to carotid sinus pressure (CSP) elevations from 70 to 210 mm Hg (n = 18) and from 70 to 150 mm Hg (n = 14) from the propranolol control trials. The response in coronary flow and coronary sinus oxygen tension (Po2) was significantly less (P < 0.01) at the lower level of carotid sinus hypertension. Data are expressed as the differences from the average of the values 20, 15, 10, and 5 seconds before the stimulus onset. The prestimulus values before the step to 210 mm Hg were: coronary blood flow 0.36 ± 0.03 (SEM) ml/min per g; coronary sinus oxygen tension 20.5 ± 0.8 mm Hg; mean aortic pressure (MAP) 79.1 ± 3.0 mm Hg. The prestimulus values before the step to 150 mm Hg were: coronary blood flow 0.38 ± 0.03 ml/min per g; coronary sinus oxygen tension 20.4 ± 0.9 mm Hg; mean aortic pressure 83.1 ± 3.7 mm Hg. The statistical significance between the responses at the two stimulus levels was determined using an unpaired t-test at the time point indicated by the ±1 se bars.

Carotid Sinus Denervation

To verify that the carotid sinus was the origin of the reflex, the carotid sinuses were surgically and chemically denervated following completion of the

FIGURE 4. Effects of carotid sinus pressure (CSP) elevation in the atropine-first group. The control responses (propranolol) in coronary flow and coronary sinus oxygen tension (Po2) were greatly attenuated (P < 0.01) by the administration of atropine. The addition of phenoxybenzamine after atropine further reduced these changes (P < 0.01). Data are expressed as differences from the average of the values 20, 15, 10, and 5 seconds before the stimulus onset. Each point represents the average of values obtained in six dogs. The prestimulus control values for the propranolol control trial were: coronary flow 0.39 ± 0.06 (SEM) ml/min per g; coronary sinus oxygen tension 22.6 ± 1.9 mm Hg; mean aortic pressure (MAP) 80.9 ± 5.9 mm Hg. The prestimulus values for the atropine trial were: coronary blood flow 0.44 ± 0.06 ml/min per g; coronary sinus oxygen tension 26.1 ± 2.6 mm Hg; mean aortic pressure 77.5 ± 6.3 mm Hg. The prestimulus values for the atropine + phenoxybenzamine trial were: coronary blood flow 0.57 ± 0.10 ml/min per g; coronary sinus oxygen tension 31.3 ± 2.1 mm Hg; mean aortic pressure 70.2 ± 4.9 mm Hg. The statistical significance between the responses after each treatment was calculated using a paired t-test at the time point indicated by the ±1 se bars.
Propranolol control runs in three animals. Before denervation, a step change in carotid sinus pressure from 70 to 210 mm Hg resulted in a 0.27 ml/min per g increase in coronary blood flow above the prestimulation value of 0.31 ml/min per g. Average oxygen tension in the coronary sinus rose 9.5 mm Hg above the prestimulation value of 20.7 mm Hg. After denervation, the same step elevation in carotid sinus pressure produced no change in coronary flow or coronary sinus oxygen tension from the prestimulation values of 0.32 ml/min per g and 23.8 mm Hg.

Discussion

These data indicate that stimulation of carotid sinus baroreceptors with a pressure stimulus produces reflex vasodilation of the coronary vascular bed by activation of parasympathetic vasodilator fibers and inhibition of sympathetic vasoconstrictor fibers. The data confirm the results obtained with electrical stimulation of the carotid sinus nerve and extend the observations to reflexes produced by functional pressure stimulation. The results may be conveniently discussed in relation to the major factors that influence coronary blood flow: (1) coronary perfusion pressure, (2) extravascular compression of coronary vessels, (3) local metabolic control, and (4) neural control.

Perfusion Pressure

The left main coronary artery perfusion pressure was held constant at 100 mm Hg with a servo-controlled pump. Therefore, the observed increase in coronary flow during carotid sinus hypertension was probably not due to changes in perfusion pressure.

Extravascular Compression

During each cardiac systole, the contracting myocardium compresses the coronary vessels and increases their resistance to flow above that during diastole. The magnitude of this extravascular component of coronary resistance is related to heart rate, systolic pressure, and myocardial contractility (Feigl, 1983). In the present experiments, the ventricles were paced at a constant rate and aortic pressure was stabilized. Therefore, the possibility that alterations in these two variables could explain the observed results is slight.

A reflex negative inotropic effect of carotid baroreceptor stimulation has been well described (Sarnoff et al., 1960; DeGeest et al., 1964; Levy et al., 1966a) and is due to both inhibition of sympathetic discharge (Sarnoff et al., 1960; DeGeest et al., 1964) and parasympathetic activation (Levy et al., 1966a). The observation that the negative inotropic effect of parasympathetic activation is accentuated by simultaneous cardiac sympathetic excitation (Hollenberg et al., 1965; Levy et al., 1966b; Levy and Zieske, 1969) suggests that an interaction between the auto-
nomic pathways may also be involved. Cholinergic prejunctional inhibition of sympathetic norepinephrine release is a suggested mechanism for this effect (Vanhoutte and Levy, 1979; Vanhoutte, 1981). In the present study, sympathetically mediated alterations in inotropic state were avoided by β-receptor blockade with propranolol at the outset of all experiments.

The possibility that there was a direct negative parasympathetic inotropic effect, independent of sympathetic mechanisms, cannot be ruled out in the present experiments. However, the parasympathetic inotropic effect is small when sympathetic activation is low or absent (Hollenberg et al., 1964; Levy et al., 1966a, 1966b). Also, relatively large reductions in cardiac contractile state have minor effects on the extravascular component of coronary resistance (Snyder et al., 1975). Thus, it seems unlikely that a reflex decrease in systolic myocardial compression was primarily responsible for the observed coronary vasodilation.

**Metabolic Control**

Cardiac metabolism is a major influence on coronary blood flow through a local regulatory mechanism. The two major correlates of myocardial oxygen consumption are heart rate and systolic pressure (Rooke and Feigl, 1982). In the present experiments, the heart was paced at a constant rate and aortic pressure was stabilized. Sympathetically mediated changes in contractility were minimized by β-receptor blockade. Although the reflex decrease in aortic pressure due to peripheral vasodilation was blunted with the blood reservoir, small decreases in aortic pressure could not be prevented (Fig. 3). A decrease in cardiac afterload (aortic pressure) would result in a diminished myocardial metabolism and a secondary coronary vasconstriction, rather than the observed vasodilation. A change in coronary sinus oxygen tension may be interpreted as an alteration in the balance between coronary blood flow and oxygen metabolism. The increase in coronary sinus oxygen tension observed during carotid sinus hypotension (Fig. 3) indicates that coronary blood flow increased more than any concomitant change in metabolism. Therefore, the reflex coronary vasodilation observed in the present study was probably not secondary to an augmented cardiac metabolism.

**Neural Control**

Direct parasympathetic cholinergic coronary vasodilation and sympathetic α-receptor vasoconstriction have been demonstrated in numerous laboratories (Feigl, 1983). These neural pathways can be reflexly activated by several stimuli. Parasympathetic coronary vasodilation is part of the Bezold-Jarisch reflex (Feigl, 1975) and the carotid body chemoreflex (Hackett et al., 1972; Vatner and McRitchie, 1975; Murray and Vatner, 1983; Murray et al., 1984). Reflex sympathetic α-receptor coronary vasoconstriction in response to carotid sinus hypotension has been reported in preparations with β-receptor blockade (Feigl, 1968; DiSalvo et al., 1971; Powell and Feigl, 1979) and without β-receptor blockade (Mohrman and Feigl, 1978).

Electrical stimulation of the afferent carotid sinus nerve has been shown to produce inhibition of coronary sympatoconstrictor tone (Vatner et al., 1970; Religa et al., 1972) and parasympathetic cholinergic coronary vasodilation (Hackett et al., 1972). However, it is difficult to equate a given nerve stimulation frequency with a carotid sinus pressure that physiologically stimulates baroreceptors. The present results confirm the previous results obtained with electrical stimulation of the carotid sinus nerve and demonstrate that baroreceptor activation with functional pressure stimuli produces a reflex coronary vasodilation.

Parasympathetic coronary vasodilation has been observed with elevations in carotid sinus pressure from 30 to 110 mm Hg in dogs with right heart bypass (Limet et al., 1975). However, this result is clouded by the observation that carotid body chemoreceptor activity is increased at carotid sinus pressures below 50–60 mm Hg (Biscoe et al., 1970). White et al. (1976) stimulated carotid and aortic baroreceptors with increased arterial pressure by inflating a balloon in the thoracic aorta of paced, heart-blocked dogs. The increase in cardiac afterload produced by this maneuver complicates the interpretation of direct reflex involvement in the response, since coronary vascular resistance changes secondary to altered cardiac metabolism may have been involved. White et al. (1976) observed an increase in coronary conductance that could be partially reduced by methscopolamine, suggesting a reflex parasympathetic cholinergic vasodilation. α-Receptor blockade further reduced the coronary conductance increase, indicating that inhibition of sympathetic constrictor tone to coronary vessels also was involved. However, deafferentation of the arterial baroreceptors abolished only the parasympathetic component of the coronary response, leaving open the possibility that reflexes from other receptors may have been involved. The present results confirm baroreceptor reflex parasympathetic coronary vasodilation.

The abolition of the reflex response in coronary flow and sinus oxygen tension after denervation of the carotid sinus region indicates that the reflex originates from the carotid sinus. Although a carotid body chemoreceptor reflex influence on coronary vessels has been demonstrated (Hackett et al., 1972; Vatner and McRitchie, 1975; Murray and Vatner, 1983; Murray et al., 1984), these receptors have been shown to be relatively insensitive to arterial pressure in the range of 60–220 mm Hg (Biscoe et al., 1970; Mancia, 1975). Thus, the reflex observed in the present study most likely originated from carotid sinus baroreceptors.
The efferent path for reflex coronary vasodilation includes both the sympathetic and parasympathetic divisions of the autonomic nervous system. Vagal parasympathetic vasodilation appears to be the predominant pathway, as was shown by the large reduction or abolition of the response in coronary flow and coronary sinus oxygen tension by the administration of atropine or vagotomy (Figs. 4 and 5). α-Receptor blockade blunted the reflex coronary flow and coronary sinus oxygen tension responses to carotid sinus hypertension (Fig. 4). This indicates that inhibition of sympathetic vasoconstrictor tone in coronary vessels is part of the carotid sinus reflex. Although the sympathetic component appears to be smaller than the parasympathetic component, its magnitude is dependent upon the level of pre-existing sympathetic tone. In the "phenoxybenzamine-first" experiments, the administration of phenoxybenzamine did not significantly alter the control coronary response to carotid hypertension (Fig. 5).

Hackett et al. (1972) observed that the early abrupt reflex coronary vasodilation was due to parasympathetic activation, whereas the delayed response was due to sympathetic inhibition. The present results confirm this, and it is likely that the faster onset and greater magnitude of parasympathetic vasodilation (Fig. 4) masked the smaller, more slowly developing sympathetic component. Thus, only when the parasympathetic component was first removed was the sympathetic mechanism revealed (Fig. 4).

The coronary vasodilation observed in response to carotid hypertension was graded (Fig. 3). Step increases in carotid sinus pressure from 70 to 150 mm Hg resulted in increases in coronary flow and coronary sinus oxygen tension that equaled approximately 50% of the response elicited with the step to 210 mm Hg. This graded feature of the baroreceptor reflex coronary vasodilation was due to parasympathetic fibers (Potter, 1982). It is also probable that inhibition of sympathetic vasoconstrictor tone in coronary vessels is part of the carotid sinus reflex. Adaptation to steps in coronary vessels is part of the carotid sinus reflex. Although the sympathetic component appears to be smaller than the parasympathetic component, its magnitude is dependent upon the level of pre-existing sympathetic tone. In the "phenoxybenzamine-first" experiments, the administration of phenoxybenzamine did not significantly alter the control coronary response to carotid hypertension (Fig. 5).

Hackett et al. (1972) observed that the early abrupt reflex coronary vasodilation was due to parasympathetic activation, whereas the delayed response was due to sympathetic inhibition. The present results confirm this, and it is likely that the faster onset and greater magnitude of parasympathetic vasodilation (Fig. 4) masked the smaller, more slowly developing sympathetic component. Thus, only when the parasympathetic component was first removed was the sympathetic mechanism revealed (Fig. 4).

The coronary vasodilation observed in response to carotid hypertension was graded (Fig. 3). Step increases in carotid sinus pressure from 70 to 150 mm Hg resulted in increases in coronary flow and coronary sinus oxygen tension that equaled approximately 50% of the response elicited with the step to 210 mm Hg. This graded feature of the baroreceptor reflex has been demonstrated in the reflex control of heart rate and the vascular resistance of many peripheral beds (Kendrick et al., 1972; Kirchheim, 1976). The vasodilation in the present experiments peaked approximately 10 seconds after the beginning of the reflex, and was followed by a lower plateau until the end of the stimulus (Fig. 3). The reasons for the peak and decline are not elucidated by the present experimental design; conceivably, adaptation of any of the elements involved in the reflex could give this effect. Adaptation to steps in nonpulsatile pressure has been described for baroreceptors (Sleight et al., 1977) and for the pathway from carotid sinus baroreceptors to cardiac vagal efferent fibers (Potter, 1982). It is also probable that there was a competition between neural vasodilation and local metabolic coronary control that reduced the flow following the peak response.

In conclusion, carotid sinus hypertension elicits a graded baroreceptor reflex coronary vasodilation that is independent of myocardial metabolic mechanisms. The coronary vasodilation is primarily mediated by activation of parasympathetic vasodilator fibers, but also involves inhibition of sympathetic α-receptor vasoconstrictor fibers to coronary vessels.

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