Rapid Baroreceptor Resetting in Chronic Hypertension
Implications for Normalization of Arterial Pressure

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The purpose of this study was to examine the ability of baroreceptors of renal hypertensive rabbits to reset rapidly during acute changes in arterial pressure. The carotid sinus (CS) was vascularly isolated and baroreceptor activity was recorded during slow ramp increases in CS pressure in hypertensive (one-kidney, one wrap; 127±3 mm Hg) and normotensive (one-kidney, no wrap; 85±3 mm Hg) rabbits anesthetized with chloralose. Control measurements were made after holding pressure for 10–15 minutes at the level of arterial pressure recorded before each experiment. Baroreceptor threshold pressure (PtJ) was higher in hypertensives (78±4 mm Hg) compared with normotensives (55±3 mm Hg, p<0.05), and nerve activity was less in hypertensives over a wide range of pressure. CS distensibility (sonomicrometers) was not significantly different in the two groups. After increasing holding pressure from control by 30 and 60 mm Hg for 10–15 minutes, the extent of baroreceptor resetting (ΔPa/Δholding pressure x 100%) in normotensives was 39±6% and 33±2%, respectively, but only 14±5% and 9±3% in hypertensives (p<0.05). After decreasing holding pressure by 30 and 60 mm Hg, resetting was similar in normotensives (32±6% and 28±3%) and hypertensives (34±3% and 30±4%). In hypertensive rabbits, acute (10–15 minutes) exposure of baroreceptors to normotension (71±4 mm Hg) decreased Pa, to 62±4 mm Hg and increased nerve activity to levels not significantly different from those of normotensive animals without altering CS distensibility. The results indicate that in chronic renal hypertension: 1) further upward resetting of baroreceptors during acute increases in pressure is suppressed; 2) in contrast, downward resetting during acute decreases in pressure is preserved; 3) baroreceptor activity is restored rapidly after brief exposure of the CS to normal pressure; and 4) changes in CS distensibility do not explain decreased baroreceptor activity in chronic hypertension nor restoration of activity after acute normalization of pressure. Impairment of acute upward resetting and preservation of downward resetting should be beneficial since they would oppose further increases in pressure and facilitate lowering of pressure. (Hypertension 1991;17:72–79)

Baroreceptors buffer fluctuations in arterial pressure by causing reflexly mediated reciprocal changes in both heart rate and sympathetic nerve activity.1 These changes keep the level of arterial pressure at a predetermined operating level or set point. When changes in pressure are sustained for several minutes, however, baroreceptors are reset rapidly and the baroreceptor pressure–activity curve shifts in the direction of pressure change to function at a new set point.2–5 This allows baroreceptors to buffer fluctuations of arterial pressure effectively because the new pressure set point remains on the steep portion of the reset pressure–activity curve. However, resetting provides positive feedback in the control of arterial pressure. During acute hypotension, baroreceptor activity increases as baroreceptors reset. This prevents pressor systems from remaining reflexly activated and contributes to the decline in

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pressure. Conversely, during acute hypertension, pressor systems do not remain inhibited because baroreceptor activity decreases as baroreceptors reset, and this may contribute to the development of chronic hypertension.

Baroreceptors are impaired in chronic hypertension and are said to become chronically reset.6-10 This is characterized by elevations in pressure threshold and decreases in baroreceptor activity. The purpose of our study was to examine the ability of baroreceptors to reset rapidly during acute changes in arterial pressure in chronically hypertensive animals.

It has been suggested that baroreceptor impairment in hypertension is caused by a decrease in the distensibility of the carotid sinus and aortic arch due to chronic structural changes such as hypertrophy of vascular smooth muscle and increases in collagen content of the arterial wall.7,10,11 This implies that reversal of baroreceptor impairment in hypertension would require not only restoration of arterial pressure but also the reversal of structural changes. The protocol in our study allowed us to test this hypothesis.

Methods

Induction of Hypertension

Hypertension was induced in 12 New Zealand White rabbits (3–4 lb) of either sex.12,13 The rabbits were anesthetized with ketamine (40 mg/kg i.m., Ketalar, Parke-Davis, Morris Plains, N.J.) and acetylpromazine (1 mg/kg i.m., Acepromazine, Tech America, Elwood, Kan.) and the kidneys were exposed via a midline abdominal incision using sterile technique. The renal artery, vein, and ureter were ligated and cut on one side and the kidney removed; the contralateral kidney was wrapped with dialysis membrane as described previously.12 The incision was closed in layers and the rabbits were allowed to recover. Eleven other rabbits had one kidney removed and the other kidney exposed but not wrapped and served as the sham-operated normotensive controls. Arterial pressure was measured each week postoperatively with a Grant-Rothschild capsule.14 Pressure had risen from approximately 80 mm Hg to over 110 mm Hg within 4–13 weeks after surgery.

Acute Experiment

Ten to 24 weeks after surgery, and 3–16 weeks after the animals had become hypertensive, rabbits were anesthetized with thiopental sodium (25–30 mg/kg i.v.) and chloralose (100 mg/kg i.v.). A tracheotomy was performed and animals were mechanically ventilated with a mixture of room air and 100% oxygen. Catheters were placed in the femoral artery and vein for measurement of arterial pressure and administration of anesthetic. To eliminate muscular movement, gallamine triethiodide (1 mg/kg i.v.) was administered before nerve recordings were made. Supplemental doses of chloralose and gallamine were given as needed.

The carotid sinus was vascularity isolated by ligating all visible branches of the common and external carotid arteries. Catheters were placed in the common and external carotid arteries and the internal carotid was ligated. The sinus region was filled with a physiological saline solution.13 The solution was equilibrated with a 95% O2–5% CO2 gas mixture and warmed to 37°C in a temperature-controlled water jacket before use (PO2>200 mm Hg, PCO2=25–40 mm Hg, pH=7.3–7.4). The carotid sinus was periodically refilled with fresh warmed solution. The common carotid catheter was connected to a pressure bottle filled with the physiological saline, and carotid sinus pressure was controlled by regulating the inflow of air to the bottle from a pressurized air source. Carotid sinus pressure was measured through the external carotid catheter with a Statham pressure transducer (model P231a, Gould, Inc., Hato Rey, Puerto Rico). Baroreceptor activity and carotid sinus diameter were recorded during slow (2–4 mm Hg/sec) nonpulsatile ramp increases in carotid sinus pressure from 0 to 150 mm Hg.

Carotid Sinus Nerve Recordings

The vagus, aortic, and cervical sympathetic nerves were cut below the sinus. Under a dissecting microscope, the carotid sinus nerve was identified, cut, and placed on bipolar platinum electrodes. The nerve and electrodes were covered with Wacker Sil-Gel and the sinus region was bathed with physiological saline.13,15,16 Carotid sinus nerve activity was recorded using a Grass high-impedance probe (model HIP511E, Grass Instrument Co., Quincy, Mass.) and a Grass P511 preamplifier (30 Hz to 3–10 kHz bandwidth), displayed on a Tektronix oscilloscope (model 5113, Tektronix, Beaverton, Ore.) and monitored with a loudspeaker. A nerve traffic analyzer (model 605C, University of Iowa Bioengineering, Iowa City) counted action potentials that exceeded a selected voltage. The chosen voltage eliminated baseline electrical noise as well as any activity in the carotid sinus nerve that was present at carotid sinus pressures less than 30 mm Hg. This ensured that all recorded activity was pressure-sensitive and allowed estimation of the baroreceptor pressure threshold. With the slow ramp increase in pressure the baroreceptors often began to discharge at a frequency of approximately 8–20 Hz but then ceased to fire for various periods of time before discharging again as pressure continued to increase. Threshold was defined as the pressure during the ramp required to trigger a relatively sustained activation of baroreceptor fibers that exceeded the selected voltage window with only very short periods (less than 800 msec) where activity was absent. Nerve activity, arterial pressure, and carotid sinus pressure were recorded on a Soltec chart recorder (model 3414, Soltec, Sun Valley, Calif.).
Carotid Sinus Diameter Recordings

Carotid sinus diameter was measured using sonomicroscope crystals as described previously. A low resistance stainless steel clip holding two miniature piezoelectric crystals (5 MHz) was placed across the carotid sinus and sutured to the adventitia. The diameter of the sinus was determined from the transit time of acoustic signals between the crystals. Increases in diameter were measured during ramp increases in carotid sinus pressure. The system was able to distinguish differences in diameter of approximately 9-16 μm, which caused negligible changes in nerve activity.

Protocol

Carotid sinus nerve activity was recorded in six normotensive and nine hypertensive rabbits. Carotid sinus diameter was measured in five normotensive and five hypertensive rabbits. In two of the hypertensive rabbits, both carotid sinus nerve activity and diameter were measured.

The control holding pressure in the carotid sinus for each animal was the mean arterial pressure recorded from that animal via the femoral artery after administration of thiopental. This pressure was not significantly different from that measured in the central ear artery in the conscious state. Measurements of baroreceptor activity or carotid sinus diameter were made after maintaining the control holding pressure for 10-15 minutes and again after lowering the holding pressure to 30 and 60 mm Hg below the control level. Measurements were repeated after holding pressure was elevated to 30 and 60 mm Hg above the control holding pressure. Ramps were always performed after the pressure had been held at a constant level for 10-15 minutes.

Data Analysis

Carotid sinus nerve activity is expressed in spikes per second and plotted against carotid sinus pressure to obtain pressure–activity curves. We analyzed baroreceptor activity in absolute units (spikes/sec) instead of normalizing to a percent of maximum activity because of the concern that normalization would artificially force the levels of activity at high pressure to be equivalent in the normotensive and hypertensive rabbits. Previous studies have demonstrated that impaired baroreceptor function in chronic hypertension is evident with recordings of both whole nerve and single fiber activity. Our findings concerning rapid resetting of baroreceptors in both groups of animals were also apparent when the data were normalized to a percent of maximum nerve activity. The degree of rapid baroreceptor resetting was calculated by dividing the change in threshold pressure by the change in holding pressure and multiplying by 100%.

All values represent mean±SEM. The carotid sinus pressure–baroreceptor activity relations in normotensive versus hypertensive rabbits were compared with analysis of variance. Unpaired t tests were used to compare the levels of baroreceptor activity and carotid sinus diameter at equivalent pressures as well as pressure threshold between normotensive and hypertensive animals. Analysis of variance with a repeated-measures design and Scheffé's multiple comparison test were used to compare the effects of changes in holding pressure within each group. Statistical significance was assumed if p<0.05.

Results

At the time of the study, arterial pressure averaged 127±3 mm Hg in 12 hypertensive rabbits and 85±3 mm Hg in 11 normotensive rabbits (p<0.05). Baroreceptor threshold pressure was significantly elevated in the hypertensives (n=9) compared with the normotensives (n=6) (78±4 versus 55±3 mm Hg, p<0.05). Baroreceptor activity was significantly less in the hypertensives than in the normotensives over a range of carotid sinus pressures from 60 to 135 mm Hg (Figures 1A and 2), whereas carotid sinus diameter was similar between the groups over this range of pressure (Figure 1B). The pressure–diameter relation was not significantly altered after exposure to higher or lower distending pressure in either the normotensive or hypertensive animals (Table 1).

Rapid Resetting During Increases in Holding Pressure

Threshold pressure increased significantly in the normotensive rabbits after carotid sinus holding pressure was increased above the control level by 30 and 60 mm Hg (39±6% and 33±2%, respectively, n=6). In hypertensive rabbits, however, increases in threshold pressure were significantly less than in the normotensives (14±5%, n=7; 9±3%, n=5, respectively, Figures 2 and 3A). Shifts in the baroreceptor pressure–activity curve were also less in the hypertensives compared with normotensives (Figure 4).

Rapid Resetting During Decreases in Holding Pressure

After carotid sinus holding pressure was decreased from the control level, threshold pressure decreased to the same degree in both normotensives (n=6) and hypertensives (n=7) (Figure 3B). At the holding pressure 30 mm Hg below the control level, resetting was 32±6% in the normotensives and 34±3% in the hypertensives. At 60 mm Hg below control, resetting was 28±3% in the normotensives and 30±4% in the hypertensives.

At 60 mm Hg below the control level, the holding pressure in the hypertensives was 71±4 mm Hg, which was lower than the control holding pressure in the normotensive rabbits (83±3 mm Hg). During this brief period of normotension, threshold pressure in the hypertensives decreased from 80±5 mm Hg to 62±4 mm Hg, a level that was not significantly different from the threshold pressure of 55±3 mm Hg in the normotensives. The baroreceptor pressure–activity curve in the hypertensive group shifted significantly to the left after normalization of the hold-
ing pressure, and baroreceptor activity was not significantly different from that of the normotensives at any pressure (Figure 5). The restoration of the baroreceptor pressure–activity curve of the hypertensive animals toward normal was not associated with any significant change in the carotid sinus pressure–diameter relation (Table 1).

**Discussion**

In normotensive animals, rapid or acute resetting of baroreceptors increases the range over which fluctuations in arterial pressure can be effectively buffered. However, this rapid resetting provides a form of positive feedback that can be detrimental in long-term pressure control. When pressure remains elevated for more than a few minutes, baroreceptors will be reset to operate at the new higher level; baroreceptor activity will decrease after the initial rise, thus tending to promote the development of hypertension. When pressure falls for more than a few minutes, baroreceptors will reset and activity will increase after the initial fall, thus tending to promote hypotension.

The results of the present study indicate that acute baroreceptor resetting in hypertensive rabbits is altered. During increases in carotid sinus pressure above the level of mean arterial pressure, baroreceptors failed to reset to the same degree as in

**Figure 1.** Panel A: Baroreceptor pressure–activity curves in normotensive (n=6) and hypertensive (n=9) rabbits. Panel B: Baroreceptor pressure–diameter curves in normotensive (n=5) and hypertensive (n=5, n=4 at 30, 45, 135, and 150 mm Hg) rabbits. Diameter recordings were made in only four hypertensives at pressures of 30, 45, 135, and 150 mm Hg. Data represent mean±SEM. *p<0.05 in hypertensive vs. normotensive rabbits.

**Figure 2.** Original records from a normotensive rabbit (left panels) and a hypertensive rabbit (right panels) showing integrated carotid sinus nerve activity during ramp increases in carotid sinus pressure after holding pressure at the level of mean arterial pressure (middle panels) and after holding pressure 60 mm Hg above that level (bottom panels). Baroreceptor activity is proportional to the slope of the lines on the integrated trace. Pressure ramps were superimposable within each experiment, so only one is shown for clarity. Activity was less in the hypertensive rabbit than the normotensive rabbit after the control holding pressure. Decrease in activity after the high holding pressure was more pronounced in the normotensive than the hypertensive animal.
TABLE 1. Carotid Sinus Diameter During Ramp Increases in Pressure After Increases and Decreases in Carotid Sinus Holding Pressure

<table>
<thead>
<tr>
<th>Carotid sinus pressure (mm Hg)</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>Diameter (μm) (Rabbits n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>1,393±55</td>
<td>1,938±102</td>
</tr>
<tr>
<td>After increasing HP by 60 mm Hg</td>
<td>1,426±71</td>
<td>1,955±111</td>
</tr>
<tr>
<td>After decreasing HP by 60 mm Hg</td>
<td>1,360±48</td>
<td>1,898±106</td>
</tr>
</tbody>
</table>

Values are mean±SEM of carotid sinus diameter in micrometers measured at carotid sinus pressures of 30, 90, and 150 mm Hg. Rapid resetting of baroreceptors with both increases and decreases in holding pressure (HP) was not accompanied by a change in pressure–diameter relation from control. NS, diameters after increasing or decreasing HP were not significantly different from control in normotensive and hypertensive rabbits at any level of carotid sinus pressure.

normotensive rabbits. On the other hand, during decreases in holding pressure below mean arterial pressure, rapid baroreceptor resetting was completely normal. The limited ability of baroreceptors to reset in response to acute increases in pressure limits the tendency for further increases in arterial pressure in animals that are chronically hypertensive. However, because rapid resetting during acute decreases in pressure is normal, any tendency for pressure to fall will be enhanced. Thus, impairment of resetting during increases in pressure in hypertensive animals would be beneficial since it would prevent further increases in arterial pressure. Conversely, preservation of resetting during decreases in pressure would be beneficial since it could help promote the restoration of arterial pressure to normal levels. Restoration of baroreceptor function in hypertensive animals after only 10–15 minutes of normotension without changes in mechanical properties indicates that structural changes in the carotid sinus in hypertension cannot completely account for chronic baroreceptor resetting in this disease. Furthermore, the restoration of baroreceptor activity after a brief period of normotension helps to maintain pressure at the lower level.

Several other investigators have studied acute baroreceptor or baroreceptor reflex resetting in chronic hypertension. Studies by Sapru and Wang and Sapru and Krieger showed that aortic baroreceptors in an isolated aortic arch preparation of spontaneously hypertensive rats did not reset or reset only minimally in response to an acute increase in holding pressure from 100–120 to 160 mm Hg. In contrast, Moriera et al recently showed that aortic baroreceptors in renal hypertensive rats maintained their ability to reset to sustained increases in arterial pressure in vivo. In their study, Moriera et al used phenylephrine infusions to increase arterial pressure to cause rapid resetting of the baroreceptors. Phenylephrine may alter baroreceptor sensitivity or compliance of the aortic arch, either by a direct action or by reflexly mediated changes in sympathetic outflow to the arch. In addition, the rapid withdrawal and infusion of blood used to measure pressure threshold could also have caused significant fluctuations in sympathetic activity to the arch. We avoided these potential limitations by using an isolated and sympathetically denervated carotid sinus preparation. In our study, any acute change in baroreceptor threshold was rapidly reversible when holding pressure was restored to the control level. In the study by Moriera et al, however, the increases in threshold during phenylephrine-induced hypertension were not reversed 30 minutes after restoration of pressure, suggesting that the resetting during phenylephrine infu-
Arterial baroreceptor function is impaired in chronic hypertension. This is evident in the present study from the elevated threshold pressure for baroreceptor activation and the decreased baroreceptor activity in hypertensives compared with normotensives at several levels of carotid sinus pressure. Hypertension may be associated with decreases in the distensibility of the carotid sinus and aortic arch. Less stretch of baroreceptor endings during increases in pressure has been proposed as a mechanism for chronic baroreceptor resetting in hypertension. In the present study, however, the pressure–diameter relations from normotensive and hypertensive animals were not significantly different over a range of carotid sinus pressures from 60 to 150 mm Hg. When the data are analyzed as changes in diameter with increases in pressure (distensibility) there is still no significant difference between the normotensive and hypertensive rabbits, although there is a tendency for decreased distensibility in the hypertensives. Furthermore, when carotid sinus holding pressure was reduced by 60 mm Hg to near normotensive levels for only 10–15 minutes in the hypertensive animals, threshold pressure and baroreceptor activity were restored to near normal. The carotid sinus pressure–diameter curve and calculated wall strain were not altered during this period (i.e., the relation between strain and nerve activity was shifted as a result of the change in holding pressure). Thus, baroreceptor function was restored in the absence of any change in mechanical properties of the carotid sinus. This suggests that decreased baroreceptor activity in chronic hypertension cannot be explained solely by decreased distensibility of the carotid sinus.

Restoration of baroreceptor function after reversal of hypertension has been demonstrated by other investigators. However, restoration was apparent only after 6 hours of normotension, or after...
FIGURE 5. Baroreceptor pressure–activity curves after holding pressure at the control level in normotensive (n=6) and hypertensive (n=7) rabbits and in the hypertensives after holding pressure 60 mm Hg below the control level. Data represent mean±SEM. *p<0.05, hypertensive vs. normotensive rabbits. At “control” levels of holding pressures, the pressure–activity curve was shifted to the right in the hypertensives, their baroreceptor activity increased significantly and the pressure–activity curve was not significantly different from that in the normotensives.

several weeks of antihypertensive treatment, and then only if accompanied by regression of structural changes.21,22 The uniqueness of our findings is the rapidity of this reversal, with normalization of baroreceptor activity without any change in the mechanical properties of the sinus.

Impairment of rapid baroreceptor resetting during transient increases in pressure in chronic hypertension may have significant clinical implications. It is conceivable that large, rapid increases in arterial pressure may increase baroreceptor activity to near maximum levels so that one is located on the plateau portion of the pressure–activity curve. Normally, if the elevated pressure is maintained, rapid baroreceptor resetting reduces nerve activity, which returns the operating point to the steep portion of the curve.3 Thus, the significance of rapid baroreceptor resetting is that it maintains the sensitivity of the receptors to rapid transient changes in pressure that may occur around the new higher setpoint level of pressure. The disadvantage is that the reduction of baroreceptor activity tends to maintain or exacerbate the increase in pressure. We speculate that in chronic hypertension, the impaired rapid resetting in response to further acute increases in pressure might result in the operating point remaining on the relatively flat plateau portion of the pressure–activity curve. This may limit the ability of baroreceptors to buffer transient and rapid changes in pressure and therefore lead to more pronounced fluctuations in arterial pressure. Conversely, these bouts of elevated pressure may not provoke a decline in baroreceptor activity; thus, the positive feedback due to rapid resetting may not occur. This may limit the extent of arterial pressure elevation in hypertension and tend to prevent progression of the disease.

Preservation of rapid resetting during decreases in pressure leads to facilitation of transient falls in pressure. Because baroreceptor function in hypertension can be rapidly restored by acute hypotension, transient decreases in pressure may be maintained, which may help restore arterial pressure to normal levels. This is suggested by a recent case report27 in which two hypertensive patients were treated with nitroprusside infusion to achieve normal levels of arterial pressure for 36 hours. After discontinuation of nitroprusside, arterial pressure remained at normotensive levels for up to 31 days.

The present study focused on baroreceptor function in hypertension. Changes in the regulation of the circulation in hypertension are only partially due to changes in the behavior of baroreceptors. Abnormalities of the central mediation of the baroreceptor reflex28–30 as well as abnormalities of norepinephrine release and end organ responsiveness in hypertension28 must also be taken into account when considering the overall effect of changes in the baroreceptors in hypertension.

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References


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