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Effects of chronic baroreceptor unloading on blood pressure in the dog

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Thrasher, Terry N. Effects of chronic baroreceptor unloading on blood pressure in the dog. *Am J Physiol Regul Integr Comp Physiol* 288: R863–R871, 2005. First published November 24, 2004; doi:10.1152/ajpregu.00489.2004.—We have developed a new model of chronic baroreceptor unloading (CBU) in the dog. Initial characterization of the model indicated that CBU increased mean arterial pressure (MAP) by an average of 22 mmHg for 7 days. The goal of the present study was to replicate the previous study using telemetry to record MAP continuously and to determine the effects of CBU (n = 7) on chronic regulation of MAP. We also prepared a group of dogs with sinoaortic denervation (SAD, n = 6) to compare the time course of changes in MAP in the two models. Control levels (7 day average ± SE) of MAP in the CBU and SAD groups were 94 ± 2 and 94 ± 1 mmHg, respectively. MAP averaged 124 ± 8 and 103 ± 4 mmHg during the first and second weeks after SAD (both P < 0.05) and then declined to levels not different from control during weeks 3–5. In the CBU group, MAP averaged 120 ± 4 mmHg during the first week, declined to 111 ± 4 mmHg during the second week, and stabilized at 104 mmHg during weeks 3–5 (all P < 0.05 compared with control). Plasma norepinephrine levels were increased significantly for the first week after SAD and for 2 wk after CBU but were not different from control for the remainder of the study. These results indicate that the initial increase in MAP after CBU is not sustained but declines to a level that is modestly higher than control. However, because MAP did not fall to control levels, the results are compatible with the hypothesis that baroreceptor input can influence the long-term level of MAP.

neurogenic hypertension; arterial baroreceptors; plasma norepinephrine; renin; aldosterone

There is general agreement that arterial baroreceptors play a vital role in the short-term (seconds to minutes) stabilization of mean arterial pressure (MAP) (2, 5, 8). However, it is also well established that arterial baroreceptors play no role in setting the long-term level of MAP (2, 5, 8). The scientific basis for this conclusion has been succinctly reviewed by Cowley (5). The most compelling evidence that baroreceptors cannot be involved in the long-term regulation of MAP is that complete denervation of carotid sinus and aortic baroreceptors (SAD) has no long-term effect on the level of MAP (6, 19, 22) and that baroreceptors adapt to experimentally induced changes in MAP (12, 17). These observations provide the basis to argue that, because removal of baroreceptors has no effect on the level of MAP, something else must regulate MAP chronically and, if baroreceptors reset to the prevailing level of MAP over time, they cannot provide a chronic error signal to medullary circuits controlling sympathetic outflow.

We have developed a new model of chronic baroreceptor unloading (CBU) in the dog that is based on the ligation of the carotid artery proximal to an innervated sinus with all other baroreceptor areas denervated (28). Initial experiments to characterize the model determined that systemic MAP increased significantly, averaging $22 \pm 2$ mmHg above control over 7 days, whereas carotid sinus pressure (CSP) was not different from control levels, averaging $-2 \pm 2$ mmHg below control (28). These results appear at odds with the arguments described above. There are three possibilities that may account for the sustained elevation in MAP observed in the CBU model. First, in the CBU model,afferent input from baroreceptors is maintained, whereas it is lost in the SAD model. Experimental evidence of central adaptation to loss of baroreceptor input has been reported by Schreihofer and Sved (23). They observed that lesions of the nucleus of the solitary tract caused acute hypertension in baroreceptor-intact rats but had no effect in rats previously subjected to SAD. Thus the loss of baroreceptor input led to alterations in the control of the baroreflex arc. Furthermore, it has been reported that renal sympathetic nerve activity is elevated acutely after SAD in rats, whereas it is normal in the chronic SAD condition (10). Thus the presence of normal pulse synchronous input from baroreceptors may account for much of the difference between responses to SAD and CBU.

Second, baroreceptor resetting may be minimized in the CBU model compared with other models of elevated MAP because pressure in the sinus is apparently normal, although the pulse pressure is reduced ~50% (28). It is well known that baroreceptor resetting requires that the receptors be exposed to the elevated pressure (11). It has also been reported that exposing baroreceptors to a pulsatile pressure signal prevents or attenuates acute resetting of carotid baroreceptors (3). Finally, even if baroreceptor resetting does occur, it may be that it requires much longer than the 7 days of observation reported previously and it may never be complete. Munch et al. (18) analyzed a number of studies of baroreceptor responses to increases and decreases in MAP and defined the completeness of resetting as the ratio of the change in threshold pressure to the overall change in MAP. Their analysis indicated little difference in this ratio, whether the resetting was caused by acute changes in MAP or sustained changes in MAP in chronic
models of hypertension. The overall average resetting based on their analysis of 19 studies was 0.56, suggesting that, from the standpoint of the baroreceptors themselves, resetting is not complete.

The aim of the present study was to determine whether the increase in MAP in response to CBU is sustained chronically and to compare the responses to measurements made under the same conditions in the SAD model of baroreceptor unloading. If the initial increase in MAP is sustained, the results would indicate a lack of both central adaptation and baroreceptor resetting in the CBU model. If the results mirror the changes in MAP obtained in the SAD model, the results would argue that central adaptation may explain the changes in MAP in the CBU model as well. If the changes in MAP after CBU differ both in time course and magnitude, the results could be explained by incomplete resetting of the baroreceptors or vascular adaptations to circumvent the ligature between the heart and the baroreceptors or both.

METHODS

General. All procedures described in this paper were in accordance with the National Institutes of Health guidelines involving animal experimentation and were approved by the institutional animal care and use committee. Experiments were performed on adult purpose-bred male and female mongrel dogs at least 1 yr old and weighing between 16 and 24 kg (Butler Farms, Clyde, NY). The dogs were housed individually in 4 × 7-ft pens with 9 ft of overhead clearance. The pens were in a room maintained at 22 ± 2°C and 70% humidity with a 12:12-h light-dark cycle. The dogs were fed at 1400 and administered oral prophylactic antibiotic treatment (40 mg of sulfamethoxazole plus 80 mg of trimethoprim). The diet consisted of a mixture of dry chow and canned food sufficient to maintain a constant body weight. The food was always consumed within 60 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 them 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 every 2 days. Rectal temperatures were obtained at least weekly to ensure that the animals were free of infection throughout all aspects of the study.

Surgical procedures. The surgical preparation of the CBU model has been described in detail previously (28). The initial procedure in all dogs was to denervate the aortic arch. Under sedation with acepromazine maleate (0.2 mg/kg iv; Tech America, Elwood, KS), the dogs were anesthetized with pentobarbital sodium (20 mg/kg iv). These results are referred to as the 1CBR condition. At least three arterial blood samples were collected for determination of plasma norepinephrine (NE), plasma renin activity (PRA), and plasma aldosterone concentration. Ten-milliliter samples were collected (and replaced with an equal volume of saline) and divided into ice-cold tubes containing EDTA and heparin. The tubes were centrifuged at 4°C, and the plasma was stored at −70°C until assayed. The dogs rested quietly in a sling during the blood collection. Continuous measurements of MAP and HR were continued for 5 wk after SAD and at least three samples per week thereafter. Seven days of control measurements in the 1CBR condition preceded ligation of the carotid proximal to the innervated sinus to induce CBU (n = 7), followed by continuous measurements of MAP and HR for 5 wk. Blood samples were collected as described for the SAD treatment.

Additional measurements of MAP and HR were performed under laboratory conditions with the dog resting quietly in a sling. These measurements were used to assess baroreflex control of HR in response to acute increases and decreases in MAP in response to bolus injections of phenylephrine (Winthrop-Breon Laboratories, New York, NY; 2–7.5 μg/kg) and nitroglycerine (American Critical Care, McGaw Park, IL; 10–30 μg/kg). HR was divided into 5-s bins over the 30 s after injection of the drug, and the peak change within a bin was used for data analysis. At least two determinations were made
during the 2CBR and 1CBR conditions and during the first, third, and fifth week after SAD and CBU.

Methods of measurement. We performed laboratory measurements of arterial pressures using Cobe transducers, which were 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 200 Hz and digitized with a Biopac Systems (Santa Barbara, CA) data-acquisition system. The data were saved to disk for subsequent analysis. Continuous records of blood pressure data were sampled at 200 Hz, digitized, and stored using software provided by DSI (St. Paul, MN). The resulting data were stored in 60-s bins for calculation of the daily MAP and HR and associated standard deviation (SD) of each variable. Note that the MAP referred to in the results is equivalent to the average or electronically damped pressure signal and not calculated MAP.

Plasma NE was determined by a radioenzymatic assay obtained from American Laboratory Products (Windham, NH). The within- and between-assay coefficients of variation of the assay were 4.0% and 10.5%, respectively. PRA was determined by RIA with a kit obtained from DiaSorin (Stillwater, MN). The within- and between-assay coefficients of variation of the assay were 12.4% and 18.6%, respectively. Plasma aldosterone was also determined by RIA with a kit obtained from ICN Pharmaceuticals (Costa Mesa, CA). The within- and between-assay coefficients of variation of the assay were 4.5% and 17.1%, respectively. To reduce between-assay variability, all samples from a given dog were analyzed within assays.

Data analysis. The 60-s bins of MAP, SD of MAP, HR, and SD of HR were averaged over the 20-h recording to yield a single mean for each variable per day per dog. These daily means provided data for subsequent statistical analysis. A single-factor repeated-measures ANOVA (29) was used to determine whether altered baroreceptor input affected each of the four variables within the three treatments, i.e., 2CBR vs. 1CBR, 2CBR vs. SAD, and 1CBR vs. CBU. The cardiovascular and hormone data were also averaged over weeks and analyzed as above. Dunnet’s test was used to determine differences in treatment means compared with the average of the control period (30).

In all cases, a difference was considered significant if \( P < 0.05 \). Comparisons between the CBU and SAD condition were performed with a two-factor ANOVA with repeated measures within treatment (29). Post hoc comparisons between treatments utilized Neuman–Keuls procedure (30). The means and SE of the control values were used to construct 95% confidence intervals for each variable (30). Linear regression analysis was used to determine the slope relating the change in HR to the change in MAP for each dog based on the baroreflex tests (30).

RESULTS

Effect of treatments on MAP and HR. The effects of 1CBR \((n = 6)\), SAD \((n = 6)\), and CBU \((n = 7)\) on the daily averages of MAP and the SD of MAP are shown in Fig. 1. The main effect of each treatment on MAP was highly significant \((P < 0.001)\). Post hoc analysis indicated that the initial increase in MAP above control was maintained for 7 days in the 1CBR condition, for 8 days in the SAD condition, and for 35 days in the CBU condition. In both the 1CBR and SAD conditions, MAP fell within the 95% confidence interval based on the control means at the beginning of the fourth week after the manipulation of baroreceptor input. The MAP and SD of MAP data for each treatment are shown averaged over weekly intervals in Fig. 2. Analyzing the data based on weekly averages facilitates comparisons of between-treatment effects on MAP. All three treatments produced statistically similar increases in MAP during the first experimental week. MAP in the 1CBR group declined to control levels during the second week after baroreceptor manipulation. In the SAD group, MAP remained elevated during the second week but was not different from control thereafter. In the CBU group, MAP declined during the second week and then stabilized at a level significantly above control for the next 3 wk. MAP in the CBU treatment was also significantly different compared with the SAD and 1CBR treatments during weeks 2–5 of observation.

There was a highly significant effect of all three treatments on the daily SD of the MAP (Fig. 1). Post hoc analysis indicated that the SD of MAP in the SAD group was significantly different from the control mean for the first 8 days after SAD and sporadically thereafter. However, the mean SD during the 5 wk of observation was always above the 95% confidence limits based on the control values. In contrast, the SD of MAP was increased only on days 2–4 after 1CBR and fell within the 95% confidence limits by 9 days after altering baroreceptor input. In the CBU group, the SD of MAP increased significantly on days 6–9 after baroreceptor unloading and then fell within the 95% confidence limits of the control level 10 days after baroreceptor manipulation. The weekly averages of the SD of MAP are shown in Fig. 2. The SD of MAP in the SAD treatment differed significantly from control during all 5 wk and from the CBU mean at each time interval.

The effects of 1CBR, SAD, and CBU on the daily averages of HR and the SD of HR are shown in Fig. 3. There was a highly significant effect of each treatment on HR. Post hoc tests indicated that HR was significantly increased on days
8–25 in the SAD group and fell within the 95% confidence limits of the control mean by day 33. A significant increase in HR in the 1CBR condition occurred between days 8–17 and days 20, 21, and 23. CBU caused a significant increase in HR on day 8 and days 11–19 compared with control and then stabilized along the upper limit of the control 95% confidence interval. The weekly averages of HR are shown in Fig. 4. HR were significantly increased above their respective control levels in both the SAD and 1CBR conditions for 3 wk after baroreceptor manipulation and for 2 wk in the CBU condition. HR was significantly higher in the SAD condition compared with the CBU treatment during the first week after baroreceptor manipulation.

The daily changes in the SD of HR in three treatment groups are shown in Fig. 3, and the weekly averages are shown in Fig. 4. There were no significant differences in the SD of HR after baroreceptor manipulation within groups or between groups.

**Effect of CBU and SAD on circadian variations in MAP and HR.** The weekly averages of MAP and HR during the light and dark phases of the day in the CBU condition are shown in Fig. 5. There was a significant difference in MAP between the light and dark periods in the control week and during the 5 wk of CBU. There was a significant increase in MAP in the dark phase during the 5 wk after CBU. In contrast, during the light phase, MAP differed from control during weeks 1, 2, and 5 of observation. There was a significant circadian pattern in HR in all weeks except week 4 following CBU. Compared with control, HR was significantly elevated during the light phase in weeks 1–3 and weeks 1 and 2 during the dark phase.

The effects of SAD on the circadian patterns of MAP and HR are shown in Fig. 6. A circadian variation in MAP was observed during the control week and the first week after SAD, but the rhythm was not significant during weeks 2, 3, and 4 and finally reestablished during week 5. MAP was elevated significantly in both the light and dark phases only during the first week after SAD. Circadian variations in HR were significantly different in all weeks except the fifth week following SAD. Comparing treatment to control levels indicated that HR was significantly elevated in the dark phase during weeks 1–3 but only weeks 1 and 2 during the light phase.

**Effect of CBU and SAD on plasma NE, PRA, and aldosterone.** The effects of CBU and SAD on the weekly averages of plasma NE, PRA, and plasma aldosterone are shown in Fig. 7. Plasma NE was increased significantly during the first 2 wk after CBU and then declined to control levels over the remainder of the experiment. The average PRA increased above control during all 5 wk after CBU, but the change was not statistically significant. However, comparing the daily means during the first week after CBU to control indicated that PRA
was significantly elevated on days 1, 4, and 6. There were no significant changes in plasma aldosterone in response to CBU.

In the SAD treatment, plasma NE was increased during the first week but was not different from control during the second through fifth week of observation. It is worth noting that plasma NE was uniformly elevated in all dogs during the first week after SAD but highly variable both between and within dogs during the following weeks. Also, plasma NE in the SAD group differed significantly from levels in the CBU group during both control and treatment weeks. SAD had no effect on PRA either daily during the first week or on a weekly basis. In contrast, plasma aldosterone was significantly elevated during the fourth and fifth weeks following SAD.

Effect of CBU on CSP. The effects on chronic CBU on CSP are shown for two dogs in Fig. 8. One of these dogs was part of the present study, and the other was from an earlier study (28). Pressure measurements were collected from dogs while they rested quietly in a sling under laboratory conditions. During the control period (days 1–7), there was no difference between systemic MAP (measured in the abdominal aorta) and CSP, as would be expected. In the dog shown in Fig. 8, top, the pressure drop across the ligature averaged 22.8 mmHg during the first week after CBU and declined to 9.4 mmHg by the fifth week after CBU. In the dog shown in Fig. 8, bottom, the pressure drop across the ligature averaged 33.5 mmHg during the first week of CBU and 17.2 mmHg during the fifth week.

Effect of treatments on baroreflex control of HR. The mean slope of the regression of change in HR onto change in MAP induced by bolus injections of phenylephrine and nitroglycerine was $-1.83 \pm 0.18$ beats/mmHg before SAD and fell to $-0.03 \pm 0.08$ beats/mmHg (average of first, third, and fifth weeks of testing). The slope was not different from zero in the SAD condition, and changes in HR in response to either increases or decreases in MAP were random, indicating complete denervation of all baroreceptor afferents. The slope relating HR changes to MAP in the 2CBR condition was $-1.92 \pm 0.24$ and fell to $-1.10 \pm 0.23$ after 1CBR ($P < 0.05$). In the CBU treatment, the mean slope relating changes in HR to MAP was $-1.42 \pm 0.29$ beats/mmHg and did not differ from the 1CBR condition.

DISCUSSION

The increases in MAP and HR recorded via telemetry during the first week after CBU are very similar to results published previously based on daily recordings with the dog resting...
quietly in a sling under laboratory conditions (28). The effects of CBU on PRA were also replicated; PRA was elevated on some days during the week following CBU but never suppressed below control levels. Furthermore, we also observed a significant increase in plasma NE in response to CBU. All of these responses are compatible with the hypothesis that CBU caused an increase in sympathetic outflow. However, contrary to our expectations, the initial increases in MAP, HR, and plasma NE were not sustained. Plasma NE and HR declined to control levels by the third week after CBU (Figs. 4 and 7). There was also a decline in MAP over the same time period, but MAP stabilized at a level that averaged $100 \pm 3$ mmHg above control during the third to fifth weeks after CBU (Fig. 2). There are a number of possibilities that could explain the decreases in MAP and other variables, and these are considered next.

One explanation for the gradual decrease in MAP is that the baroreceptors reset to a lower CSP. In our earlier study (28), we observed that CSP fell on average $-2 \pm 2$ mmHg below control after ligation of the carotid proximal to the sinus and reduction of pulse pressure in the sinus to $\sim 50\%$. One could hypothesize therefore that resetting to the lower CSP would lead to a decrease in sympathetic outflow and a fall in systemic MAP. However, a decline in systemic MAP would be expected to cause CSP to decline proportionately and thus lead to further resetting to the new CSP and so on. If the baroreceptors completely reset to the original level of firing, one would predict that MAP would fall to control levels and the pressure drop across the ligature would be maintained, assuming there were no cerebrovascular adaptations. However, if the resetting process is not complete, one would predict that MAP

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**Fig. 6.** Weekly averages of MAP (top) and HR (bottom) in the light phase (open bars) and the dark phase (solid bars) of the circadian cycle during the control week and for 5 wk after SAD. One SE is indicated for each mean. *$P < 0.05$ compared with the light or dark control mean. ‡Difference ($P < 0.05$) between light and dark means.

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**Fig. 7.** Weekly averages of plasma norepinephrine (NE; top), plasma renin activity (PRA; middle), and plasma aldosterone (Aldo; bottom) during the control week and for the 5 wk after either CBU or SAD. *$P < 0.05$ compared with within-subject control mean. ‡Difference ($P < 0.05$) between treatments.
would stabilize at an intermediate level. The results (Fig. 2) clearly show that MAP stabilizes at an intermediate level, indicating complete resetting did not occur. In the two dogs in which long-term measurements of CSP were made, the pressure drop across the ligature decreased in both (Fig. 8). Thus the data are compatible with the possibility that the baroreceptor resetting occurred but was incomplete.

Another possibility is that the pressure impulse reaching the baroreceptors became stronger over time. In the dog, anastomotic connections of arterial blood vessels associated with the Circle of Willis provide a pathway around the ligature placed on the common carotid, allowing perfusion of the innervated sinus distal to the ligature (4). If vascular remodeling in this pathway produced an increase in arterial diameter, the resulting decrease in resistance would allow systemic MAP to decline while maintaining the same load on the receptors. Support for this hypothesis is based on visual inspection of the vasculature in the region of the carotid bifurcation at death. There was an obvious increase in the diameter of the external carotid such that it was often larger than the parent common carotid proximal to the ligature. Furthermore, there were new blood vessels in the area that must have developed after the surgery to ligate the internal carotid and other vessels arising from the external carotid. In some cases, a small artery was visible running along the carotid sinus nerve. In other cases, small vessels arising from the external carotid were visible. Second, if the decline in systemic MAP was due to improved transmission of the pressure pulse to the sinus area, then the difference in pressure across the ligature should decrease with time. The data in Fig. 8 indicate that the pressure drop across the ligature became smaller over time. Thus cerebrovascular adaptations distal to the ligature could account for the decline in MAP over time. It is worth noting that the ability of the vascular system in the dog to adapt to insult is prodigious. While trying to create a cerebral ischemic model of hypertension in the dog, Taylor and Page (27) tied off both common carotids and vertebral arteries simultaneously. There were no deaths, and, after a few days, they observed that the dogs appeared normal. Unfortunately, their measurements of MAP were uninterpretable because they were performed with acute femoral artery puncture in restrained dogs. In all probability, a combination of baroreceptor resetting and vascular remodeling occurred, and both mechanisms contributed to the fall in MAP after CBU.

It is important to note, however, that neither process leads to complete restoration of MAP to control levels after 5 wk of observation. This fact suggests that the maintained elevation in MAP was most likely due to a continuous error signal arising from the baroreceptors distal to the ligature. Additional evidence of a change in the general level of sympathetic tone arises from the maintained increase in MAP during the dark phase of the circadian cycle (Fig. 5). Thus these results support the hypothesis that, under certain conditions, the baroreceptors can influence the long-term level of MAP.

The responses to SAD were also unexpected. Based on the classic study by Cowley et al. (6), we anticipated a brief period lasting 1 or 2 days in which MAP was elevated before returning to control levels. In contrast, MAP averaged 20 mmHg above control for the first 10 days and required more than 3 wk before it fell within the 95% confidence interval derived from the control values (Fig. 1). The time course of the decline in MAP roughly paralleled the declines in plasma NE and HR. Because all three variables are influenced by the level of sympathetic outflow, one could hypothesize that the fall in MAP reflects the rate of central adaptation to complete loss of baroreceptor input.

We found two previous studies in the literature that observed the time course of changes in MAP recorded over 16–24 h per day following SAD. Saito et al. (22) used a chronically implanted arterial catheter attached to a tethering system to record MAP in rabbits in their home cages. They reported that MAP was significantly above control for 6 days after SAD and did not return to the same mean level of pressure until the eighth day after denervation. Shade et al. (26) also used a tethering system to record MAP in baboons. They reported a large increase in MAP on the day after SAD and then a gradual decline over the next 4 wk to a level that was 11 mmHg above control. Osborn and England (19) measured MAP daily in SAD rats during the light phase. They reported that MAP fell to control levels by the third day after SAD. Whether MAP was elevated over a longer period during the dark phase, when rats are most active, is not known. It is interesting to note that the time required for MAP to return to control in these studies is roughly proportional to the size of the species being studied. This could be a simple coincidence. On the other hand, it could...
reflect the possibility that central adaptation to loss of baroreceptor input is slower in large animals.

There is one obvious difference between the conditions of the present study and those in the study of SAD dogs by Cowley et al. (6). They measured pressure continuously using a tethering system that allowed the dogs limited movement within the cage. The dogs could move forward and backward, left and right, but could not turn around, roll onto their backs, or jump because the vertical dimension of the cage was 5 ft. The dogs in the present study were unrestrained and had much more freedom of movement, including the ability to jump, dance on their hind legs, and squirm on their backs. All of these activities reflect arousal and were associated with increases in MAP. Thus it is possible that the prolonged increase in MAP observed in the present study could be explained by the greater activity level in dogs with no arterial buffering mechanism. However, there was no obvious change or decrease in the activity level during the weeks after SAD. Thus the gradual decrease in MAP would seem more likely to result from central adaptation to loss of baroreceptor input and normalization of sympathetic outflow. In this regard, it has been reported that renal sympathetic nerve activity (RSNA) returns to normal 20 days after SAD in the rat (10). However, there are no data that document the time course of changes in RSNA after SAD.

We have previously reported that unilateral carotid sinus denervation following aortic baroreceptor denervation in the dog causes a significant but temporary increase in MAP when measured under laboratory conditions (28). In the present study, we measured the changes in MAP after unilateral carotid denervation using the same telemetry system used to record MAP following CBU (many but not all of the ICBR dogs became the CBU group). When the results were plotted together with the changes in MAP after CBU and SAD, it became apparent that all three treatments produced quantitatively similar effects on MAP and HR during the first week following baroreceptor manipulation (Figs. 1 and 3). Furthermore, all three treatments caused significant increases in the variability of MAP (i.e., increased SD of MAP) during the first week after baroreceptor manipulation. The main difference among the treatments was the time course of adaptation. The increase in variability of MAP after SAD was expected and is because there are no baroreflexes to smooth out fluctuations in MAP. In the 1CBR treatment, the reflex changed from a bilateral input to a unilateral input overnight. Given this change, it is not difficult to imagine that time would be required for the baroreflex system to reorganize. The increased variability in the CBU treatment is more problematic to explain. These animals had at least 4 wk to adapt to a unilateral input; therefore, it is unlikely to be caused by altered baroreflexes per se. It may be related to the fact that the ligature introduced a time delay between a change in systemic pressure and change in pressure in the sinus and thus led to overshooting of reflex responses. The recovery of MAP to control levels differed between the SAD treatment (normal by third week) and the 1CBR treatment (normal by second week). This difference suggests the possibility that it takes more time to adapt to complete loss of baroreceptor input and thus for normalization of sympathetic tone, compared with partial loss of remaining input. However, HR did not return to control until the fourth week in both the SAD and 1CBR treatments, indicating that, whatever the central adaptations were, they did not follow the same time course for normalization of MAP and HR. Interestingly, HR fell to normal levels 1 wk earlier in the CBU treatment, even though MAP remained above control levels. The fact that it appears to take relatively long periods of time before adaptations are complete in any of the three treatments indicates that results obtained in shorter term studies of baroreflex function may not reflect steady-state conditions.

The principal finding in this study is the sustained, albeit modest increase in MAP following CBU. As argued above, this finding suggests that baroreceptor input does not completely reset after 5 wk. A number of recent studies have also provided evidence suggesting that baroreceptor adaptation may not be rapid or complete. Barrett and colleagues (1, 16) reported that a chronic increase in MAP by infusion of ANG II for 7 days in conscious rabbits is accompanied by a sustained decrease in RSNA. They also observed classic resetting in terms of baroreflex control of HR but no resetting of baroreflex control of RSNA. Lohmeier et al. reported indirect evidence (split-bladder preparation to examine renal responses in denervated and innervated kidneys) of sustained inhibition of RSNA in a sodium loading model (13) and ANG II-induced model of hypertension (15). Furthermore, combined cardiopulmonary denervation and SAD eliminated the inhibition of RSNA during ANG II infusion and unmasked a stimulatory effect of ANG II on RSNA (14).

There are a number of studies that compared the effects of altered dietary sodium intake on MAP in intact and SAD rats (7, 9, 20, 21). Increases in sodium intake that caused no effect on MAP in baroreceptor-intact animals led to increases in MAP in SAD animals. Furthermore, the ability of rats to increase sodium excretion during excess intake and decrease excretion during reduced intake was compromised in SAD rats (7). These results are consistent with the hypothesis that baroreceptor reflexes were chronically suppressing RSNA, allowing more efficient excretion of the daily sodium load and thus preventing volume expansion and a rise in MAP.

The examples cited above provide functional evidence that baroreceptor resetting in response to increased load may not always be complete. It is known that there are two populations of baroreceptors, i.e., type 1 receptors with A-fiber afferents and type 2 with C-fiber afferents, and that the properties of the two receptors differ substantially (25). More importantly, it has been shown that type 1 receptors undergo acute resetting, whereas type 2 receptors do not. This difference has led to the hypothesis that type 1 receptors are involved in the second-to-second stabilization of MAP and type 2 receptors are involved in signaling the absolute level of MAP (24). Unfortunately, there appear to be no studies that determined whether both type 1 and type 2 receptors adapt similarly during chronic states of altered MAP. However, many of the functional indications that baroreceptors do not completely adapt could be explained if the type 2 receptors provide a nonadapting signal to the brain.

In summary, the results based on the CBU model presented here provide additional evidence that baroreceptor input can affect the long-term level of MAP. These observations challenge the notion that baroreceptor adaptation precludes any possibility that the input could generate an error signal capable of altering MAP. However, whether altered baroreceptor input under physiological or pathophysiological conditions contributes to hypertension remains to be determined.

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