Unloading arterial baroreceptors causes neurogenic hypertension

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Received 26 July 2001; accepted in final form 4 December 2001

Thrasher, Terry N. Unloading arterial baroreceptors causes neurogenic hypertension. Am J Physiol Regulatory Integrative Comp Physiol 282: R1044–R1053, 2002; 10.1152/ajpregu.00431.2001.—We developed a new model to examine the role of arterial baroreceptors in the long-term control of mean arterial pressure (MAP) in dogs. Baroreceptors in the aortic arch and one carotid sinus were denervated, and catheters were implanted in the descending aorta and common carotid arteries. MAP and carotid sinus pressure (CSP) averaged 104 ± 2 and 102 ± 2 mmHg (means ± 1 SE), respectively, during a 5-day control period. Baroreceptor unloading was induced by ligation of the common carotid artery proximal to the innervated sinus (n = 6 dogs). MAP and CSP averaged 127 ± 7 and 100 ± 3 mmHg, respectively, during the 7-day period of baroreceptor unloading. MAP was significantly elevated (P < 0.01) compared to control, but CSP was unchanged. Heart rate and plasma renin activity increased significantly in response to baroreceptor unloading. Removal of the ligature to restore normal flow through the carotid resulted in normalization of all variables. Ligation of the carotid below a denervated sinus (n = 4) caused a significant decrease in CSP but no systemic hypertension. These results indicate that chronic unloading of carotid baroreceptors can produce neurogenic hypertension and provide strong evidence that arterial baroreceptors are involved in the long-term control of blood pressure.

blood pressure; plasma renin activity; dogs

The hypothesis that arterial baroreceptors could play a role in the development of hypertension arose in the first half of the 20th century (see Ref. 15 for review). Baroreceptors are stretch-sensitive fibers located primarily in the arch of the aorta and also bilaterally in the carotid sinuses. They provide the afferent signal to a negative-feedback circuit in the medulla that maintains mean arterial pressure (MAP) at normal levels. Thus an increase in MAP stimulates baroreceptors and causes a reciprocal reduction in sympathetic outflow to resistance vessels and the heart to restore MAP to normal levels; conversely, a decrease in MAP unloads baroreceptors and leads to increased sympathetic outflow. This mechanism suggested the hypothesis that sinoaortic denervation (SAD) would result in chronically increased sympathetic outflow and therefore cause neurogenic hypertension.

Initial tests of the hypothesis resulted in reports of striking increases in MAP after SAD (11, 15); however, the classical studies of Cowley and colleagues (9) led to its demise. They measured MAP continuously for 3–5 days in dogs with chronic SAD and observed tremendous lability in MAP, but the average 24-h blood pressure measurements were only modestly increased compared with animals with intact baroreceptors. Later, Cowley and co-workers (10) reviewed data obtained in a much larger population of dogs with SAD and reported that the average pressures over 3–5 days of continuous measurement were 107 mmHg (n = 41) compared to 105 mmHg (n = 40) measured in intact dogs under similar conditions. The effects of SAD on MAP have also been examined in rats (27), rabbits (32), cats (30), and monkeys (5) with similar results: increased lability of MAP but no significant hypertension. Only baboons have been reported to maintain a chronic increase in MAP, which averaged 11 mmHg above control levels 4 wk after SAD (34).

A second argument against baroreceptor participation in the long-term control of blood pressure is the observation that the receptors adapt to imposed changes in MAP. This was first demonstrated by McCubbin and colleagues (26) in renal hypertensive dogs. Recordings from baroreceptor afferents in hypertensive dogs indicated a marked increase in the threshold pressure and a normal phasic response at pressures >200 mmHg. More recently, it has been shown that baroreceptor resetting begins in as little as 20 min (4) and is essentially complete within 48 h based on electrophysiological criteria (22). If, in fact, the normal operating point of the baroreceptors completely resets to the prevailing arterial pressure, it would seem to be an unlikely mechanism to cause hypertension. However, this has never been demonstrated experimentally.

A third argument is that the reflex gain of the baroreceptor control system is not sufficiently strong to explain the long-term constancy of blood pressure (6). Various studies in anesthetized dogs and rabbits have shown that arterial baroreceptors provide only 65–75% compensation for a given change in arterial pressure (6, 21). Furthermore, Cowley and colleagues (9) re-
ported that the 24-h pressure variability in the dogs with SAD was twice that observed in intact dogs. Based on this observation, they calculated the overall gain of the baroreceptor reflex to be approximately −1, which is a value much too low to explain the long-term stability of blood pressure. Taken together, the results summarized here have led to the conclusion that baroreceptor input is crucial for the moment-to-moment control but does not participate in the long-term control of MAP (6).

However, a number of recent studies have provided evidence that requires reexamination of these arguments. For example, the fact that chronic SAD does not result in a sustained elevation in MAP in most species is considered to be compelling evidence against baroreceptor unloading as a causative factor in hypertension. A serious flaw in this argument is that it assumes no remodeling of neural structures in the baroreceptor pathway after loss of afferent input. This is unlikely to be true. Lesions of the nucleus tractus solitarius (NTS), which is the central terminal for baroreceptor afferents, cause dramatic acute increases in MAP in rats (as would be expected; Ref. 33). However, lesioning the NTS in rats with chronic SAD has no effect on MAP, which indicates that adaptation to loss of baroreceptor input must have occurred somewhere in the medullary baroreceptor pathway. Furthermore, renal nerve activity and MAP are increased acutely after SAD, but chronically, both variables return to control levels (2, 16). Normalization of renal nerve activity indicates that adaptation to loss of inhibitory input from baroreceptors must have occurred. These results indicate that SAD is most likely not a good model to simulate chronic baroreceptor unloading.

There is no doubt that hypertension induced by various experimental manipulations does lead to baroreceptor resetting. However, evidence obtained in recent studies suggests that baroreceptor reflex activity is maintained in response to chronic challenges to blood pressure homeostasis. Osborn and Hornfeldt (28) recorded MAP continuously during 4 wk of dietary salt loading in baroreceptor-intact rats and rats with SAD. Salt loading caused minimal changes in MAP in baroreceptor-intact rats but caused significant increases in MAP in rats with SAD. These results indicate that the baroreceptors were chronically buffering the effects of large increases in dietary sodium chloride intake on MAP. Lohmeier and co-workers (24) studied responses to salt loading in dogs using a split-bladder preparation and unilateral renal denervation. Although MAP was elevated for 3 of 5 days of increased sodium intake, sodium excretion from the innervated kidney was significantly greater compared with the denervated kidney over the entire study. These results complement the report by Osborn and Hornfeldt (28) and provide evidence that the buffering mechanism at least partially involves suppression of renal sympathetic nerve activity. King and colleagues (20) recorded MAP in dogs that were infused continuously with noradrenaline (NE) in quantities sufficient to raise plasma levels >2,000 pg/ml for 21 days. MAP did not change, but heart rate (HR) and cardiac output were reduced throughout the period of infusion. Atropine administration or ganglionic blockade resulted in immediate increases in HR and hypertension, which indicate sustained buffering of the pressor action of NE. Each of these studies is consistent with the hypothesis that baroreceptors participate in the long-term control of MAP.

We have developed a new model of chronic baroreceptor unloading to examine the role of the baroreceptor reflex in the long-term control of MAP in conscious dogs. In the model, aortic and carotid baroreceptors in one sinus are denervated chronically, and baroreceptors in the other carotid sinus are left functional. These innervated receptors are chronically unloaded by placement of a ligature on the common carotid artery proximal to the sinus. Here we present evidence that unloading these functional baroreceptors leads to a significant and sustained increase in MAP. Furthermore, the results show that the reflex gain of the baroreceptor reflex is much greater than the value estimated from the pressure variability in dogs with SAD. Taken together, these observations indicate that arterial baroreceptors can play an important role in the long-term control of MAP.

METHODS

General Parameters

Experiments were performed on adult purpose-bred male mongrel dogs that weighed 22–35 kg (Butler Farms, Clyde, NY). The dogs were individually housed in a room maintained at 22 ± 2°C with 70% humidity on a 12:12-h light-dark cycle. Each day between 1300 and 1800, the dogs were administered oral prophylactic antibiotic treatment (400 mg of sulfamethoxazole plus 80 mg of trimethoprim) and fed a mixture of dry chow and canned food sufficient to maintain a constant body weight. The food was always consumed within 15 min of presentation, and sodium intake on this diet averaged 2–3 meq·kg⁻¹·day⁻¹. Water was available ad libitum.

Patency and sterility of the vascular catheters were maintained by filling the catheters with a mixture of heparin (1,000 U/ml; Elkins-Sinn, Cherry Hill, NJ) and penicillin G potassium (20,000 U/ml; Eli Lilly, Indianapolis, IN), which was replaced a minimum of every 72 h. To ensure that the dogs were free of infection throughout all aspects of the study, rectal temperatures were taken daily before the recording sessions. Rectal temperatures were always below 39°C, which indicates that the dogs were free of infection throughout the duration of the study.

Surgical Procedures

The dogs were sedated with acepromazine maleate (0.2 mg/kg body wt iv; Tech America, Elwood, KS) and anesthetized with pentobarbital sodium (25 mg/kg body wt iv; Fort Dodge Laboratories, Fort Dodge, IA) for all major surgical procedures (thoracotomies and carotid sinus preparations). Analgesia after thoracotomies was provided by application of a Duragesic patch (Janssen Pharmaceutica) that delivered fentanyl transdermally at a dose of 50 μg/h for 3 days. Analgesia after neck surgery to prepare one carotid sinus and denervate the other was provided by administration of Buprenex buprenorphine as required (0.015 mg/kg body wt sc;
Reckitt and Colman Pharmaceuticals). During the postoperative periods after major surgical procedures, the dogs were treated with Baytril (enrofloxacin, 2.5 mg/kg body wt; Mobay, Shawnee, KS) twice daily to provide antibacterial coverage. Minor surgical procedures (to ligate the common carotid proximal to an innervated or denervated carotid sinus and subsequently to remove the ligature) were performed with the dog under Pentothal Sodium anesthesia (20 μg/kg body wt iv).

Preparation of the model involved two separate surgical procedures. In the first procedure, the heart was exposed via a left lateral thoracotomy (fourth interspace). All visible nerves in the region of the aortic arch were cut, and the adventitia of the aorta was stripped beginning at the origin of the ascending aorta to the level of the second intercostal artery. Also, the adventitia of the brachiocephalic and subclavian trunks was stripped to the level of the second bifurcation of each vessel. Finally, the vessels were painted with 5% phenol in isopropyl alcohol. The chest was closed and negative pressure was reestablished to insure complete expansion of the lungs. Tygon catheters (0.5 in ID, 0.9 in OD) were also placed in the left atrium via the left atrial appendage and the abdominal aorta and vena cava via a femoral approach. The catheters were tunneled subcutaneously to exit between the shoulder blades and were protected by placement in a pouch sewn to the underside of a nylon jacket (Alice King Chatham Medical Arts, Los Angeles, CA). At least 2 wk were allowed for recovery before the second surgical procedure. The carotid baroreceptors were exposed via a ventral midline neck incision. Baroreceptors on one side were denervated by sectioning of the cranial thyroid and internal carotid arteries and all other vessels originating from the external carotid proximal to the lingual artery. The adventitia between the cranial thyroid artery and the lingual artery was stripped and painted with 5% phenol in isopropyl alcohol. On the side to remain innervated, the internal carotid artery was ligated ~1 cm from its origin with care taken to preserve the sinus nerve. The cranial laryngeal artery was ligated and sectioned. A ligature was placed around the origin of the occipital and ascending pharyngeal arteries in all dogs thus separating the carotid body from the carotid circulation. In some dogs, these vessels and associated carotid-body afferents were sectioned distally thus denervating the chemoreceptors. In other dogs, the carotid body was left intact, but perfusion was retrograde via the occipital artery. A Tygon catheter with a polyurethane tip (0.04 in ID, 0.05 in OD; Braintree Scientific) was inserted into the common carotid usually via the cranial thyroid artery with the tip positioned at least 1 cm below the innervated sinus. A Silastic cuff (6 mm ID; Harvard Apparatus) was placed on the common carotid proximal to the cranial thyroid artery, and a second Silastic cuff (5 mm ID) was implanted on the external carotid distal to the innervated sinus. In some of the dogs, the common carotid on the denervated side was also cannulated (as described) and prepared with a Silastic cuff proximal to the catheter. At least 3 wk were allowed after the second stage of denervation for recovery. Before surgical preparation and during the two recovery periods, the dogs were acclimated to the laboratory and trained to recline in a sling for 90 min/day, which is the same pattern used for data collection. During training sessions, the cuff below the innervated sinus was inflated to elicit the carotid occlusion reflex. Initially, the increases in MAP were variable, but by the third week of recovery, the responses to carotid occlusion were consistent. Inflation of the cuff below a denervated sinus had no effect on MAP.

A total of 14 dogs were used in the development of the model. However, six dogs failed due to thrombus formation in the common carotid artery. We used three different types of catheters; Tygon, Tygon with a Silastic tip, and Tygon with a polyurethane tip. We also used two methods to cannulate the vessel. In one, the catheter was inserted directly into the vessel after puncture with an 18-gauge needle and was held in place with a purse-string suture. In the other, the cannula was inserted into the largest of the cranial thyroid branches and was advanced into the common carotid; this approach was not always possible, because in some dogs the cranial thyroid immediately broke into tiny branches. The combination of polyurethane tip and cranial thyroid cannulation produced the most successful preparations. The ligation and subsequent removal of the ligature on the common carotid also proved complex. Silastic tubing (0.065 in OD) that had been tightened just enough to prevent flow without crushing the vessel wall could usually be removed 7 days later, and flow could be restored by gentle massage of the vessel. In one dog, we waited until 9 days after ligation and observed that the vessel could not be reopened. By autolytic action of common suture material that caused visible distortion of the vessel wall invariably resulted in permanent occlusion of the vessel.

It was also noted that ligation of the common carotid artery resulted in vascular remodeling of the vessels downstream, particularly in the external carotid. This vessel became visibly larger with an increase in internal diameter, and presumably the vessels in the anastomotic pathway between the circle of Willis and the external carotid also increased in size. The consequence was a reduction in the pressure drop across the ligature such that carotid sinus pressure (CSP) remained constant while systemic MAP declined over time. It is for this reason that a cuff (5 mm ID) was placed on the external carotid artery distal to the carotid sinus. The cuff provided a means to fix the diameter of the external carotid and thus minimize increases in the retrograde pressure wave reaching the sinus area.

**Experimental Protocol**

Measurements of MAP, CSP, left atrial pressure, and HR were recorded for at least 60 min between 0900 and 1300 in an isolated room with only the investigator present. Classical music was played throughout each session to provide background noise. Typically, the dogs dozed throughout the recording sessions, and sleeping was interrupted by occasional attempts to groom or lick the sling. Blood samples were collected at the beginning and end of each recording period to establish baseline levels of plasma renin activity (PRA), arginine vasopressin (AVP), cortisol, plasma electrolytes, and protein. Averages of the two determinations were used for data analysis. The blood samples were immediately aliquoted into chilled tubes containing either 0.3 M EDTA for measurement of PRA or heparin for measurement of plasma AVP, cortisol, electrolytes, osmolality, and protein. All samples were stored on ice until centrifuged, and plasma for hormone determination was frozen at −20°C. Fresh plasma was used to determine sodium and potassium concentrations, osmolality, and protein concentration. Observations were recorded during a 5-day control period, 7 days of baroreceptor unloading (initiated by ligation of the carotid below the innervated sinus), and a 4-day recovery period after removal of the ligature. In the first dog of this series, the ligature was left in place for 9 days. Unfortunately, this dog died under anesthesia due to a malfunction of the respirator while we were trying to remove the ligature and thus is not included in the recovery observations. We were unable to reopen the ligated
carotid in this dog and hence the period of ligation was reduced to 7 days in all subsequent dogs. The experimental protocol was repeated in 4 dogs with the carotid artery on the denervated side occluded. Some of the dogs were housed in metabolism cages during the protocols to allow for measurements of water and sodium metabolism.

In 3 dogs, HR responses to increases and decreases in CSP in the innervated sinus were determined during the control period and during the experimental period after ligation of the common carotid below the innervated sinus. These responses were measured at the end of the daily measurement of hemodynamic variables and collection of blood samples. Increases and decreases in MAP were induced by bolus injection of phenylephrine (5 μg/kg body wt; Winthrop-Breon Laboratories, New York, NY) and nitroglycerine (15 μg/kg body wt; American Critical Care, McGaw Park, IL), respectively. HR changes were determined over a 5-s interval corresponding to the peak change in CSP. At least two determinations were made during the control and experimental periods.

Methods of Measurement

Arterial pressures were measured using Cobe transducers and recorded on a Grass model 7D polygraph. The pressure transducers were adjusted to heart level for each dog. The analog signals from the polygraph were sampled at 100 Hz and digitized using a Biopac Systems data-acquisition system (Santa Barbara, CA). The data were saved to disk for subsequent analysis. Note that the MAP referred to (see RESULTS) is equivalent to the average or electronically damped pressure signal and not the calculated MAP.

Plasma osmolality was determined by freezing-point depression (model 3W, Advanced Instruments), and plasma protein was determined by refractometry. Plasma and urinary sodium and potassium concentrations were determined by flame photometry (model 343, Instrumentation Laboratories). Plasma AVP was determined by RIA after extraction with bentonite (19, 35). Recovery of AVP averaged 70 ± 2%, and the values are not corrected for recovery. The intra- and interassay coefficients of variability were 9 and 12%, respectively. PRA was measured using a RIA for ANG I and is expressed as nanograms of ANG I generated per milliliter of plasma during a 1-h incubation at pH 6.0 (NEON Life Sci Products, Boston, MA). The intra- and interassay coefficients of variability were 5 and 12%, respectively. Plasma cortisol was measured using a kit (Diagnostic Products, Los Angeles, CA). The intra- and interassay coefficients of variability were 11 and 16%, respectively.

Data Analysis

The effects on measured variables of unloading baroreceptors or ligation of the common carotid artery below a denervated sinus were analyzed by using a single-factor repeated-measures ANOVA (38). Each analysis included 5 control and 7 experimental days. Data recorded during the recovery period were not included in the ANOVA. A significant effect was accepted if the ANOVA indicated a P < 0.05. When a significant effect was detected, post hoc comparisons of means during experimental days were compared with the average control mean using Dunnett's test (39). For some variables, the average of the control values was compared with the average of the experimental values using the paired t-test. The slope of the line relating the change in HR to the change in CSP in the innervated sinus was estimated using the least-squares approach (39). Data enumerated in the text are means ± 1 SE.

RESULTS

The hemodynamic responses to chronic unloading of baroreceptors are shown in Fig. 1A. During the control period (days 1–5), MAP and CSP averaged 104 ± 2 and 102 ± 2 mmHg, respectively, and the means were not different (n = 6). During the experimental period of baroreceptor unloading (days 6–12), MAP averaged 22 ± 2 mmHg above control (P < 0.01). In contrast, there was no statistically significant change in CSP, although the average value was 2 ± 2 mmHg below control over the experimental period. In half of the dogs, both carotid and aortic chemoreceptors were denervated; in the other half, the carotid chemoreceptors on the innervated side remained intact but were separated from the external carotid by a ligature at the base of the occipital artery. The increases in MAP in response to unloading carotid baroreceptors were similar in both groups of dogs (ranging between 20 and 25 mmHg above control), and the results were pooled to produce the data shown in Fig. 1. In the dog in which...

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Fig. 1. A: mean changes in systemic mean arterial pressure (MAP, ⋄) and carotid sinus pressure (CSP, ⊖) during the control period (CON, days 1–5, n = 6), experimental period of baroreceptor unloading (EXP, days 6–12, n = 6), and recovery period (REC, days 13–16, n = 5). Average values of systemic MAP and CSP during the control period were 104 ± 2 and 102 ± 2 mmHg, respectively. B: daily means for heart rate (HR, ⋄) and left atrial pressure (LAP, ⊖) during the control, experimental, and recovery periods. *P < 0.05, experimental means that differ from average control mean; bars, 1 SE of daily means. bpm, Beats/min.
the ligature was in place for 9 days, the increase in MAP was maintained throughout the 9 days of observation. There was a significant increase in HR in response to baroreceptor unloading but no change in left atrial pressure (Fig. 1B). During the recovery period after removal of the ligature (n = 5), MAP and HR returned to control levels. The gain of the baroreceptor reflex estimated from the steady-state changes in MAP and CSP (ΔMAP/ΔCSP) during the 7 days of baroreceptor unloading was −11.

The responses to ligation of the common carotid below a denervated carotid sinus are shown in Fig. 2. During the 5-day control period, MAP and CSP averaged 105 ± 2 and 103 ± 2 mmHg, respectively. There was a significant increase in MAP on the first day after carotid ligation, but MAP was not different from control over the remaining 6 days of observation. In contrast, carotid ligation proximal to the denervated sinus led to a significant decrease in CSP that averaged 17 ± 2 mmHg below control (P < 0.01). There were no statistically significant changes in either HR or left atrial pressure in response to ligation of the carotid artery below a denervated sinus.

Although the reflex response to carotid ligation below an innervated sinus restored mean CSP to control levels (see Fig. 1A), carotid sinus pulse pressure was reduced ~50% below control (Fig. 3). Therefore, a continuous state of baroreceptor unloading was maintained throughout the experimental period. Ligation of the carotid proximal to the denervated sinus also resulted in a significant reduction in carotid sinus pulse pressure.

The effect of ligation of the common carotid below an innervated or a denervated sinus on the SD of MAP is shown in Fig. 4. Note that the SDs plotted in the figure are derived from 60-s means of MAP that were obtained during the daily recording period. Unloading baroreceptors had no effect (P = 0.2) on the SD of the daily MAP compared with the control SD. Similarly,
ligation of the carotid below a denervated sinus did not alter the SD of the MAP compared with control values. Tests to determine the relationship between CSP and HR were completed on three dogs during the control and experimental periods. Increases and decreases in CSP were induced by injections of nitroglycerine and phenylephrine (see METHODS for details). The slope of the line relating the change in HR to the change in CSP in the innervated sinus averaged \(1.13 \pm 0.24\) in the control period and \(1.03 \pm 0.20\) in the experimental period. The slope decreased in two dogs during the period of baroreceptor unloading and increased in the third dog compared with the slopes obtained during the control period. The change was not significant by paired \(t\)-test. These results indicate that baroreflex control of HR remained intact during the period of baroreceptor unloading.

The effects of chronically unloading baroreceptors on PRA, plasma AVP, and plasma cortisol concentration are shown in Fig. 5. PRA was significantly elevated on the first 2 days after baroreceptor unloading compared to the control period (Fig. 5A). During the subsequent 5 days, PRA declined to levels that were on average above control, but the differences did not reach statistical significance. In contrast, ligation of the common carotid artery proximal to a denervated sinus had no effect on either water intake or daily urine output (Fig. 8B).

The effects of unloading baroreceptors on the daily urinary excretion of sodium and potassium are shown in Fig. 6. Food intake was constant throughout the experiment in all dogs; therefore, intake of sodium and potassium was also constant. Assuming fecal excretion of both ions remained relatively constant, changes in urinary sodium and potassium excretion should reflect changes in sodium and potassium balance. There was a significant effect (\(P < 0.01\)) of unloading baroreceptors on urinary sodium excretion. Sodium excretion decreased on the first day after baroreceptor unloading, declined further on the second experimental day, and then returned to control levels by the fourth experimental day. Baroreceptor unloading had no effect on urinary potassium excretion. Ligating the common carotid below a denervated carotid sinus did not have a significant effect on either sodium or potassium excretion (Fig. 7).

Changes in water intake and urine volume in response to unloading of carotid baroreceptors are shown in Fig. 8A. Water intake tended to increase on day 1 of baroreceptor unloading and was significantly elevated on day 2; subsequently, water intake declined to control levels. Daily urine volume did not change significantly in response to baroreceptor unloading. Ligation of the common carotid artery proximal to a denervated sinus had no effect on either water intake or daily urine output (Fig. 8B).

Fig. 5. Daily means for plasma renin activity (PRA, A), arginine vasopressin (AVP, B), and cortisol (C), respectively, in the control, experimental, and recovery periods. Responses to baroreceptor unloading (\(\bullet\), \(n = 6\)) and carotid ligation below a denervated sinus (\(\circ\), \(n = 4\)) are shown. *\(P < 0.05\), significantly different compared to control means; bars, 1 SE of daily means.

Fig. 6. Daily urinary sodium excretion (\(U_{NaE}\), A) and potassium excretion (\(U_{KE}\), B) in the control period, experimental period of baroreceptor unloading, and recovery period (\(n = 4\)). *\(P < 0.05\), means that differ from control means; bars, 1 SE of daily means for sodium and potassium excretion.
The control and experimental period averages of body weight, plasma electrolyte, and plasma protein concentrations are shown in Table 1. There were no effects from either unloading carotid baroreceptors or ligating the common carotid below a denervated sinus on any of these variables.

DISCUSSION

The results presented here clearly demonstrate that unloading baroreceptors in a single carotid sinus can cause a significant increase in MAP of at least 7 days duration (see Fig. 1). The increase in MAP is not related to disruption of cerebral blood flow caused by ligation of the common carotid proximal to the innervated sinus, because ligation of the common carotid below a denervated sinus did not cause a sustained increase in MAP (see Fig. 2). Furthermore, the increase in systemic MAP does not depend on chemoreceptor stimulation, because there was no difference between dogs with denervated chemoreceptors and dogs with functional chemoreceptors on the innervated side. Thus it seems reasonable to propose that the increase in systemic MAP is a reflex response to unloading baroreceptors distal to the ligated common carotid aimed at restoring pressure in the sinus to the normal operating range at least under resting conditions. The daily means for CSP in the sinus did not differ from the mean during the control period by ANOVA. However, the pulse pressure recorded in the sinus was reduced compared with pressures recorded with the sinus perfused normally via the common carotid. Hence, a continuous error signal from the baroreceptors was present that could explain a sustained increase in sympathetic outflow and the increase in systemic MAP.

Sympathetic efferent activity was not directly assessed in this study. However, the results do provide evidence in support of the hypothesis that sympathetic drive was increased during the period of baroreceptor unloading. First, a significant increase in HR was evident throughout the period of baroreceptor unloading (see Fig. 1B), which is consistent with a sustained increase in sympathetic activity. Second, PRA was increased significantly during the first 2 days after baroreceptor unloading and then declined toward control but never fell below control (see Fig. 5A). The normal response to an increase in renal perfusion pressure is inhibition of renin secretion (37). The only plausible mechanism to explain the PRA responses in the presence of a sustained increase in renal perfusion pressure is increased renal nerve activity to the renin-
Secreting cells in the afferent arteriole (37). Third, the increase in renal perfusion pressure should have resulted in a pressure natriuresis (13). However, sodium excretion was reduced significantly on day 2 of baroreceptor unloading and returned to normal levels during the next 5 days of observation (see Fig. 6A). The fact that sodium excretion was normal in the presence of a sustained increase in renal perfusion pressure must mean that the excretory ability of the kidneys was altered. This could be explained by a sustained increase in renal nerve activity for the purpose of promoting sodium retention either directly or indirectly via activation of the renin-angiotensin system (37). Although a chronic study in dogs indicates that the latter mechanism may be more important (31), either of these responses is compatible with the hypothesis that baroreceptor unloading caused a sustained increase in sympathetic nerve activity.

Earlier attempts to create a model of neurogenic hypertension focused on responses after SAD or SAD combined with various methods to denervate cardiopulmonary receptors. Although results based on short-term measurements of MAP (e.g., 30- to 90-min recording sessions) frequently obtained evidence of increased pressure (11, 17, 29), different results were usually obtained when continuous measurements of MAP were used (6, 9, 10, 18). However, both methods provided clear evidence that the variability of MAP, quantified as the SD of the individual pressure measurements, was markedly increased after SAD. It has been argued that the reason MAP appears to be elevated in many studies after SAD is because any environmental or arousing stimuli occurring during the recording session produces much larger increases in MAP in the absence of baroreceptor buffering (6). Hence only continuous measurements of MAP can be used to adequately assess the actual MAP under these conditions. However, this argument does not invalidate the results obtained here. Animals with only one set of carotid baroreceptors demonstrated normal resting levels of MAP and no change in the SD of the individual MAPs during the period of chronic baroreceptor unloading compared to the control period (see Fig. 4). Furthermore, the animals clearly retained baroreflex-mediated responses during the period of baroreceptor unloading. The slope of the relationship relating the change in HR to a change in CSP was similar in the control and experimental periods. Therefore, the sustained increase in systemic MAP in response to chronic baroreceptor unloading cannot be explained as an artifact caused by excessive pressor responses to environmental stimuli.

It is generally believed that the process of baroreceptor adaptation to imposed changes in the prevailing MAP precludes participation in the long-term control of MAP. Cowley and colleagues (7, 8, 23) obtained experimental evidence in support of this assumption by comparing the increases in MAP in response to experimental hypertension in intact and dogs with SAD. The final increases in MAP in response to constriction of the remaining renal artery (other kidney removed; see Ref. 23), chronic ANG II infusion (7), and salt loading combined with reduced renal mass (8) were similar in intact and dogs with SAD. The only difference observed was that pressure increased more rapidly in dogs with SAD compared with dogs with baroreceptors intact. Because MAP increased to the same degree in both baroreceptor-intact dogs and dogs with SAD in all three models, it is obvious that the buffering capacity of the baroreceptor reflex was exceeded. However, a different perspective is obtained from more recent studies. As noted in the introduction, the studies by Lohmeier and co-workers (24) and Osborn and Hornfeldt (28) provided evidence of sustained baroreceptor participation in preventing hypertension during salt loading in two different animal models. Evidence of a sustained baroreceptor response to buffer ANG II-induced hypertension has also been observed. Lohmeier and co-workers (25) reported that sodium excretion in an innervated kidney increased twofold compared to excretion in a denervated kidney during continuous ANG II infusion in baroreceptor-intact dogs with a split-bladder preparation, which indicates sustained inhibition of the renal nerves. In contrast, ANG II infusion in dogs with combined cardiopulmonary denervation and SAD resulted in sodium retention in the innervated kidney, which indicates increased renal nerve activity. The rise in MAP in both intact and denervated dogs was similar in response to the ANG II infusion. This study shows that even during a chronic increase in MAP, which should cause baroreceptor resetting, there was a sustained alteration in renal

Table 1. Effects of chronic baroreceptor unloading on body weight and plasma electrolytes

<table>
<thead>
<tr>
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<th>Baroreceptors Unloaded</th>
<th>Baroreceptors Denervated</th>
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<tbody>
<tr>
<td></td>
<td>Control (n = 6)</td>
<td>Experimental</td>
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<tr>
<td></td>
<td>Control (n = 4)</td>
<td>Experimental</td>
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<tr>
<td>Body wt, kg</td>
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<td>27.2 ± 1.1</td>
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<td>27.1 ± 1.7</td>
<td>27.2 ± 1.6</td>
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<td>Plasma osmolality, mosmol/kg</td>
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<td>295.4 ± 0.8</td>
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<td></td>
<td>296.7 ± 1.6</td>
<td>295.9 ± 1.6</td>
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<tr>
<td>Plasma [Na], mmol/l</td>
<td>147.1 ± 0.2</td>
<td>146.7 ± 0.2</td>
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<td></td>
<td>146.4 ± 0.1</td>
<td>146.6 ± 0.2</td>
</tr>
<tr>
<td>Plasma [K], mmol/l</td>
<td>3.8 ± 0.2</td>
<td>3.8 ± 0.1</td>
</tr>
<tr>
<td></td>
<td>4.0 ± 0.1</td>
<td>4.0 ± 0.2</td>
</tr>
<tr>
<td>Plasma protein concentration, g/dl</td>
<td>5.9 ± 0.2</td>
<td>5.8 ± 0.2</td>
</tr>
<tr>
<td></td>
<td>6.4 ± 0.4</td>
<td>6.3 ± 0.4</td>
</tr>
</tbody>
</table>

Values are means ± SE. Each mean (±1 SE) represents the average of individual means over the control (days 1–5) and experimental (days 6–12) periods. Baroreceptor unloaded indicates that the common carotid artery was ligated proximal to innervated baroreceptors; baroreceptor denervated indicates that the carotid was ligated proximal to a denervated sinus. No experimental means differed significantly from control means within group. [Na] and [K], sodium and potassium concentrations, respectively.

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sodium excretion that was mediated by the renal nerves. These more recent studies clearly show that if the buffering capacity of the baroreflex system is not overwhelmed, the baroreceptors can drive a sustained reflex that is directed toward normalizing the MAP.

The present results also suggest that an error signal arising from baroreceptor unloading can generate a long-term change in MAP without adaptation. In this case, however, the reflex response is the cause of the increase in MAP rather than a mechanism to attenuate a rise in MAP in response to increased sodium intake (24, 28). In some ways, the response to ligation of the common carotid proximal to an innervated sinus is analogous to constriction of the renal artery; in both cases, systemic MAP rises in an attempt to restore the normal pressure in the region of the pressure sensors. It is well accepted that the renal response to reduced perfusion pressure is nonadapting (13). In the present study, the increase in systemic MAP is sufficient to maintain CSP in the normal operation range in the new steady state; hence there is no a priori reason to conclude that adaptation of the baroreceptors should occur.

In summary, the results presented here show that ligation of the common carotid artery below an innervated sinus caused a significant increase in systemic MAP of 22 ± 2 mmHg that was sustained for at least 7 days without a change in CSP. Significant increases in HR and PRA together with a significant decrease in urinary sodium excretion accompanied the increase in systemic MAP, and all suggest increased sympathetic efferent activity. These results are compatible with the hypothesis that chronic unloading of arterial baroreceptors can generate neurogenic hypertension and provide strong evidence that arterial baroreceptor input is important in the long-term control of blood pressure.

**Perspectives**

It is interesting to speculate whether the present results could have any bearing on human hypertension. The modern view of human essential hypertension is that the condition arises from a complex interplay of a number of genetic and environmental factors (14). It has long been known that hypertension correlates with stress, age, and various indices of obesity (14). There may be a causal relation underlying these correlations. Solberg and Eggen (36) examined neck arteries of 961 subjects as part of the International Atherosclerosis Project. They observed fibrous plaques in the carotid arteries of 80% of subjects >55 years of age. The prevalence of the lesions was greatest in one area, the bifurcation of the carotid artery and adjoining sinus area, and the pattern was independent of age, sex, or geographic origin. It is well known that deposition of lipid in the walls of arteries reduces arterial distensibility. A decrease in wall distensibility will reduce baroreceptor discharge at a given perfusion pressure, as has been demonstrated in atherosclerotic rabbits by Angell-James (1). Thus decreasing wall distensibility could set in motion a process whereby baroreceptor firing declines, thereby eliciting a reflex response to increase sympathetic outflow and therefore MAP to restore the level of baroreceptor firing to normal. If this hypothesis is correct, signals from arterial baroreceptors could be a contributory factor in the development of essential hypertension.

The author acknowledges the excellent technical assistance of Cornelia Sill. All other contributors of this study. The author would also like to thank Dr. Lanny Keil for the generous donation of the AVP antibody used in this study.

This study was supported by the National Heart, Lung, and Blood Institute (Grants HL-41313 and HL-67329) of the National Institutes of Health.

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