Carotid Baroreceptor Function in Dogs With Chronic Norepinephrine Infusion


Carotid baroreceptor function, the compliance of the carotid sinus wall, and the structure of the carotid artery were examined in dogs with elevated plasma norepinephrine (2,000–4,000 pg/ml) for 28 days. The dogs with high norepinephrine were normotensive (100±4.0 versus 98±4.0 mm Hg; p>0.05) with bradycardia (65±4.0 versus 87±16 beats/min; p<0.05) compared with normal dogs in the conscious state. However, after pentobarbital anesthesia blood pressure was significantly higher in dogs with chronic norepinephrine infusion (165 ±6 mm Hg) compared with normal dogs (132±6 mm Hg). To assess baroreceptor sensitivity, multiunit carotid baroreceptor activity was recorded from the right carotid sinus nerve, and the carotid sinus wall compliance (sonomicrometers) was measured during nitroglycerin and phenylephrine injections. The threshold and saturation pressures increased from 96±3.9 to 117±4.2 mm Hg and from 145±4.3 to 171±5.7 mm Hg, respectively, in the normal dogs compared with the high norepinephrine dogs. The most striking differences were the marked increases in sensitivity of carotid baroreceptors (0.47±0.05 versus 1.99±0.45 spikes • sec⁻¹ • mm Hg⁻¹; p<0.01) and maximum firing frequency of the baroreceptors (24±3.1 versus 48±4.4 spikes/sec; p<0.01), whereas the carotid sinus wall compliance was unchanged (0.014±0.003 versus 0.012±0.002 mm/mm Hg; p>0.05). Similar alterations were observed using single fiber recordings, that is, an increase in threshold and saturation pressures and slope of baroreceptor units in dogs with elevated norepinephrine. The wall thickness and area of the carotid artery were determined. Both increased significantly (0.77±0.06 versus 1.30±0.12 mm and 9.0±0.8 versus 11.9±0.9 mm²; p<0.05) in dogs chronically infused with norepinephrine while the dry weight-to-wet weight ratio of left carotid artery tissue also increased from 26.0±0.73% to 29.0±0.57%. These studies indicate that 1) one of the possible mechanisms responsible for bradycardia in the conscious dogs with high norepinephrine is enhanced sensitivity of carotid baroreceptors; 2) the enhanced sensitivity of carotid baroreceptors is not due to a change in compliance of the carotid sinus wall; and 3) chronic elevation of norepinephrine causes hypertrophy or hyperplasia of the wall of the common carotid artery. (Hypertension 1991;17:745–754)

Chronic elevations in plasma arterial catecholamine concentrations are observed in several diseases including mitral valve prolapse, chronic myocardial failure, and pheochromocytoma. These diseases may exhibit sustained or episodic hypertension, dysautonomia, hyperadrenergic states, and hypervagotonia. Previous studies from this laboratory have shown that despite chronically high levels of norepinephrine (NE) (2,000–4,000 pg/ml), conscious dogs were normotensive due to bradycardia and low cardiac output. These data suggest that reflex buffering mechanisms are responsible for the maintenance of systemic arterial pressure, especially since hexamethonium or atropine in these dogs caused tachycardia and hypertension. We hypothesized that the arterial baroreceptor reflex plays a key role as a buffering mechanism in this model. Heymans et al demonstrated in 1953 that local application of NE onto the carotid sinus induced stimulation and sensitization of the baroreceptors, leading to intense activation of the baroreceptor reflex in dogs. Blacket et al showed that intravenous infusion of catecholamines for 8 days caused only transient hypertension in rabbits and that thereafter the rabbits were normotensive with bradycardia. As yet, there have been no studies docu-
menting the effects of chronic elevation of NE on carotid sinus baroreceptors (CSBs). The goal of the present experiments was to determine if chronic elevation of NE altered CSB function and whether the baroreceptors might be responsible for normalizing systemic arterial pressure in awake dogs with chronically elevated NE.

Methods

A total of 37 mongrel dogs of either sex, weighing 20–34 kg, were used in four sets of experiments. All dogs were anesthetized with sodium pentobarbital (30 mg/kg i.v.). Supplemental doses of anesthetic were given as necessary throughout the experiment. The protocol and methods were approved by the IACUC of New York Medical College and of the University of Nebraska Medical School and conform to the Guiding Principles for the Use and Care of Laboratory Animals of the American Physiological Society and the National Institutes of Health.

Effects of Chronic Elevation in Plasma Norepinephrine on Carotid Sinus Baroreceptor Function

Dogs in group 1 were used to determine the CSB function in six dogs with chronic NE infusion and in five normal dogs. A Tygon (Norton Plastics, Akron, Ohio) catheter was implanted in the descending thoracic aorta and secured with a purse-string suture through a thoracotomy in the fifth left intercostal space using sterile surgical techniques. The chest was closed in layers and the pneumothorax reduced. The dogs were allowed 2–3 weeks to recover. The mean arterial blood pressure and heart rate were measured from the implanted catheter connected to a strain-gauge transducer (Statham P23ID, Oxnard, Calif.) with the dogs in the conscious state. The procedure was performed for dogs with chronic NE infusion as described by us previously. In brief, two Alzet osmotic pumps (model 2ML4, Palo Alto, Calif.) containing NE (equivalent to 0.5 μg/kg/min for 28 days) were implanted subcutaneously in the dorsal aspect of the neck using local anesthesia with 2% lidocaine. After 10 days, another osmotic pump containing 30% of the original concentration of NE was implanted to maintain a NE plasma level of 2,000–4,000 μg/ml. Arterial pressure and heart rate were measured at the first, second, and third week after the elevation of plasma NE. At the 28th day of high NE, mean arterial pressure and heart rate were measured first in the conscious state. Then, in both normal dogs and dogs with high NE, CSB activity was recorded from the carotid sinus nerve (CSN) after pentobarbital anesthesia.

In brief, a midline cervical incision was used to expose the right carotid sinus. The dissection was carefully continued to define the glossopharyngeal nerve and the CSN. The CSN was cleaned of surrounding connective tissue and cut at its junction with the glossopharyngeal nerve. With the aid of a dissecting microscope, the sheath of the peripheral end of the CSN was removed, and the nerve was placed on platinum bipolar electrodes. The nerve impulses were preamplified using a P15D AC preamplifier (Grass Instruments, Inc., Waltham, Mass.) (gain of 1,000; 30-Hz to 3-KHz bandpass); nerve activity was displayed on an oscilloscope (type 565, Tektronix Inc., Portland, Ore.) and simultaneously transferred into a window discriminator (model 120, W-P Instruments Inc., Hamden, Conn.). The lower window was set above the noise level, and the upper level window was set high enough to incorporate all the moderate and large spike activity that was visible on the oscilloscope. Only a few very large spikes whose amplitude was higher than the upper window and only those spikes that became silent after injection of nitroglycerin were counted. The rastor/stepper (rate meter) was set to count the discriminated spikes and then reset after counting 16 spikes. In reality, we counted only a few large fibers in each preparation. The CSN was covered by warm mineral oil to prevent dehydration of the nerve. The phasic and mean arterial pressures, original nerve discharge, discriminator output, and rate meter output were recorded on a strip-chart recorder (1000ES, Gould, Rahway, N.J.).

The arterial pressure was decreased and increased after intravenous bolus injections of nitroglycerin (25–100 μg/kg) and phenylephrine (5–10 μg/kg), respectively. Nitroglycerin was always administered first. Phenylephrine was given when the arterial pressure, the original nerve discharge, and the discriminated spikes had returned to control values. The doses of nitroglycerin that we used were large enough to completely inhibit all nerve activity. The protocol was then repeated but with phenylephrine given first. The pressure at which the CSB firing disappeared was designated as threshold pressure and the pressure at which the CSB activity no longer increased, even though arterial pressure continued to increase, was designated as saturation pressure. The pressure–discharge data for nitroglycerin and phenylephrine were combined and a function curve (see below) of CSB discharge versus arterial pressure was constructed and the peak gain of the curve was calculated. In addition to recording multiunit activity, we also obtained threshold and saturation pressure and gain in five single units from two dogs with high NE and five single fibers from four normal dogs.

Effects of Chronic Elevation in Plasma Norepinephrine on Carotid Sinus Wall Function and the Maximum Firing Rate of Carotid Sinus Baroreceptor

The second group (group 2) was designed to measure the diameter of the carotid sinus and the maximum firing rate of CSB in the same dogs. Ten dogs were used. Six dogs were given chronic NE infusion for 28 days. Another four dogs served as controls. A Millar microtip pressure transducer...
(Millar Instruments, Houston, Tex.) was advanced into the right carotid sinus through the thyroid artery to permit high fidelity measurement of the intrasinus pressure. Two ultrasonic dimension transducers attached to a Dacron backing were sutured to the bottom and the top of the carotid sinus to give continuous measurements of carotid sinus diameter. Arterial blood pressure was changed by intravenous injections of nitroglycerin and phenylephrine. The received ultrasonic signal was monitored on an oscilloscope during placement and during the experiment and the output was displayed on a strip-chart recorder. Dimensions were measured using a Transit Time ultrasonic dimension gauge. The relation between intrasinus systolic pressure and carotid sinus diameter, as well as between carotid sinus diameter and CN discharge, was determined and the slopes of these curves were calculated. In these experiments, the original CN discharge was also sent to a Heathkit counter (model IM-4100, Benton Harbor, Mich.) to quantify spike frequency. Because of potential interference between the system for measuring carotid wall diameter and nerve recording, we were careful to ground between the diameter crystals and the recording electrode. In all of the animals, nitroglycerin and phenylephrine were given while measuring pressure and diameter and then given again while measuring pressure and spike activity. The order of these studies was then reversed. Pressure was measured each time and thus assured that each injection had similar effects. In three of the dogs, two with NE and one normal dog, we were able to record spike activity and diameter simultaneously.

**Determination of Morphological Changes in Carotid Sinus Wall**

The third group of dogs (group 3) was used to determine the external and internal diameters, area, and wall thickness of the right carotid sinus by a planimetric technique using a Videoplan Image Analyzer (Zeiss, Hawthorne, N.Y.). The right common carotid artery including the carotid sinus was perfused with formalin at 100 mm Hg in 10 dogs (high NE, n=4; normal, n=6) and then the carotid artery was cut transversely into at least three rings just adjacent to the carotid sinus for planimetric measurements. Since the carotid artery bifurcates at the level of the carotid sinus, if these rings were cut at the carotid sinus there would have been a septum making it impossible to measure the luminal diameter. Mean values for these data were obtained in each dog and then averaged in dogs with high NE and in control dogs. The left carotid artery was collected in four dogs with high NE and in seven control dogs. The dry weight-to-wet weight ratio of the artery was examined and compared between dogs with and without high NE.

**Data Analysis**

For multifiber preparation, the CSB function curve was fitted using a Sigmoid computer program based on the five parameter logistic equations by Ishikawa et al.

### Table 1. Influences of Pentobarbital Anesthesia and Chronically Elevated Norepinephrine on Mean Arterial Pressure and Heart Rate in Dogs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Condition</th>
<th>Conscious</th>
<th>Anesthetized</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>Control</td>
<td>98±4.0 (n=5)</td>
<td>132±6.0* (n=6)</td>
</tr>
<tr>
<td></td>
<td>High NE</td>
<td>100±4.0 (n=5)</td>
<td>165±6.0* (n=5)</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>Control</td>
<td>87±16 (n=5)</td>
<td>143±16* (n=6)</td>
</tr>
<tr>
<td></td>
<td>High NE</td>
<td>65±4.0* (n=5)</td>
<td>185±14* (n=6)</td>
</tr>
</tbody>
</table>

NE, norepinephrine.

*p<0.05 compared with conscious state.

fp<0.05 compared with control.

and was plotted using MULPLT (Decus, Marlboro, Mass.) on a PDP 11/73 computer. The maximum gain was determined by calculating the first derivative of this curve. Strain was calculated as radius minus unstressed radius divided by radius. Unstressed diameter was taken at a pressure of 40 mm Hg. Statistical analysis was performed using Student's t test to evaluate the significance of differences between two means from dogs with high NE and control dogs. Statistical significance was determined at the p<0.05 level. The results are expressed as mean±SEM.

**Results**

Table 1 shows the influence of barbiturate anesthesia on mean arterial pressure and heart rate both in dogs with high NE and in normal dogs. In the conscious state, there was no significant difference in mean arterial pressure between normal dogs and those with high NE. However, dogs with high NE had a marked bradycardia. After anesthesia, mean arterial pressure and heart rate rose more in the dogs with high NE than in control dogs (p<0.05).

**Effects of Chronic Elevation in Plasma Norepinephrine on Carotid Sinus Baroreceptor Function**

After injection of nitroglycerin and phenylephrine, the threshold and saturation pressures of CSBs were measured. Figure 1 shows an original recording from one dog with high NE. The window discriminator pulse in this figure clearly shows that only a few of the larger units were counted. As can be seen during nitroglycerin administration, a threshold pressure is reached at which discharge ceases. We found that the average threshold pressure and saturation pressure of CSB were significantly elevated in dogs with high NE. Figure 2 illustrates typical curves from one control dog and one dog with high NE. Although both curves follow a characteristic sigmoid relation, threshold pressure, saturation pressure, and the slope of the linear portion of the curve are all elevated in the dog with high NE. The mean data for gain and
FIGURE 1. Threshold pressure of carotid sinus in one dog with chronically elevated norepinephrine. Traces are, from top to bottom, spike activity from the window discriminator, the raw nerve activity, the output of the rate meter, and change in phasic and mean arterial pressure. Nitroglycerin (nitro) completely shut off the baroreceptor activity.

threshold and saturation pressures are shown in Figure 3. The threshold pressure and saturation pressure were 117±4.2 and 171±5.7 mm Hg and 96±3.9 and 145±4.3 mm Hg in dogs with high NE and control dogs, respectively. The gain of the CSB curve was 1.99±0.45 spikes · sec⁻¹ · mm Hg⁻¹ in

FIGURE 2. Two baroreceptor discharge–mean arterial pressure (MAP) curves from a dog with high norepinephrine (NE) and a normal dog. Note that the maximum discharge rate as well as the maximum gain are increased in the dog with high NE.
dogs with high NE, which was significantly \( p < 0.05 \) higher than \( 0.47 \pm 0.05 \) spikes \( \cdot \) sec\(^{-1} \cdot \) mm Hg\(^{-1} \) in control dogs.

To determine if similar results could be obtained on single baroreceptor units, five single fibers from two high NE dogs and five fibers from four normal dogs were examined. The gain, threshold pressure, and saturation pressure for single fiber preparations of CSN were \( 1.89 \pm 0.4 \) spikes \( \cdot \) sec\(^{-1} \cdot \) mm Hg\(^{-1} \), \( 97 \pm 2.9 \) mm Hg, and \( 166 \pm 17.5 \) mm Hg in dogs with high NE and \( 0.54 \pm 0.11 \) spikes \( \cdot \) sec\(^{-1} \cdot \) mm Hg\(^{-1} \), \( 88 \pm 11 \) mm Hg, and \( 148 \pm 6.6 \) mm Hg in control dogs, respectively. Thus, there is a consistent increase in the CSB gain in dogs with chronically elevated NE using either single or multifiber recordings.

**Effects of Chronic Elevation in Plasma Norepinephrine on Carotid Sinus Wall Function and the Maximum Firing Rate of Carotid Sinus Baroreceptor**

As is shown in Figure 4, in dogs with high NE, the carotid sinus systolic pressure–carotid sinus diameter curve was shifted downwards in a parallel fashion compared with normal dogs. The slopes of these two curves were not different \( p > 0.05 \). However, NE produced a significant change in carotid sinus diameter, despite the similar average body weights for the two groups \( 25 \pm 2.2 \) kg and \( 26 \pm 3.6 \) kg, respectively. Figure 5 shows the relation between carotid sinus diameter and CSB discharge in these 10 dogs. The activity of CSBs in dogs with high NE increased significantly more than that of control dogs despite the initial smaller diameter, whereas the changes in carotid sinus diameters were similar. Second, dogs with high NE showed a dramatic increase in CSB firing rate when carotid sinus diameter exceeded 4.3 mm; above this diameter, the carotid sinus exhibited little additional deformation as pressure increased.

The maximum adapted firing rate above saturation pressure was measured both in dogs with high NE and in control dogs. Maximum firing rate was counted from the original CSN impulses by two methods, one using the raster (resetting rate meter) and the second using the Heathkit counter. A striking increase in maximum CSN firing rate from dogs with high NE was observed. In dogs with high NE, the maximum firing rate was \( 48 \pm 4.4 \) spikes/sec \((n=12)\) using the raster, whereas in control dogs the maximum firing rate was \( 24 \pm 3.1 \) spikes/sec \((n=10)\). The difference between dogs with high NE and control dogs was significant \( p < 0.01 \). Similar results were found in single fiber preparations indicating an increase in the gain and maximum firing rate of the carotid baroreceptors in dogs with chronically elevated plasma NE (Table 2).
Table 2. Increases in Gain and Maximum Firing Rate of Carotid Baroreceptors in Dogs With Elevated Plasma Norepinephrine

<table>
<thead>
<tr>
<th>Measure</th>
<th>Conditions</th>
<th>Gain (spikes/sec-mm Hg)</th>
<th>Maximum firing rate (impulses/sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single fiber</td>
<td>Control</td>
<td>0.54±0.11</td>
<td>30±2.1</td>
</tr>
<tr>
<td></td>
<td>High NE</td>
<td>1.89±0.40*</td>
<td>58±4.2*</td>
</tr>
<tr>
<td>Window dis</td>
<td>Control</td>
<td>0.47±0.05</td>
<td>24±3.1*</td>
</tr>
<tr>
<td></td>
<td>High NE</td>
<td>1.99±0.45*</td>
<td>48±4.4*</td>
</tr>
<tr>
<td>Heathkit counter</td>
<td>Control</td>
<td>.</td>
<td>497±17</td>
</tr>
<tr>
<td></td>
<td>High NE</td>
<td>.</td>
<td>989±29</td>
</tr>
</tbody>
</table>

Single fibers control n=5, norepinephrine n=5; window discriminator control n=5, norepinephrine n=6; Heathkit counter control n=4, norepinephrine n=6. NE, norepinephrine; dis, discriminator. *p<0.05 compared with control.

To determine whether there may be a change in the mechanical function of the carotid sinus in dogs with chronically elevated plasma NE, we calculated wall strain and plotted this as a function of baroreceptor activity. Figure 6 shows the relation between wall strain and spike activity as arterial pressure changed using an injection of nitroglycerin and phenylephrine. At low-to-intermediate wall strains, the relation between strain and spike activity was shifted to the right in dogs with chronically elevated plasma NE; however, at high wall strains baroreceptor activity increased dramatically.

**Determination of Morphological Changes in Carotid Sinus Wall**

Figure 7 illustrates the results of wall dimension measurement of the carotid arteries in both high NE and control dogs. At a perfusion pressure of 100 mm Hg, the wall thickness and area of the carotid artery were significantly increased (p<0.05), and the internal diameter was significantly decreased (p<0.05) in dogs with high NE. The external diameters of the carotid sinus measured by sonomicrometry and planimetric techniques at 100 mm Hg were similar: 3.93±0.13 mm (sonomicrometer) and 4.14±0.12 mm (planimetry) in dogs with high NE (p<0.05) and 4.9±0.15 mm (sonomicrometer) and 4.8±0.17 mm (planimetry) in control dogs (p>0.05). The dry weight-to-wet weight ratios of carotid arteries from dogs with high NE and control dogs were 29.0±0.57% and 26.0±0.73%, respectively (p<0.05).

**Discussion**

In previous studies, we found that dogs with chronically elevated plasma NE are not hypertensive, because of low cardiac output secondary to a marked bradycardia, and that these dogs became hypertensive when the bradycardia was interrupted. Our study implied that reflex buffering mechanisms are responsible for maintenance of systemic arterial pressure. The present study suggests that intense activation of CSB reflex buffering mechanisms may play an important role in controlling blood pressure in dogs with high NE.

In dogs with high NE, we found that the activity of CSBs was altered in two ways: first, the maximum slope of CSB function curve was significantly increased whether we used multifiber or single fiber preparations. In the present study, the slope averaged 0.45±0.05 impulses/sec•mm Hg⁻¹ in normal dogs. Data from other laboratories indicate that the sensitivity of the large- and medium-sized CSB discharges is 0.29–0.50 impulses • sec⁻¹ • mm Hg⁻¹ in normal dogs. In chloralose-anesthetized dogs, Chapleau and Abboud found multitunit activity ranging between 3.38 and 7.04 spikes/sec/mm Hg and single unit activity to be 0.59–1.25 spikes/sec/mm Hg. The CSN impulses picked up by the window discriminator in our study, whether they come from multifiber or single fiber preparations from the present study, were most likely large and intermediate spikes or medullated (A-type) fibers based on the setting of the window discriminator (more than 40 μV) and the characteristics of the discharge. The maximum firing rate also increased in dogs with high NE. Landgren observed that the fibers in the CSN with the largest impulses fire at 250–350 spikes/sec and the small impulse units at 50–150 spikes/sec. However, it is believed that the total maximum firing rate in a multifiber preparation is the algebraic sum of the changes occurring in individual fibers. We did not find any studies that reported maximum firing rate in a whole CSN preparation of normal dogs. The results of the present study show that the maximum firing rate of CSBs increased. These results are also consistent with the observation by Goldman and Saum using an in vitro aortic arch preparation. These investigators found that NE produced a nonparallel
shift in the aortic baroreceptor function curve and an increase in the maximum firing frequency. The increase in slope of CSB function curve in the high NE dogs suggests that the augmented CSB activity enters the brain stem (especially as pressure rises), and the increase in maximum firing rate also signifies that the maximum "gain" of the CSBs was elevated. The increased gain may result in enhanced baroreceptor control of cardiac autonomic activity, may inhibit peripheral sympathetic nervous activity, and facilitate vagal outflow to promote the reflex lowering of arterial pressure.

Additional evidence for the elevated vagal tone resulting from the arterial baroreceptor reflex in dogs with high NE was the increase in arterial pressure and tachycardia after pentobarbital anesthesia, as shown in Table 1. Pentobarbital anesthesia was found to depress the arterial baroreceptor reflex of the dog. Korner and collaborators demonstrated that pentobarbital specifically blocked diencephalic regions influencing vagal efferents. Because the vagal efferent component was completely blocked by pentobarbital anesthesia, the dogs with high NE had significantly greater increases in mean arterial pressure and heart rate than normal dogs simply because of the anesthesia. In other words, conscious dogs with high NE had very high vagal tone. Despite the relatively small bradycardia in dogs with chronic NE infusion, at a constant stroke volume of about 45 ml a reduction in heart rate from 87 to 65 beats/min would result in a calculated reduction of cardiac output from 3,915 to 2,925 ml/min or 25%. Thus, this increase in vagal tone can significantly reduce cardiac output. Minimum heart rates in dogs without A-V block are 40–50 beats/min. These estimates of cardiac output are similar to our previously published study. Another way of describing the level of vagal tone would be to subtract the heart rate in the conscious state from that in the same group after anesthesia. This difference is 120 beats/min in the control group compared with only 56 beats/min in the control group. This provides an additional estimate of the degree of vagal tone in dogs with chronic elevation of plasma NE and of the important role of the baroreceptor reflexes in the control of arterial pressure through altering heart rate and cardiac output.

A question arises concerning whether the difference in arterial pressure between control dogs and dogs with high NE is responsible for the increased slope that we observed. Tomomatsu and Nishi used the same concentration of NE (10^-9 M) as in our study and found that NE might lower, have no effect, or elevate the threshold pressure of rabbit CSBs in vitro. Although an increase in pressure may limit the evaluation of the threshold pressure and saturation pressure of the CSBs, the slope of CSB function curve was not altered by the elevated mean arterial pressure. When baroreceptors are reset, the function curve is shifted in a parallel fashion with no consistent change in gain. Increases in the slope of the function curve only occurred at 15 minutes of sustained pressure elevation. The threshold pressure and slope of the baroreceptor function curve may be independently regulated and resting blood pressure does not affect the receptor gain. In the present study, the delay between inducing anesthesia and recording nerve activity was always longer than 2 hours, so there is no reason to suspect a significant influence of blood pressure on the slope of CSB function curve.

The enhanced sensitivity and maximum firing frequency of CSBs could be due to either the direct effect of NE on the CSBs or the indirect effect of NE on the smooth muscle of the carotid sinus wall. One possible conclusion of the present study is that NE had direct biochemical effects on the CSN endings. The parallel downward shift of the carotid sinus systolic pressure–carotid sinus systolic diameter curve in dogs with high NE suggests that the compliance of carotid sinus was not affected by NE. This implies that baroreceptors are equally stretched by the mechanical deformation of carotid sinus wall due to increasing intrasinus pressure in dogs with NE and normal dogs. These results are consistent with the report by Tomomatsu and Nishi in the rabbit carotid sinus where the compliance of the carotid sinus did not change when perfused with the same concentration of NE (10^-9 M) as we used in our experiment (5,000 pg/ml·1 pmol/267 pg·1,000 ml/l=19×10^-14 M). Carotid sinus diameter decreased in our study, which might be partially due to the vasoconstrictor effect of NE.
NE released from sympathetic nerve endings by electrical stimulation and sympathomimetic drugs could affect carotid sinus wall compliance, which might result in a shift of slope of CSB function curve. However, mechanical stimulation resulting from a change in wall tension or diameter of the carotid sinus by NE may also increase CSB activity. The technique for carotid sinus diameter measurement that we used in this study directly addresses this question (Figure 8). At higher arterial blood pressure with large pulse pressures, the carotid sinus was stiffer (less deformation), and at lower arterial blood pressures with smaller pulse pressures, the carotid sinus was more deformable (more compliant). CSBs were firing continuously at high arterial blood pressure and firing intermittently in a synchronous fashion at lower arterial blood pressure. Bell et al suggested that a reduction of carotid sinus diameter will cause a decrease in CSB activity or the receptors in parallel with the carotid sinus wall will unload and the receptors in series with the carotid sinus wall will fire. The final CSB output will presumably be decreased. This did not occur in the present study as an increase in the CSB activity was observed even though the compliance of carotid sinus did not change and the diameter of carotid sinus was reduced. The relation between the diameter of carotid sinus and CSB activity suggests that saturation pressure of the CSBs should coincide with the point when the carotid sinus diameter ceases to increase linearly with intrasinus pressure. In the present study, the CSB firing was increased dramatically even after the diameter of carotid sinus was maximal.

Andresen and colleagues suggested that the baroreceptor firing is more directly related to circumferential wall strain as the ratio of change in vessel radius to initial radius, which is considered to be a good index of vessel mechanical properties.

\[ \sigma = \frac{R_p - R_o}{R_o} \]

where \( R_p \) is radius at a given pressure and \( R_o \) is the unstressed minimum radius that was recorded at minimum arterial pressure in the present study. Minimum radius was measured at 40 mm Hg arterial pressure, whereas maximum radius was measured at saturation pressure. Strain was higher (\( p < 0.01 \)) in dogs with high NE (0.123±0.04 versus 0.09±0.009). CSBs in dogs with high NE required greater vessel wall distortion to become excited than did those in control dogs.

This is supported when baroreceptor firing is plotted as a function of wall strain (Figure 6). At low-to-intermediate levels of wall strain, dogs with chronically elevated plasma NE had reduced sensitivity to changes in wall strain. This may result from some degree of resetting due to the significantly greater arterial pressure when dogs with chronically elevated plasma NE are anesthetized (Table 1). At elevated wall strains, there is an exponential increase in baroreceptor firing rate that may indicate an additional property of NE to directly stimulate or sensitize baroreceptors. Based on these observations, it seems likely that the excitatory effects of NE on CSBs resulted partially from direct biochemical effects, including stimulation or sensitization of CSBs. This is probably the primary effect of chronic NE infusion in the awake dog, in which arterial pressure is normal (i.e., 100 mm Hg) and where there would be no resetting due to hypertension.

There is general agreement that CSBs are nerve endings that respond to deformation of the vessel walls in which they are located. Our results measuring carotid sinus diameter are difficult to interpret in this context. Our experiments indicated that CSBs fire more at high intrasinus pressure in either high NE or control dogs, at a time when the wall was fully distended and less deformation occurred during each systole. The possible explanations are: first, that the stress on the CSBs is determined by the transmural pressure (Pt), the internal radius (Ri) of carotid sinus, and the carotid sinus wall thickness (D):\[ S = \frac{P_t \cdot R_i}{D} \]

This equation shows that at high intrasinus pressure, Pt and Ri increase, whereas D decreases, resulting in an increase in S. In this case, the increase in CSB firing may be proportional to the elevated wall stress. This explanation is unlikely since the deformation of...
The carotid sinus wall during each systole was reduced at high pressure in our study. Alternatively, a change in strain may be responsible for the enhanced CSB firing at high intrasinus pressures. Since unstressed diameter is lower in dogs with chronic NE infusion, maximum strain or the change in strain at large diameters will also be greater leading to the generation of increased CSB activity.

Second, the increased firing rate might be related to the arrangement of the CSB within the carotid sinus wall. Presumably, the majority of CSBs are in parallel with the carotid sinus wall and are activated at high pressure. Only the receptors in series with the carotid sinus wall keep firing within the low pressure range. In this regard, Landgren et al suggested that CSBs were "in parallel" with the smooth muscle of carotid sinus wall, whereas Bergel et al believed that the receptors were "in series" with the carotid sinus wall. A third reason for the increased firing rate was suggested by Kirchheim, who divided CSN fibers into two groups. The first fiber group firing coincides with the "high-distensibility region" in which the receptor-carrying vessel transforms transmural pressure into circumferential stretch. These stretch receptors transmit the dynamic components of blood pressure: dP/dt. The firing range of the second fiber group, according to Kirchheim, coincides with the "low-distensibility region" of the receptor-bearing vessel. These units are likely to sense mainly mean pressure. Kirchheim concluded that baroreceptor activity is attributed to the mechanical deformation of the vessel wall no matter how one divides the baroreceptor activity. Whether the enhanced sensitivity in the present study results from greater stress, strain, or some specific anatomic arrangement of CSB cannot be determined.

Historically, Landgren et al, Heymans et al, and a number of other investigators have demonstrated that NE or other catecholamines affect the activity of baroreceptors in various species and in different experimental preparations including local administration of NE on the outside of the carotid sinus and perfusion of the carotid sinus with a solution containing NE in either in vivo or in vitro studies. The results of these observations are consistent with the hypothesis that NE increases the activity of CSBs due to either an effect on smooth muscle of the carotid sinus wall or the direct excitatory effects on CSBs. More recent studies have supported the later conclusion. Kunze et al demonstrated the direct excitatory effects of NE on the receptor activity when the aortic arch was superfused with NE at concentrations of 10⁻⁷ to 10⁻⁵ M. Goldman and Saum reported similar results (i.e., aortic baroreceptor activity was significantly increased by 10⁻⁷ to 10⁻⁵ M NE). Similar findings were reported by Tomomatsu and Nishi who used very low concentrations of NE (10⁻⁷ M). The concentration of NE used in the present study was 10⁻⁹ M.

Bell et al suggested that the physiological significance of the effects of NE on CSBs might reduce the sympathetic efferent activity and modulate blood pressure during hemorrhagic hypotension. This hypothesis is supported by the present study. NE has two opposing effects on modulation of arterial pressure, namely increases in myocardial contractility, heart rate, and total peripheral resistance, leading to an increase in arterial pressure. On the other hand, NE also stimulates and sensitizes CSBs resulting in reflex decreases in heart rate, myocardial contractility, and total peripheral resistance due to high vagal tone and the reduction of sympathetic effenter activity. The final arterial pressure will be determined by the interaction of these two opposing actions and the degree and duration of hemorrhage. In the dogs with chronically elevated plasma NE, reflex modulation appears to be dominant in maintaining normal arterial pressure. This hypothesis may provide a more reasonable explanation for the changes in arterial pressure in some pathological states that are characterized by high catecholamine levels. The present study suggests that this feedback system may play an important role in the regulation of blood pressure, perhaps through the excitatory action on arterial baroreceptors during high catecholamine states. The concept of CSB resetting may also be modified by the present study, in that the working range of CSBs is not only rapidly adjustable to the prevailing pressure but also that the effects of chronic NE on CSBs prevent systemic hypertension. The influences of chronic elevation of NE on central nervous system were not studied so that some potential effects of high NE on cardiovascular centers could not be ruled out.

Finally, the present study clearly demonstrates that the chronic elevation of NE causes morphological changes in the common carotid artery without changes in compliance of the carotid sinus. Catecholamines can stimulate the growth of vascular smooth muscle in cell culture. Bevan reported that sympathetic nerves had influences on the development of normal and hypertrophied vessels through an arterial pressure-independent action. Casals-Steenzel et al and Lever et al found that chronic elevation of plasma NE in rats caused hypertrophy of large arteries. The results from our study indicate that increases in wall thickness and in the area of the common carotid artery wall by the chronic elevation of NE were due to hypertrophy or hyperplasia.

In a recent study, Nejima et al reported that dogs with chronic infusion of NE had a slight, but statistically insignificant, bradycardia. However, after ganglionic blockade in all groups of dogs that were infused with NE, heart rate increased to a larger degree compared with control (before pumps). In a group of cardiac-denervated dogs with chronic NE infusion, heart rate increased compared with control (before pumps). These studies indicate that some reflex mechanism is responsible for preventing tachycardia during NE infusion. Our data suggest that the baroreceptors are responsible.
References


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