Effects of Carotid Sinus Nerve Stimulation on the Coronary Circulation of the Conscious Dog

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ABSTRACT

Control of the coronary circulation by the carotid sinus was studied in intact, unanesthetized dogs instrumented with Doppler ultrasonic flow probes on the left circumflex coronary artery, miniature pressure gauges in the aorta, and stimulating electrodes on the carotid sinus nerves. A radiofrequency pacemaker was used to stimulate the nerves in dogs at rest, during sleep, exercise, and after autonomic blockade. Thirty-second periods of stimulation in the resting conscious dog resulted in an average decrease in aortic pressure of 28%, an average decrease in mean coronary flow of 7%, while heart rate decreased by 13% at the beginning of stimulation and then returned to control levels. Mean and late diastolic coronary resistances decreased by an average of 22% from control. Similar results occurred with carotid sinus nerve stimulation during sleep and during treadmill exercise. Combined beta-receptor blockade with propranolol and atropine prevented the changes in heart rate with carotid sinus nerve stimulation but not the decrease in arterial pressure or the coronary dilatation. After alpha-receptor blockade with phenoxybenzamine or sympathetic blockade with guanethidine, coronary dilatation was not observed with carotid sinus nerve stimulation. Thus sympathetic constrictor tone is present in the resting conscious dog and the coronary dilatation observed with electrical stimulation of the carotid sinus nerves is due to a reduction in resting sympathetic constrictor tone.

ADDITIONAL KEY WORDS: coronary vasodilatation, atropine, alpha receptor, coronary sinus reflex, sympathetic blockade, baroreceptor, exercise, coronary blood flow.

Although the general circulatory effects of activating the carotid sinus reflex have been well described, particularly in anesthetized preparations, the influence of this reflex on the coronary circulation has not been established. There is substantial evidence that coronary blood flow is regulated primarily by the metabolic requirements of the myocardium; though it is clear that the coronary vascular bed is innervated, neurogenic control of the coronary circulation has been considered to be of lesser importance (1, 2).

Stimulation of the carotid sinus nerves decreases arterial pressure, heart rate, and the myocardial contractile state (3, 4), all of which tend to reduce myocardial oxygen consumption. If coronary vascular resistance were determined solely by the metabolic requirements of the myocardium, it would be expected that the lowering of these demands produced by electrical stimulation of the carotid sinus nerves or with carotid sinus hypertension would increase coronary resistance. Indeed, there has been some experimental evidence to support this hypothesis. Anrep and Segall (5) and Stella (6) used a Morawitz cannula to measure coronary sinus...
outflow and observed that carotid hypertension resulted in coronary constriction. Heymans and Neil concluded that the "sinoaortic reflexes exert a relatively unimportant effect on the (coronary) circulation" (3). More recently, investigators have reported conflicting results with carotid hypotension. On the one hand carotid hypotension has been shown to produce coronary constriction (7-9), while on the other it has also been shown to produce coronary dilatation (10, 11). Feigl has shown that some of the differences in the effects of carotid hypotension on the coronary circulation which have been noted can be explained by the opposing influence of metabolically mediated dilatation and neurally mediated constriction. He observed in anesthetized dogs that after beta-receptor blockade carotid hypotension leads to coronary vasoconstriction (10).

Earlier studies in our laboratory have shown that the effects of carotid sinus nerve stimulation are modified significantly by the state of consciousness of the animal (unpublished observations), while Gregg and his co-workers have demonstrated that coronary vascular dynamics are significantly modified by general anesthesia (2). Accordingly, in the present investigation to clarify the response of the coronary vascular bed to carotid sinus nerve stimulation, the carotid sinus nerves were stimulated in intact unanesthetized dogs instrumented for the measurement of instantaneous coronary flow and arterial pressure.

Methods

Experiments were conducted on 12 conscious, mongrel dogs weighing between 23 and 32 kg. At operation, using sterile surgical technique and adequate general anesthesia, Doppler ultrasonic blood flow transducers were placed around the
Response to carotid sinus nerve stimulation (CSNS) in the resting, conscious dog in which coronary blood flow increased with a decrease in aortic pressure. In this and subsequent figures, the bars at the top and bottom show the 30-second period of stimulation.

left circumflex coronary artery, miniature solid state pressure gauges (12) were implanted into the central aorta, and stimulating electrodes were placed on both carotid sinus nerves.

The experiments were conducted 2 to 10 weeks postoperatively, when the dogs appeared healthy and the discomforting side effects of carotid sinus nerve stimulation, i.e., local somatic irritations, were minimal. A radiofrequency stimulator (13) with a .3-msec pulse having a rectangular waveform, and a frequency of 50 Hz was employed. The amplitude was adjusted to between 2.5 and 7.0 volts for each dog at the beginning of the experimental day and was then held constant. The strength of stimulus was the highest that could be utilized without the dog presenting any evidence of being aware of stimulation. Experiments were conducted in 12 conscious dogs at rest; in five of these dogs while asleep; during treadmill exercise in five dogs; after atropine (0.2 to 0.5 mg/kg) in eight dogs; after beta-receptor blockade with propranolol (1 to 3 mg/kg) in five dogs; after combined propranolol and atropine in three dogs; after alpha-receptor blockade with phenoxybenzamine (5 to 10 mg/kg) in five dogs; and after chronic sympathetic blockade with guanethidine (5 mg/kg/day X 7) in two dogs.

The signals from the Doppler ultrasonic flowmeter (14) and the aortic pressure gauge were telemetered. The internal cross-sectional area of the blood vessel was measured at autopsy and blood flow rate was calculated from the blood flow velocity, which in turn was derived from the Doppler equation. Volume calibrations per-
formed by timed collection of blood flow in three animals verified the linear relationship between blood flow velocity as measured by the ultrasonic flowmeter and volume flow. The relationship between blood flow velocity and volume flow remains linear as long as the diameter of the vessel within the transducer does not change. At autopsy in these dogs, the vessels were found to be fixed to the transducer shell through scarring and fibrosis, thereby preventing changes in vessel caliber within the flow transducer. The aortic gauges were calibrated in vivo with a Statham P23Db strain-gauge manometer which was calibrated against a mercury manometer.

Mean aortic pressure and mean coronary flow were derived using RC electronic filters with a 2-second time constant. Mean coronary vascular resistance was calculated as the quotient of mean aortic pressure and mean coronary blood flow and expressed in mm Hg/ml/min. In addition, late diastolic coronary resistance was calculated as the quotient of late diastolic aortic pressure and late diastolic coronary flow. The changes in resistance from control represent those occurring at the time of maximum decrease in aortic pressure during a 30-second period of carotid sinus nerve stimulation. In some dogs the effects of longer periods of stimulation, up to 5 minutes, were also studied. A cardiotachometer (Beckman Model 9057B) triggered by the electrical signal from the aortic pressure pulse provided instantaneous and continuous records of heart rate. Data were recorded on a multichannel chart recorder and magnetic tape recorder.

**Results**

*Response in Resting and Sleeping Dog.*

In the 12 dogs studied, awake and at rest, a 30-second period of carotid sinus nerve stimulation produced an average maximum decrease in mean aortic pressure of 28% ± 2%.
Response to carotid sinus nerve stimulation (CSNS) after combined beta-receptor blockade with propranolol (1 mg/kg) and atropine (0.2 mg/kg).

Pressure began to fall within 5 seconds, the decrease was maximum at approximately 20 seconds, began to return toward control levels during the latter 10 seconds of stimulation and reached control within 15 seconds after stimulation was stopped. Heart rate decreased at the onset of stimulation and reached a minimum within 3 to 5 seconds (average decline = 13% of control) falling from an average of 84 to 73 beats/min. Heart rate returned to control levels within 10 to 15 seconds of the onset of stimulation and in some animals rose to levels above control toward the end of the stimulation period.

The effects of carotid sinus nerve stimulation on left circumflex coronary blood flow were variable. Coronary flow typically remained close to control levels, but in some dogs it decreased (Fig. 1), while in other cases it actually increased during carotid sinus nerve stimulation (Fig. 2). At the time of the maximum decrease in aortic pressure, when heart rate had returned to control levels, mean coronary blood flow had declined by an average of 7% ± 2% (avg = 43 to 40 ml/min). In all experiments mean circumflex coronary blood flow did not decrease proportionately as much as did arterial pressure. At the nadir of the aortic pressure drop, the average decrease in mean coronary resistance was 22% of control (Fig. 7) (avg = 2.16 to 1.68 mm

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Hg/ml/min); late diastolic resistance showed similar changes. Coronary resistance tended to return toward control near the end of the 30-second stimulation period and with longer periods of stimulation of 2 to 5 minutes, coronary resistance cyclically fluctuated about a level below control throughout stimulation.

In 5 of the 12 animals the effects of carotid sinus nerve stimulation during sleep were studied. A similar decrease in coronary resistance occurred as in the resting conscious animal. Mean arterial pressure decreased from an average of 96 to 66 mm Hg, while coronary flow remained essentially unchanged (39 to 38 ml/min) and calculated resistance decreased by an average of 29% from 2.46 to 1.74 mm Hg/ml/min.

**Treadmill Exercise.**—During treadmill exercise at 4 mph in five dogs, coronary flow increased from an average of 45 to 85 ml/min, while aortic pressure remained within 10% of control levels. Carotid sinus nerve stimulation during exercise produced an additional decrease in coronary vascular resistance (Fig. 3). Mean aortic pressure decreased from an average of 104 to 73 mm Hg and coronary flow decreased from 85 to 73 ml/min, resulting in a decrease in calculated resistance averaging 18% ± 3% from the exercising control level (avg = 1.22 to 1.00 mm Hg/ml/min).

**Atropine.**—Atropine (0.2 to 0.5 mg/kg) in eight dogs increased heart rate from an average control of 82 to 156 beats/min and arterial pressure from 96 to 111 mm Hg, while mean coronary blood flow rose from an average of 43 to 94 ml/min, and coronary
resistance decreased from an average of 2.23 to 1.18 mm Hg/ml/min. Carotid sinus nerve stimulation following atropine decreased mean aortic pressure from an average of 111 to 86 mm Hg and coronary flow from 94 to 90 ml/min producing a further decrease in coronary vascular resistance, averaging 19% ± 3% from the postatropine control level of 1.18 to 0.96 mm Hg/ml/min.

**Beta-Receptor Blockade.—**Propranolol (1 to 3 mg/kg) in five dogs decreased both heart rate and coronary blood flow by 10%, but did not alter arterial pressure. Carotid sinus nerve stimulation reduced arterial pressure while coronary flow remained constant, resulting in a decrease in calculated coronary resistance by an average 26% ± 1%, (avg = 2.65 to 1.91 mm Hg/ml/min), while heart rate declined by 9% (avg = 66 to 60 beats/min). Combined beta-receptor (1 mg/kg propranolol) and atropine (0.2 mg/kg) in three dogs did not alter the dilatation which occurred with carotid sinus nerve stimulation; mean aortic pressure decreased from an average of 108 to 85 mm Hg and calculated coronary resistance declined by an average of 20% from 1.26 to 1.01 mm Hg/ml/min; no change in heart rate was observed (Fig. 4).

**Alpha-Receptor Blockade.—**Phenoxybenzamine (5 to 10 mg/kg) in five dogs produced partial alpha-receptor blockade and decreased the pressor response to 1 µg/kg norepinephrine by an average of 83%. The dogs appeared inactive, lethargic and refused food; their heart rate had increased to an average of 135 beats/min and coronary flow to 85 ml/min, while mean aortic pressure declined by an average of 11% from control. Carotid sinus nerve stimulation, carried out 1 to 6 hours following phenoxybenzamine administration, produced a decrease in the average mean aortic pressure by 12% from 90 to 79 mm Hg, while coronary flow fell from 84 to 72 ml/min. In contrast to all of the previous observations, carotid sinus nerve stimulation did not lower coronary resistance; it remained essentially constant during stimulation (1.07 to 1.10 mm Hg/ml/min) (Fig. 5).

**Chronic Sympathetic Blockade.—**In contrast to phenoxybenzamine, guanethidine, 5
mg/kg given daily to two dogs for 7 days, did not alter their apparent vigor and health. Resting control levels for coronary vascular resistance were similar to those in dogs without blocking drugs (2.05 mm Hg/ml/min). Carotid sinus nerve stimulation produced a decrease in the average mean aortic pressure from 102 to 82 mm Hg and a slightly greater relative decrease in the average mean coronary blood flow (44 to 31 ml/min) resulting in 7% and 18% increases, respectively, in the calculated coronary resistance. In the presence of guanethidine the bradycardia, lowered arterial pressure and elevated coronary resistance induced by carotid sinus nerve stimulation, persisted for the entire duration of stimulation, even when prolonged (Fig. 6). Six weeks after discontinuation of guanethidine, the dog whose data are shown in Figure 6 was restudied and the normal control coronary vasodilator response to stimulation was observed.

Discussion

The carotid sinus nerve is a mixed nerve containing both baroreceptor and chemoreceptor fibers. In the experiments reported it appears that the response results from activating baroreceptor afferent fibers for several reasons: First, chemoreceptor stimulation is known to produce an increase in aortic pressure and vasoconstriction in muscle, kidney, and gut (3, 15, 16); yet, in the present investigation we uniformly found a decrease in aortic pressure and reductions in resistance in the iliac, renal, and mesenteric beds (unpublished observations). Second, hyperventilation was not observed. Finally, in five dogs arterial blood gases were obtained during carotid sinus nerve stimulation and Pco2, Po2, and pH were unaltered.

In the conscious dog carotid sinus nerve stimulation produces qualitatively similar, though more transient, changes in the circulation than those classically described in anesthetized preparations (3). It was noted that arterial pressure declined in association with a dilatation in the major vascular beds, primarily the vessels supplying skeletal muscle (unpublished observations). However, arterial pressure returned toward control levels even before the termination of carotid sinus

![Image of Figure 7](http://circres.ahajournals.org/)

**FIGURE 7**

Average change (± S.E.) in calculated mean and late diastolic coronary vascular resistance produced by carotid sinus nerve stimulation in dogs at rest, during exercise, and after autonomic blockades. Number in circles is number of dogs tested.
nerve stimulation, perhaps because of the opposing effects of hypotension on the aortic receptors. The bradycardia was even briefer, heart rate returning to or even exceeding control at the end of the 30-second stimulation period. Although no measurements of contractility were made in this study, on the basis of earlier experiments in anesthetized dogs in which it was shown that carotid sinus nerve stimulation results in a reduction of myocardial contractility (3,4) but carotid sinus hypotension has the opposite effect (17), it may be presumed that carotid sinus nerve stimulation reduced the contractile state of the myocardium.

If the coronary vascular bed were controlled solely by metabolic factors, then it would be expected that the reduction in myocardial oxygen consumption which accompanies the lowering of arterial pressure, myocardial contractility, and heart rate associated with carotid sinus nerve stimulation would result in an elevation of coronary vascular resistance. However, it was observed in every experiment that calculated mean and late diastolic coronary resistances declined (Fig. 7). In fact, in some instances, coronary blood flow increased in the face of reductions of arterial pressure (Figs. 2 and 4). It should be emphasized that the animals gave no evidence of being aware of the stimulation which was employed and therefore one cannot ascribe the changes in the coronary circulation to the effects of somatic stimulation. The identical effects of stimulation observed in sleeping and in conscious dogs support this view. The finding that coronary dilatation occurs with carotid sinus nerve stimulation at rest and during exercise may help to explain the relief of angina pectoris experienced by patients with ischemic heart disease during electrical stimulation of these nerves (18,19).

A number of possible mechanisms responsible for the observed coronary vasodilatation were considered. The coronary bed contains beta receptors which, if stimulated, result in dilatation (20-23). The finding that the coronary dilator response was not blocked by propranolol indicates that the coronary dilator response could not have been produced by activation of the beta receptors. These observations, as well as the studies of Aomura (24) which showed that carotid sinus nerve stimulation decreased the rate of epinephrine released from the adrenal medulla, also indicate that the coronary dilatation cannot be ascribed to an increase in circulating catecholamines.

Autoregulation of coronary blood flow could also explain the maintenance of coronary flow associated with the decrease in arterial pressure after carotid sinus nerve stimulation, and evidence for autoregulation of coronary blood flow has been presented (25, 26). However, this possibility is unlikely since autoregulatory theory postulates that flow returns to or toward but not above control levels after a step function decrease in arterial pressure. In some of our experiments carotid sinus nerve stimulation actually resulted in an increase in coronary blood flow above control levels with the decrease in aortic pressure (Fig. 2). Also, if autoregulation had been responsible for the maintenance of coronary flow in the animal without blocking drugs, sympathetic blockade should not have altered this response.

It is well-known that carotid sinus nerve stimulation increases vagal efferent activity (3). Recently, Feigl has provided evidence for the existence of parasympathetic mediated coronary vasodilatation (27). However, since atropine did not significantly alter the coronary vasodilator response to carotid sinus nerve stimulation, the coronary dilatation observed with stimulation could not be attributed to vagal mechanisms. Furthermore, when atropine was administered in addition to propranolol, carotid sinus nerve stimulation still produced a decrease in calculated coronary resistance which was similar to that observed in animals without blocking drugs (Fig. 4). Under these circumstances carotid sinus nerve stimulation produced no change in heart rate and the changes in myocardial contractility should also have been blocked.

The coronary bed is also supplied with alpha receptors (1,22,23,28,29) and with sympathetic nerve fibers which, when stimu-
lated, produce coronary vasoconstriction (30, 31). Feigl has demonstrated that adrenergic coronary constrictor activity occurs with carotid sinus hypotension after the accompanying stimulation of myocardial metabolism has been blocked with propranolol (10). The present work supports that of Feigl, since coronary dilatation was observed during carotid sinus nerve stimulation. Also, it was shown that coronary dilatation did not occur after alpha-receptor blockade with phenoxybenzamine. Since this drug produces undesirable side effects, e.g., tachycardia and a decrease in calculated coronary resistance before carotid stimulation, chronic blockade of the sympathetic nervous system was also carried out with guanethidine in two dogs. Carotid sinus nerve stimulation in these animals did not produce decreases in coronary resistance; in fact, coronary resistance increased slightly during stimulation of the sinus nerves.

The results of these experiments are consistent with the hypothesis that resting sympathetic constrictor tone exists in the coronary circulation of conscious dogs and that the decrease in calculated coronary resistance observed with carotid sinus nerve stimulation is due to a reduction in this resting sympathetic constrictor tone. Furthermore, it has been shown that this mechanism responsible for coronary vasodilatation exists not only at rest but also during treadmill exercise, when the coronary bed has already been dilated by metabolic influence. Thus, alpha-receptor constrictor tone persists in the coronary circulation during exercise.

These experiments demonstrate carotid sinus control of the coronary circulation by two pathways. First, the carotid sinus reflex can indirectly affect the coronary circulation by altering the metabolic requirements of the myocardium through changes in arterial pressure, frequency of contraction, and myocardial contractility. In addition, a second pathway involving direct neural control appears to be present.

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