Effects of Carotid Sinus Nerve Stimulation on Blood-Flow Distribution in Conscious Dogs at Rest and during Exercise

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ABSTRACT
The effects of stimulating the carotid sinus nerves on the distribution of cardiac output and peripheral vasoreactivity was studied in intact, unanesthetized dogs instrumented with ultrasonic or electromagnetic flow probes on the ascending aorta, mesenteric, renal, and iliac arteries, and miniature pressure gauges in the aorta. A radiofrequency pacemaker was used to stimulate the nerves in dogs at rest, during treadmill exercise, and after autonomic blockade. Thirty-second periods of stimulation in the resting dog resulted in an average decrease in aortic pressure of 28%, cardiac output remained unchanged, total peripheral resistance fell 29%, mesenteric flow 12%, mesenteric vascular resistance 18%, renal flow 8%, and renal vascular resistance 22%. In the iliac bed flow increased by 90% while resistance declined by 62%. Heart rate decreased initially by 13%, and returned to control during stimulation. The bradycardia was determined to be predominantly due to vagal stimulation. During treadmill exercise carotid sinus nerve stimulation resulted in similar decreases in arterial pressure, mesenteric and renal resistance, and a further decrease in iliac resistance from exercise control values. Thus, electrical stimulation of the carotid sinus nerves in the conscious dog produced a differential pattern of peripheral vasodilatation, the most profound dilatation being observed in the hind-limb circulation. This release of sympathetic tone also occurred during stimulation in exercising animals when the muscular bed was already dilated on a metabolic basis.

ADDITIONAL KEY WORDS
renal flow mesenteric flow
atropine blood pressure

The carotid sinus reflex is recognized to be of fundamental importance in the control of the circulation; activation of this reflex results in bradycardia, vascular dilatation and hypotension (1, 2). Although the circulatory effects of this important reflex have been studied extensively, most of this work has been carried out in anesthetized animals. It is important to determine whether this reflex has similar significance in the intact, unanesthetized animal in which all control systems are intact and the additional effects of anesthesia are not present.

To study the effects of the carotid sinus reflex, the carotid sinus nerves were electrically stimulated while arterial pressure, heart rate, cardiac output, and blood flow in the mesenteric, renal, and iliac beds were measured. These experiments were performed in normal conscious dogs at rest, after interruption of efferent loops through pharmacologic blockade, and also during treadmill exercise. This investigation was designed to demonstrate the extent of central neural control of the heart and peripheral circulations in the conscious animal, to examine the relative importance of changes in peripheral
resistance and cardiac output in determining the depressor response to sinus nerve stimulation, to determine the relative sensitivities of the visceral and hind-limb circulations to carotid sinus control and to ascertain the manner in which the circulatory alterations induced by exercise modify the response to carotid sinus nerve stimulation.

**Methods**

Using Na pentobarbital (30 mg/kg) for anesthesia and sterile surgical technique, blood flow transducers and bilateral carotid sinus nerve stimulating electrodes were implanted in mongrel dogs weighing between 19 and 34 kg. Flow transducers were placed on the ascending aorta (seven dogs), the cranial mesenteric artery (six dogs), left renal artery (six dogs), and left iliac artery (six dogs). Miniature blood pressure gauges were placed in the aorta.

Experiments were conducted 2 to 6 weeks after recovery from operation. At this time the apparent discomforting side effects of stimulation were minimal. A radiofrequency pacemaker generating a 0.3-msec rectangular waveform with a 50 pps repetition rate was used to stimulate the carotid sinus nerves. The amplitude (2.5 to 7.0 volts) was adjusted at the beginning of the experiment to obtain a maximal decrease in aortic pressure without the dog displaying any evidence of discomfort. Thirty-second periods of stimulation were used, since it was observed that the maximum decrease in aortic pressure occurs during this period. The effects of stimulation periods lasting 2 and 5 minutes were also determined. The effects of carotid sinus nerve stimulation were studied in seven dogs lying at rest, in four of these while running on a treadmill at 4 mph; in three dogs after beta-receptor blockade with propranolol 1 to 2.0 mg/kg; in three dogs after atropine 0.2 to 0.5 mg/kg. In five additional dogs the effects of carotid sinus nerve stimulation were studied on arterial pressure and heart rate after beta-receptor and cholinergic blockade. Blood flows and blood pressures were measured in 10 dogs; the pulsed ultrasonic flowmeter was used in five dogs, the Doppler ultrasonic flowmeter in three dogs and a Zepeda 400-cycle square wave electromagnetic flowmeter in two dogs.

When using the electromagnetic or pulsed ultrasonic flowmeters, zero flow was approximated with intravenous acetylcholine (.5 mg/kg) and confirmed during terminal calibration. When using the ultrasonic Doppler flowmeter, zero flow was determined electrically and confirmed terminally. Velocity as measured by the ultrasonic flowmeters is linearly related to volume flow as long as the cross-sectional area within the transducer does not vary. At autopsy in these animals the vessels were found to be fixed to the transducer shells, thus preventing changes in vessel diameter. Furthermore, volume calibrations carried out by timed collections of blood flow with beaker and stopwatch in three representative animals verified accuracy and linearity of the flowmeters. Aortic blood pressure was measured with miniature solid-state gauges chronically implanted in the thoracic aorta and calibrated in vivo against a Statham gauge in nine dogs. In three dogs aortic blood pressure was sampled through a catheter placed in the aorta through the femoral artery and measured with a Statham P23 Db strain gauge manometer.

Mean aortic pressure and mean blood flow were derived by electronic filters with a 3-second time constant. A cardiocapnometer (Beckman type 9857 B), triggered by the electrical signal from the aortic pressure pulse, provided instantaneous and continuous records of heart rate. Data were recorded on a multichannel oscillograph and magnetic tape recorder. Vascular resistances for the various beds were calculated as the quotient of mean aortic blood pressure and mean ascending aortic, mesenteric, renal, and iliac arterial blood flows.

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1 Medtronic, Inc., Minneapolis, Minnesota.
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Results
Arterial Blood Pressure in the Resting Dog.—A 30-second period of carotid sinus nerve stimulation produced an average maximum decrease in mean aortic blood pressure of $28\% \pm 3\%$ from control (from an average of 94 mm Hg during control to 65 mm Hg during stimulation) (Fig. 1). Pressure began to fall within the first 5 seconds of stimulation and reached a minimum level at 20 seconds. Pulse pressure usually widened considerably. Pressure began to return to control levels during the last 10 seconds of stimulation and reached control levels an average of 12 seconds after stimulation was discontinued. The magnitude and duration of the response between animals and even within animals were variable; in some cases decreases in mean pressure as great as 45% of control occurred. With longer periods of stimulation of 2 to 5 minutes, pressure returned to within 10% of control and cyclically fluctuated about this level until stimulation ceased.

A typical response to a 30-second period of carotid sinus nerve stimulation (CSNS) in the resting, conscious dog. The simultaneous responses of mean arterial pressure, phasic and mean mesenteric renal and iliac blood flow and heart rate are shown. Panel at left illustrates the wave forms at fast paper speed, one at right shows the response to stimulation at a slower paper speed.

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Heart Rate in the Resting Dog.—A 30-second period of carotid sinus nerve stimulation resulted in a prompt bradycardia, heart rate falling by an average maximum of 13% ± 4% from control (73 to 63 beats/min), within the first 10 seconds of stimulation (Fig. 1). After 15 to 20 seconds of stimulation, heart rate had returned to control levels, although pressure was still decreasing. The heart rate rose to an average of 8% above control at 30 seconds, just before the discontinuation of stimulation.

Cardiac Output and Total Peripheral Resistance.—A 30-second period of carotid sinus nerve stimulation resulted in little change in cardiac output (Fig. 1). An average decrease of cardiac output of 7% from control occurred within the first 10 seconds, at a time when heart rate was also decreased. However, after 15 to 20 seconds of stimulation, cardiac output had returned to control levels. At this point, aortic pressure was at minimum levels, resulting in a decrease in calculated total peripheral resistance averaging 29% ± 3% from control (Fig. 2).

Mesenteric and Renal Beds.—Carotid sinus nerve stimulation resulted in reduction of mesenteric flow of 12 ± 2% and renal flow of 8 ± 2%; these changes were not as marked as the decreases in arterial pressure (Figs. 2 and 3) and therefore, resistance in these two beds decreased (Fig. 2); calculated mesenteric resistance fell by an average of 18% ± 2% and renal resistance by 22% ± 3% from control. Two responses were peculiar to the renal circulation. First, the changes in the phasic wave form of renal blood flow during stimulation were the most prominent, resulting in an increase in systolic flow and a reduction in diastolic flow. Second, during recovery after...
the stimulation ceased, renal blood flow increased by an average of 12% above control levels, i.e., a secondary dilatation occurred in the renal bed (Fig. 4).

Iliac Bed.—In contrast to the mesenteric and renal beds, carotid sinus nerve stimulation uniformly produced an increase in iliac blood flow by an average of 90% ± 7% above control and a decrease in iliac vascular resistance averaging 62% ± 4%. The maximum increase in iliac flow typically preceded the maximum decrease in aortic pressure by 2 to 4 seconds.

Exercise.—Running on a treadmill at 4 mph resulted in an elevation of arterial pressure averaging 17% ± 3% (94 to 110 mm Hg), an increase in mesenteric resistance averaging 20% ± 3% and an increase in renal resistance averaging 17% ± 3%, while mesenteric and renal flows remained at control levels. Iliac flow increased by an average of 385 ± 12% of control, iliac vascular resistance fell by 70 ± 8% of control, while heart rate rose by an average of 143 ± 8% (74 to 180 beats/min). A 30-second period of carotid sinus nerve stimulation during exercise resulted in decreases in mean aortic pressure averaging 31% ± 4%, and in calculated resistances in the mesenteric and renal beds averaging 22 ± 2% and 24 ± 2%, respectively. These reductions were similar to those observed in the resting animal. Iliac flow increased even further during stimulation by an average of 17 ± 5%, resulting in a further lowering of calculated resistance by 41 ± 7% of the level that existed during exercise before stimulation (Fig. 5). Heart rate decreased by an average of 14 ± 3%, from 180 to 155 beats/min during the first 10 seconds of stimulation, but the response of heart rate after the initial bradycardia was variable.

Parasympathetic Blockade.—After atropine (0.2 to 0.5 mg/kg) heart rate increased from an average of 78 ± 3 to 144 ± 4/min. Carotid sinus nerve stimulation then produced an average decrease in heart rate of only 3%, from an
average of 144 to 140/min. With carotid sinus nerve stimulation, mean arterial pressure fell an average of 20 ± 4% (108 to 86 mm Hg), while the reductions in resistance in the mesenteric, renal, and iliac circulations averaged 19 ± 3%, 18 ± 3%, and 57 ± 6% of control, respectively.

Sympathetic Blockade.—After propranolol (1 to 3 mg/kg) heart rate decreased from an average of 72 ± 4 to 66 ± 4/min. Carotid sinus nerve stimulation lowered heart rate by an additional 9 ± 2% (avg 66 to 60/min), while mean arterial pressure decreased by an average of 30 ± 2% (92 to 64 mm Hg), and resistance decreased in the mesenteric, renal, and iliac circulations by averages of 24 ± 2%, 24 ± 2%, and 67 ± 5%, respectively.

Discussion

In the interpretation of the findings of this investigation it should be noted that the pattern of activation of the sinus nerves employed differed from that which occurs normally. In this study the electrical stimulus was at constant frequency for the entire 30-second period, whereas the normal impulse traffic in the carotid sinus nerves is rhythmic being intensified during ejection and reduced during diastole. Thus, the mode of stimulation employed herein resembles that resulting from constant rather than phasic distension of the carotid sinuses. Although it has been shown that phasic stimulation of the carotid sinus results in quantitatively different responses compared to static stimulation (8), the qualitative effects are identical. It should be noted, however, that most previous investigations on the carotid sinus reflex utilize preparations such as the one described by Moissejeff (9) which employs a nonpulsatile pressure stimulus, and thus, as in the present study, results in continuous rather than phasic stimulation.

It is recognized that the circulatory changes induced by carotid sinus nerve stimulation in an intact animal will, in turn, activate a variety of other control mechanisms. Thus, the responses observed during and immediately following carotid sinus nerve stimulation are not the isolated effects of activating the reflex, but are more complex, and involve also the superimposed effects of the organism’s responses to the induced circulatory derangements. To provide a basis for comparing the responses in different animals, maximal changes from control levels were employed, recognizing that the observed alterations might have been even more profound, though qualitatively similar, had the opposing control mechanisms been eliminated.

Carotid sinus nerve stimulation in the resting, conscious dog produces bradycardia, hypotension, and dilatation of the mesenteric, renal, and iliac circulations. These results are in general accord with earlier work performed in anesthetized preparations (1, 2), but the magnitude and duration of results in the conscious animal appear to be different. First, in the conscious animal there is considerable variability in the results produced by identical stimuli in different animals and even within the same animal on the same day. Second, in the conscious animal, recovery of arterial pressure and heart rate occurred more quickly than might have been expected from work in the anesthetized preparations (1, 2, 10). Thus, arterial pressure began to return to control levels while stimulation continued, and reached control levels shortly after stimulation ceased. Heart rate returned to control within 10 to 15 seconds and on the average a mild overshoot in heart rate occurred, even while stimulation continued. The rapid recovery of heart rate and arterial pressure during carotid sinus nerve stimulation in the conscious dog may be due to the opposing influences exerted by the aortic baroreceptors.

The observed overshoot of heart rate during carotid sinus nerve stimulation in the conscious animal suggests that the aortic receptors are more powerful than are the carotid baroreceptors in the control of heart rate, while the latter are more powerful than the former in the control of arterial pressure. Thus, the initial response to carotid sinus nerve stimulation is hypotension and bradycardia. The resulting diminished stimulation of the aortic receptors tends to restore both
arterial pressure and heart rate, the compensation being incomplete insofar as pressure is concerned, but more than complete in respect to heart rate.

Even before the rebound, maximal reduction of heart rate as a consequence of carotid sinus nerve stimulation averaged only 13% of control. These results are in accord with observations on the effects of carotid sinus nerve stimulation in conscious human subjects (11, 12). Since carotid sinus nerve stimulation resulted in a 10% decrease in heart rate after propranolol and in only a 3% decrease after atropine, it appears that in the conscious dog the bradycardia is chiefly due to vagal activation and to a lesser extent due to a decrease in sympathetic activity. These results are consistent with the findings, in both anesthetized and conscious dogs, of Glick and Braunwald (13) who observed that the bradycardia noted after pharmacologically induced hypertension was primarily due to vagal activation. They were also in accord with the recent observations in the conscious dog by Scher and Young (14) who elevated arterial pressure mechanically but they are not consistent with those of Berkowitz et al. (15) who stimulated carotid sinus nerves electrically in anesthetized dogs and found that the resultant bradycardia was not due to vagal activation. The latter differences may be accounted for by the vagolytic effects of general anesthesia (16).

Since carotid sinus nerve stimulation produced little change in cardiac output, it follows that the decrease in arterial pressure is mediated mainly by a decrease in peripheral resistance. It can be further concluded that the latter is due to a decrease in sympathetic vasoconstrictor tone (17). It is generally agreed that activation of the carotid sinus reflex causes a reduction in calculated resistance of the vessels supplying the limbs (1, 2). However, there is no unanimity concerning the magnitude of this response. In fact, some investigators have suggested that the carotid sinus reflex causes little vasodilation in the limbs and thus have implicated dilation in the splanchnic bed as being primarily responsible for the decrease in total peripheral resistance (18, 19). Other studies have shown that although carotid sinus activation produced some decrease in limb resistance, blood flow to the limb decreased (20, 21). Carotid sinus nerve stimulation in man during anesthesia resulted in no change or increased flow to the limb (22), while in conscious humans no change in forearm blood flow was observed (23). Our studies indicate that in the conscious dog carotid sinus nerve stimulation uniformly increased iliac blood flow markedly, despite the reduction in arterial pressure.

The concept that the carotid sinus exerts a differential pattern of control of the visceral as opposed to the muscular beds has been controversial. Some studies of the effects of carotid sinus hypotension have shown the vascular bed supplying the skeletal muscle to be more sensitive than that supplying the gut and kidney (10, 24), while others indicate the reverse (18, 19, 25). Our results indicate that a differential pattern of vasodilatation does occur with carotid sinus nerve stimulation. Resistance decreased by only 18% and 22% in the mesenteric and renal circulations, respectively, but by an average of 62% in the iliac bed. Thus, since iliac blood flow predominantly supplies skeletal muscle, the decreases in arterial pressure and total peripheral resistance appear to be mainly due to dilatation in the muscular beds in the conscious dog. Although the mesenteric and renal beds exhibited similar degrees of dilatation with carotid sinus nerve stimulation, the renal bed was unique in that further dilatation occurred after stimulation ceased, at a time when arterial pressure was increasing and dilatation decreasing in the mesenteric and iliac beds. This may be further evidence for autoregulation of renal blood flow.

Vasoconstriction, presumably mediated by increased sympathetic tone, has been demonstrated in the splanchnic and renal beds during exercise (26-29). This has also been observed in the resting human forearm during leg exercise (30, 31). Since carotid sinus nerve stimulation reduces sympathetic vasoconstric-
tor activity, it was not unexpected that carotid sinus nerve stimulation during exercise resulted in decreases in arterial pressure and in the calculated resistances in the mesenteric and renal beds. The presence of sympathetic vasoconstrictor activity to the resistance vessels of exercising limbs has been postulated (32, 33). However, experiments in dogs (34, 35) and cats (36) have indicated that neural factors probably play little role in regulating vascular resistance in the limbs in severe exercise, but suggest that it is controlled by local metabolic factors. The results of the present investigation indicate that this may not be the case since carotid sinus nerve stimulation during exercise caused further dilatation in the already dilated iliac bed. In our studies carotid sinus nerve stimulation during exercise produced a similar pattern as in the resting state; arterial pressure decreased and iliac blood flow, already elevated fourfold, increased even further. Thus, considerable vasoconstrictor tone must have been present in the exercising hind limb. Perhaps during exercise the simultaneously occurring neural vasoconstriction and metabolically mediated vasodilation occurred at different loci in the vascular bed. An alternative interpretation of these findings is that the increase in iliac flow with stimulation during exercise reflected an increase in blood flow to skin and bone. This explanation is less likely when considering that the fraction of iliac blood flow supplying bone and skin is small at rest and negligible during exercise.

In conclusion, these studies indicate that in the conscious resting dog, activation of the carotid sinus reflex through electrical stimulation of the carotid sinus nerves results in a bradycardia mediated primarily through the vagus nerve associated with decreases in arterial pressure and regional vascular resistance. The regional circulations exhibit a differential sensitivity to carotid sinus nerve stimulation; the greatest decreases in resistance occurred in the limb circulation with lesser effects in the visceral beds. During exercise carotid sinus nerve stimulation also resulted in a decrease in sympathetic constrictor tone not only to the visceral beds but also the muscular bed which was already dilated on a metabolic basis.

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**References**


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