Harry Goldblatt Award

Prolonged Activation of the Baroreflex Produces Sustained Hypotension

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Abstract—The role of baroreflexes in long-term control of arterial pressure is unresolved. To determine whether chronic activation of the baroreflex produces sustained hypotension, we developed a method for prolonged activation of the carotid baroreflex in conscious dogs. This was achieved by chronically implanting electrodes around both carotid sinuses and using an externally adjustable pulse generator to electrically activate the carotid baroreflex. Control values for mean arterial pressure (MAP) and heart rate were 93 ± 3 mm Hg and 64 ± 4 bpm, respectively. After control measurements, the carotid baroreflex was activated bilaterally for 7 days at a level that produced a prompt and substantial reduction in MAP, and for day 1 MAP was reduced to 75 ± 4 mm Hg. Moreover, this hypotensive response was sustained throughout the entire 7 days of baroreflex activation (day 7, MAP=72 ± 5 mm Hg). During prolonged baroreflex activation, heart rate decreased in parallel with MAP, although the changes were not as pronounced (day 7, heart rate=51 ± 3 bpm). Prolonged baroreflex activation was also associated with $\approx35\%$ reduction in plasma norepinephrine concentration (control=87 ± 15 pg/mL). After baroreflex activation, hemodynamic measures and plasma levels of norepinephrine returned to control levels. Interestingly, despite the pronounced fall in MAP, plasma renin activity did not increase during prolonged baroreflex activation. These data indicate that prolonged baroreflex activation can lead to substantial reductions in MAP by suppressing the sympathetic nervous system. Furthermore, sustained sympathoinhibitory effects on renin secretion may play an important role in mediating the long-term hypotensive response. (*Hypertension*. 2004;43[part 2]:306-311.)

Key Words: baroreflex ■ arterial pressure ■ sympathetic nervous system ■ renin-angiotensin system ■ sodium

Since McCubbin et al[1] demonstrated a marked resetting of the arterial baroreflex in chronic hypertension, there has been considerable skepticism that baroreflexes participate in long-term control of arterial pressure.[2–5] Nonetheless, because of the importance of this neural feedback mechanism in the acute regulation of sympathetic activity and arterial pressure, there has been continued interest in the possibility that baroreflexes may play a role in the pathogenesis of hypertension. Indeed, a recurrent hypothesis to account for excessive sympathetic activation in hypertension is baroreflex dysfunction, an associated finding in some forms of experimental and clinical hypertension.[2,3,6,7] However, whether impaired baroreflex suppression of sympathetic activity plays a role in the hypertensive process would appear to depend on whether baroreflexes completely reset when exposed to chronic changes in arterial pressure. If, in fact, resetting is complete and baroreflexes do not chronically alter sympathetic activity, then they could not produce functional changes that influence the severity of hypertension.

The fundamental question of whether baroreflexes completely reset and have the capacity to chronically alter sympathetic activity and arterial pressure remains unanswered. This is owing, in large part, to technical limitations that have precluded the assessment of chronic changes in sympathetic nerve activity and the long-term effects of alterations in baroreflex activity on arterial pressure.[4,5] Recently, however, a number of novel observations in chronically instrumented animals have indicated that the baroreflexes do not completely reset and are chronically activated in hypertension.[4,5,8–16] These studies also support the hypothesis that baroreflex suppression of renal sympathetic nerve activity and attendant increments in renal excretory function are key mediators of the antihypertensive response to baroreflex activation. Despite the importance of these studies in establishing a role for baroreflexes in the long-term control of arterial pressure, they provide little insight into the quantitative importance of sustained baroreflex activation in attenuating the severity of the hypertension. Further, although supporting the concept that suppression of renal sympathetic nerve activity is a critical component of baroreflex-mediated reductions in arterial pressure, additional studies are needed to further test this hypothesis.

Thus, the primary objective of the present study was to establish a technique that would permit sustained and controlled activation of the carotid baroreflex. This methodology could then be used to quantitatively evaluate the time-dependency and the mechanisms of the hypotensive response to prolonged carotid baroreflex activation. As these goals would be virtually impossible to achieve by controlling pressure in an isolated carotid sinus preparation, we elected to electrically activate the carotid sinus. We reasoned that if the carotid baroreflex did have significant long-term antihypertensive effects, prolonged electrical activation of the afferent limb of the carotid sinus baroreflex should produce appreciable long-term reductions in arterial pressure. As the kidneys play a critical role in long-term regulation of arterial pressure,[2–5,17] the impact of prolonged baroreflex activation on renal excretory function was emphasized. The temporal changes in the renin-angiotensin-aldosterone system were also carefully monitored because of the powerful long-term effects of this system on renal sodium excretion and arterial pressure[2–5,17] and the influence of sympathetic activity on renin secretion.[3–6]

Methods

Animal Preparation

All procedures were performed in accordance with National Institutes of Health guidelines and approved by the institutional animal care and use committee. Six male dogs weighing 23.0 ± 1.1 kg were used in the present study. Catheters made of Tygon microbore tubing were implanted in the lower abdominal aorta and inferior vena cava and exteriorized between the scapula.[9–11] Additionally, platinum electrodes embedded in a thin silastic sheet were implanted around each carotid sinus. The electrode lead bodies were tunneled subcutaneously and exteriorized just cephalad to the catheters, where they were connected to a pulse generator secured to the dog jacket. The electrodes and the pulse generator were provided by CVRx, Inc (Maple Grove, Minn) and were designed to electrically activate the carotid sinus baroreflex. Neither the pulse generator nor the electrodes are commercially available at present. However, they are similar in technology and size to implantable systems used clinically such as pacemakers and neurological devises. The procedures for daily maintenance of the dogs in metabolic cages have been described previously.[9–11]

Experimental Protocol

During a 3-week postoperative period and throughout the study, the dogs were given free access to water and maintained on a fixed daily diet of two 15.5-oz cans of prescription heart diet (H/D; Hill's Pet Products) supplemented with 5 mL of vitamin syrup. Two cans of H/D provide ≈ 5 mmol of sodium and ≈ 60 mmol of potassium. The dogs received a continuous infusion of isotonic saline at a rate of 350 mL/d, providing a total daily sodium intake of ≈ 60 mmol.[9–11] Water consumption was monitored daily, and 24-hour urine samples were collected at 11:00 AM each day at the time of feeding. During the 3-week postoperative period, the dogs were trained in the morning to lie quietly in their cages for collection of blood samples. Only a technician remained in the room with the dogs during each morning session. At the end of the third week after reaching steady-state conditions, control measurements were made. These were followed by 7-days of bilateral electrical activation of the carotid sinus baroreflex and, subsequently, a 7-day recovery period. On intermittent days throughout the experiment, blood samples (≈ 10 mL) were taken from one of the arterial catheters for determination of hematocrit, plasma renin activity (PRA), and the plasma concentrations of sodium, potassium, protein, aldosterone, cortisol, norepinephrine (NE), and epinephrine.

For the 7-day period of baroreflex activation, the pulse generator was programmed using the following parameters: 6.0 V, 100 Hz, and 0.5-ms pulse duration. Extrapolating the results from different experimental preparations, we deduced that these stimulation parameters would likely activate both A- and C- type afferent fibers at frequencies near the maximum recorded discharge rates[18] and at an intensity that could produce approximately a maximal hypotensive response.[19–20] The duty cycle was 9 minutes on and 1 minute off.

Relationship Between Reductions in Arterial Pressure and Intensity of Activation

After the recovery period, 4 of the dogs were subjected to baroreflex activation at the same parameters indicated above except that the pulse amplitude was adjusted to 6, 7.5, and then 4.5 V. All 3 levels of activation were sustained for 48 hours.

Analytical Methods

PRA and the plasma concentrations of aldosterone and cortisol were measured by radioimmunoassay.[9–11,22] Plasma concentrations of sodium and potassium were determined with an ion selective electrode (NOVA biomedical); plasma protein concentration, by refractometry; and hematocrit, by a micromethod. In 4 of 6 dogs, plasma NE and epinephrine concentration were measured by radioenzymatic assay.[23]

Arterial pressure and heart rate were monitored continuously, 24 h/d, from an arterial catheter as previously described.[9–11] The daily hemodynamic values presented in the Results and in Figure 1 were averaged from the 20-hour period extending from 11:30 AM to 7:30 AM. The hours excluded from the 24-hour analysis included the time required for flushing catheters, calibrating pressure transducers, feeding, and cleaning cages.

Statistical Analysis

Results are expressed as mean$\pm$SE. A 1-way ANOVA was used to compare experimental and recovery responses to control, and significant differences were established using Dunnett t test for multiple comparisons. Statistical significance was considered to be $P<0.05$. Linear regression analysis was used to determine the relationship between both reductions in MAP and heart rate, as well as the intensity of carotid sinus activation. At each of the 3 intensities, comparisons were made for the second day of baroreflex activation.

Results

During activation of the carotid baroreflex, there were no overt physiological or behavioral changes associated with the hemodynamic and neurohormonal responses described below. More specifically, baroreflex activation did not produce any extraneous muscle stimulation and did not have any appreciable effects on respiration, appetite, or the level of activity.

Hemodynamics and Urinary Electrolyte Excretion

Figure 1 illustrates the chronic changes in MAP and heart rate in response to prolonged baroreflex activation. Control values for MAP and heart rate were 93 ± 3 mm Hg and 64 ± 4 bpm, respectively. Typically, there was a 20 to 25 mm Hg decrease in MAP immediately after activation of the carotid sinus baroreflex, and for day 1, MAP was reduced by 18 ± 2 mm Hg. Most importantly, this hypotensive response was sustained throughout the entire week of baroreflex activation. On day 7 of baroreflex activation, MAP was 21 ± 2 mm Hg lower than control. Heart rate decreased in parallel with MAP, and on day 7 of baroreflex activation, heart rate was reduced by 13 ± 2 bpm. Subsequently, there were sharp increases in both MAP and heart rate toward (but
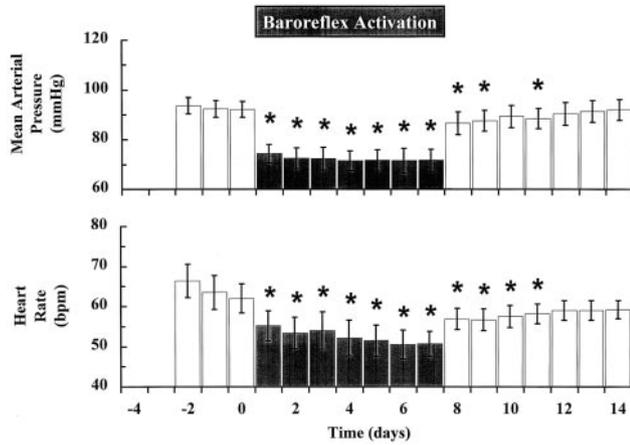
Figure 1. Effects of prolonged baroreflex activation on MAP and heart rate. Values are mean±SEM (n=6). *P<0.05 vs control. bpm indicates beats per minute.

never above) control values when activation of the baroreflex was terminated. Although MAP and heart rate returned to within 90% to 95% of control values during day 1 of the recovery period, several additional days were required before recovery was complete.

The daily changes in urinary sodium and potassium excretion during prolonged baroreflex activation are illustrated in Figure 2. During the control period, sodium and potassium excretion was 59±3 and 55±2 mmol/d, reflecting the intake of these electrolytes. During the first 24 hours of baroreflex activation, there was retention of ≈20 mmol of sodium before daily sodium balance was reestablished. This retained sodium was excreted on day 1 of the recovery period. There were no significant changes in potassium excretion during either the prolonged baroreflex activation or the subsequent recovery period.

Neurohormonal Profile
As illustrated in Figure 3, during prolonged baroreflex activation there was ≈30% reduction in plasma NE concentration from control levels (87±15 pg/mL). In contrast, there were no significant changes in the plasma concentration of
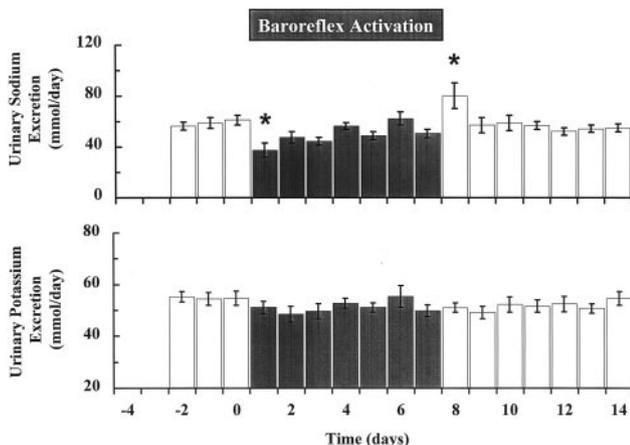

Figure 2. Effects of prolonged baroreflex activation on the daily excretion of sodium and potassium. Values are mean±SEM (n=6). *P<0.05 vs control.
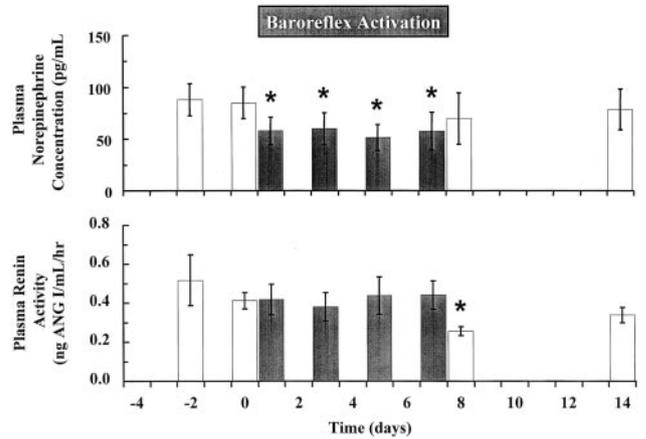

Figure 3. Neurohormonal responses to prolonged baroreflex activation. Values are mean±SEM (n=6 for PRA and n=4 for plasma NE concentration). P<0.05 vs control.

epinephrine (control=125±25 pg/mL). Of particular significance, despite the marked decrease in MAP, PRA did not increase during prolonged baroreflex activation (Figure 3). Similarly, there were no significant changes in either plasma aldosterone or cortisol concentration throughout the 7 days of carotid sinus activation (Table).

Hematocrit and Plasma Concentrations of Electrolytes and Protein
In association with the modest retention of sodium (Figure 1), there were small, but nevertheless significant, reductions in both hematocrit and plasma protein concentration during baroreflex activation (Table). Both returned to control levels during the recovery period. In addition, plasma potassium concentration increased modestly (<0.5 mmol/L) during activation of the baroreflex and remained elevated even after 7 days of recovery (Table). However, plasma potassium concentration did return to control levels during more extended recovery periods.

Relationship Between Reductions in Arterial Pressure and Intensity of Activation
Before the 3 successive levels of activation at different intensities, MAP and heart rate were 89±3 mm Hg and 58±2 bpm, respectively. As illustrated in Figure 4, reductions in MAP were significantly correlated with the intensity of activation (r=−0.6984; P=0.01). Heart rate also decreased progressively with increased intensity of activation, but this relationship did not quite achieve statistical significance (P=0.06).

Discussion
One of the most important contributions of the present study is that it establishes and characterizes a controllable model for sustained activation of the carotid baroreflex. A unique feature of this model is that it provides a means for elucidating the mechanisms whereby prolonged baroreflex activation leads to sustained reductions in arterial pressure. Furthermore, by clearly demonstrating that prolonged activation of the carotid baroreflex has the capability of producing pronounced and sustained reductions in MAP, the present study

Effects of Prolonged Baroreflex Activation in Normal Dogs

Time	P_{ALDO}, ng/dL	P_{CORT}, μg/dL	P_{Na}, mmol/L	P_K, mmol/L	P_{PROT}, g/dL	HCT
Control	4.0±0.7	1.6±0.2	149±1	4.6±0.2	5.9±0.3	0.39±0.01
Baroreflex activation						
Day 1	3.7±0.8	1.4±0.2	148±1	5.0±0.2*	5.6±0.3*	0.36±0.01*
Day 3	3.8±0.5	1.4±0.2	148±1	5.0±0.2*	5.7±0.3*	0.35±0.01*
Day 5	3.5±0.5	1.6±0.3	148±1	5.0±0.2	5.6±0.3*	0.34±0.01*
Day 7	3.4±0.5	1.5±0.4	148±1	5.0±0.2*	5.7±0.3*	0.36±0.02*
Recovery						
Day 1	3.0±0.4	1.6±0.3	149±1	4.9±0.1	6.0±0.3	0.37±0.02
Day 7	4.7±1.1	1.7±0.3	150±1	5.1±0.3*	6.2±0.3	0.38±0.02

Values are mean±SE; n=6. P_{ALDO} indicates plasma aldosterone concentration; P_{CORT}, plasma cortisol concentration; P_{Na}, plasma sodium concentration; P_K, plasma potassium concentration; P_{PROT}, plasma protein concentration; and HCT, hematrocrit.

*$P<0.05$ vs control.

adds to an emerging body of evidence indicating that baroreflexes play a role in long-term control of arterial pressure. Characterization of the neurohormonal profile suggests that sustained suppression of the sympathetic nervous system and PRA, presumably owing to inhibition of neurogenically mediated renin release, are mechanisms that mediate the long-term hypotensive response to prolonged baroreflex activation.

The idea of determining the hypotensive effects of the carotid baroreflex by electrical activation of the afferent limb of this reflex is not new. Indeed, it was not long after McCubbin et al[1] introduced the concept of baroreceptor resetting in 1956 that techniques were developed for direct stimulation of the carotid sinus nerve in anesthetized and conscious dogs.[19,20,24] The conditions and results of these studies are rather sketchy, but they clearly showed that electrical stimulation of the carotid sinus nerve produced rapid reductions in arterial pressure that persisted for the duration of the experimental periods, typically minutes to hours. However, to our knowledge, there have been no previous experimental animal studies in which the arterial pressure response to continuous electrical activation of the carotid baroreflex has been quantified beyond this acute time period. Another difference from most of the earlier studies is

Figure 4. Relationship between chronic reductions in mean arterial pressure and intensity of carotid sinus activation in 4 dogs. $r=-.0.6984$; $P=0.01$).

that we implanted the stimulating electrodes directly around the carotid sinus, rather than around the carotid sinus nerve. As the carotid sinus nerve contains chemoreceptor as well as baroreceptor fibers, one reason for electrode implantation around the sinus was to either minimize or prevent activation of chemoreceptor afferents emanating from the carotid bodies, which are just rostral to the electrode surrounding the baroreceptors in the carotid sinus. Although not critically assessed in the present study, it would appear that this goal was achieved, as there was little or no increase in respiratory rate during activation of the carotid baroreflex. Further, the advanced electrode design prevented extraneous stimulation of neighboring muscles and nerves, as reported in earlier studies.[19–21] In this regard, the absence of behavioral changes and increments in plasma levels of the stress hormones epinephrine and cortisol during prolonged baroreflex activation corroborates this contention. The rapid on- and off-transient arterial pressure responses, the ease of control, and the ability to easily achieve graded reductions in MAP are additional desirable features of this instrumentation.

The most impressive response in the present study was the pronounced reduction in MAP, which persisted throughout the entire week of continuous baroreflex activation. This was somewhat unexpected for several reasons. First, it is well established that the baroreflex resets in the direction of the prevailing pressure, and time-dependent estimates of baroreflex function suggest that baroreflex resetting may be complete within 48 hours of an abrupt change in arterial pressure.[2,25,26] In the present study, in contrast, the decrease in MAP was sustained throughout the entire 7 days of carotid baroreflex activation without any trend for adaptation of the hypotensive response. This may indicate that "central resetting of the baroreflex"—an alteration in the central nervous system that results in a level of sympathetic activation that is inappropriately high for the level of baroreceptor activity—is not normally an important component of the chronic resetting mechanism. That is, chronic baroreflex resetting may be predominantly a function of adaptations within the baroreceptors themselves resulting from sustained stretch, adaptations which result in time-dependent reductions in barorecep-
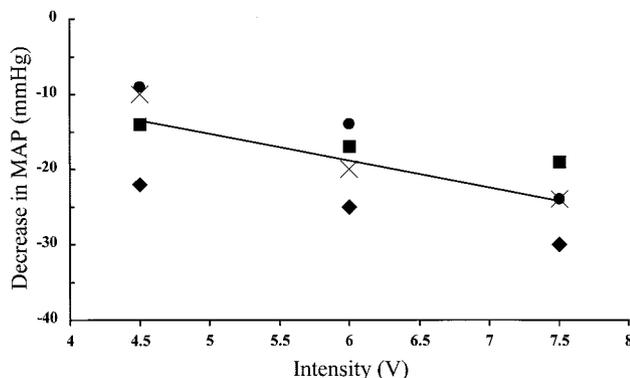
tor activity for a given amount of stretch of the vessel wall. Thus, the apparent complete absence of chronic resetting in the present study was undoubtedly owing, in part, to bypassing the pressure-encoding step of the baroreceptor by direct electrical activation of the afferent limb of the carotid baroreflex. Another reason why the MAP response to prolonged baroreflex activation was rather surprising is that as arterial pressure decreased during activation of the carotid sinus, we expected a decrease in endogenous aortic baroreceptor activity. In turn, this would be expected to increase sympathetic activity and oppose the sympathoinhibitory and hypotensive effects of prolonged carotid baroreflex activation. Finally, there was the possibility that other compensatory blood pressure control mechanisms, such as the powerful renin-angiotensin system, might be activated by baroreflex-mediated hypotension and attenuate the decrease in arterial pressure. Despite these considerations, the long-term hypotensive response to prolonged activation of the carotid baroreflex was sustained and quite substantial.

Although it is well established that the baroreflex resets in the direction of the ambient arterial pressure, the magnitude and time course of chronic resetting has not been determined with any certainty.[4,5,25] This uncertainty, in large part, has been owing to technical limitations that prevent determination of long-term changes in sympathetic activity. Nonetheless, a number of recent experimental observations in chronically instrumented animals provide strong evidence that the baroreflex does not totally reset and serves as a compensatory mechanism to attenuate the severity of hypertension.[4,5,8–16] As the kidneys play a preeminent role in long-term regulation of arterial pressure,[2–5,17] these studies have emphasized the chronic influence of baroreflexes on renal sympathetic nerve activity and the resultant effect on renal excretory function. In short, these studies indicate that baroreflex-mediated suppression of renal sympathetic nerve activity and attendant increments in renal excretory function are critical long-term responses that account for sustained reductions in arterial pressure. However, further evaluation of this hypothesis is needed. Although plasma levels of NE are a rather poor index of sympathetic activity,[27] the sustained reduction in plasma NE concentration during prolonged baroreflex activation in the present study is consistent with suppression of the sympathetic nervous system. However, as sympathetic activity is differentially regulated,[27] measurement of changes in renal sympathetic nerve activity during prolonged baroreflex activation would provide a more critical evaluation of the role of the renal nerves in mediating the hypotensive response. An even more direct test of the importance of the renal nerves in mediating the hypotension would be to determine whether prolonged baroreflex activation decreases arterial pressure after prior bilateral renal denervation. If prolonged baroreflex activation produces a sustained reduction in arterial pressure in the absence of the renal nerves, this would indicate that mechanisms other than suppression of renal sympathetic nerve activity contribute to the long-term hypotensive response. The current methodology is ideally suited to evaluate these critical issues.

A particularly striking and potentially important finding was that the hypotensive response to activation of the carotid baroreflex did not stimulate the renin-angiotensin-aldosterone system. That this powerful hormonal blood pressure feedback control mechanism was not activated by hypotension suggests the presence of an inhibitory influence on renin release during sustained activation of the carotid baroreflex. As alterations in renal adrenergic activity influence renin release,[3–6] decreased renal sympathetic nerve activity could likely account for the inhibitory effect on renin release. Indeed, elegant quantitative studies in conscious, chronically instrumented dogs have shown that reflex activation of the renal nerves by unloading carotid baroreceptors shifts pressure-dependent renin release to higher arterial pressures.[28] Conversely, reflex suppression of renal sympathetic nerve activity by electrical stimulation of the carotid sinus nerve has the opposite effect on renin secretion.[29] This latter study indicates that activation of the carotid sinus baroreflex in conscious animals has the capability of suppressing renal sympathetic nerve activity below basal levels and attenuating the normal increase in renin secretion associated with a reduction in MAP of the magnitude observed in the present study ($\approx$20 mm Hg).[28–30] Thus, it would be reasonable to assume that baroreflex-mediated renal sympathoinhibition was sustained throughout the entire period of prolonged baroreflex activation and was the primary mechanism for inhibition of renin release. Were it not for the renal sympathoinhibitory effect on renin secretion, it is quite possible that the long-term hypotensive response to baroreflex activation would have been greatly diminished.[3,4]

Maintenance of sodium balance at a reduced arterial pressure indicates prolonged baroreflex activation had a sustained effect to enhance renal excretory function.[3–5,17] Nonetheless, baroreflex activation was associated with net retention, not loss, of sodium, and expansion of body fluid volumes likely accounted for the small decrease in hematocrit and plasma protein concentration. As a result of the decrease in peripheral resistance and increase in vascular capacitance induced by baroreflex-mediated inhibition of the sympathetic nervous system, the attendant acute fall in arterial pressure would be expected to promote sodium retention during the first 24-hour of baroreflex activation.[17] Apparently, during the first 24-hour of baroreflex activation, these hemodynamic responses favoring sodium retention predominated over any natriuretic influence associated with suppression of renal sympathetic nerve activity. However, had baroreflex activation not increased renal excretory function by presumably suppressing renal sympathetic nerve activity, computer analyses of the cardiovascular system indicate that there would have been an even greater degree of sodium retention and only a transient reduction in arterial pressure.[17] Again, the current methodology for baroreflex activation will permit an experimental evaluation of these predictions from mathematical analyses of the circulation.

Although the current methodology promises to provide novel insight into the mechanisms whereby baroreflexes produce long-term changes in arterial pressure, extrapolation of the results from the present study to the normal physiology of baroreflex function must be made with several caveats in mind. First, although these results support an emerging body of evidence indicating that baroreflexes do not completely reset in hypertension, as stated above, direct electrical activation of the afferent limb of the carotid baroreflex bypasses mechanoelectric

transduction in baroreceptors, a component of the baroreflex likely involved in chronic resetting. Second, the stimulation parameters used in the present study do not reproduce the natural rhythmic neural input into the brain from carotid baroreceptors. Further, as arterial pressure decreases during prolonged activation of the carotid baroreflex, the brain would be expected to receive conflicting inputs from carotid and aortic baroreceptors. In this regard, it will be of interest in future studies to determine whether changing the duty cycle to better mimic the natural discharge pattern of carotid baroreceptors during the cardiac cycle alters the cardiovascular and neurohormonal responses to prolonged baroreflex activation. In addition, by conducting studies following deafferentation of aortic baroreceptors, it will be possible to determine whether the normal unloading of these receptors concomitant with the decrease in arterial pressure attenuates the hypotensive response to prolonged activation of the carotid baroreflex. Because of the possibility that chronic resetting is a slower process than suggested from previous studies,[2,25,26] it will also be important to extend studies beyond 7 days of carotid baroreflex activation to demonstrate the potential relevance of the current findings to pathophysiological states such as hypertension and heart failure.

Perspectives

In addition to providing a tool for better understanding the role of baroreflexes in long-term control of arterial pressure, prolonged baroreflex activation by the methodology used in the present study may have clinical application for the treatment of hypertension. Indeed, chronic electrical stimulation of the carotid sinus nerve has been used in the past for treatment of patients with advanced hypertension who are relatively unresponsive to medical treatment.[18,21,31–33] In most instances, but not all, chronic stimulation of the carotid sinus nerve has produced appreciable sustained reductions in arterial pressure in these hypertensive patients resistant to drug therapy. In regard to the clinical applicability of the present methodology, it will be important in future experimental studies to take a mechanistic approach to elucidate the forms of hypertension most sensitive to the hypotensive effects of prolong baroreflex activation. The present study suggests that the response of the renin-angiotensin system to baroreflex mediated sympathoinhibition may be a critical determinant of the clinical efficacy of prolonged baroreflex activation.

Acknowledgments

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