Partition of Carotid Sinus Baroreceptor Response in Dogs with Chronic Renal Hypertension

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SUMMARY This study was designed to determine whether resetting of the carotid sinus baroreceptors in chronic renal hypertension is due to altered distensibility of the wall, or changes in the properties of the receptor elements, or both. Dogs were made hypertensive by 50% constriction of the left renal artery with a Goldblatt clamp and by right nephrectomy one week later. Five to nine weeks after nephrectomy, when mean blood pressure had risen by 35-46 mm Hg, the isolated carotid sinus wall deformation, measured from still photographs, and gross baroreceptor nerve action potentials (N) were recorded in response to step intrasinus pressure forcings (P), ranging from zero to 300 mm Hg, in increments of 25 mm Hg. Measured wall deformation was converted to strain-energy density (SED), a scalar value, as the best indicator of the mechanical state of the sinus wall. Plots of N vs. P data followed an S-shaped pattern, but were shifted toward the P-axis, as compared to controls. Plots of SED vs. P, though linear over most of the pressure range, were shifted toward the SED-axis, as compared to controls. A plot of N vs. SED, derived from the composite plots of N vs. P and SED vs. P, followed an S-shaped pattern and also was shifted toward the SED-axis. We conclude that the nonlinearity in the N vs. P curve is due largely to the inability of the receptor elements to respond to increasing wall strain and to resetting of the baroreceptors due to changes in the receptor properties rather than in the wall elements. Circ Res 48: 267-273, 1981

IN a previous study from this laboratory (Koushanpour and Kelso, 1972), the normal baroreceptor process in the carotid sinus (defined by the pressure-nerve activity relationship) was partitioned between the mechanical properties of the wall (pressure-wall deformation relationship) and the receptor elements (wall deformation-nerve activity relationship). The carotid sinus wall deformation was defined by the strain-energy density (SED), which was calculated by measuring the circumferential and longitudinal strains in the isolated carotid sinus and then estimating the corresponding stresses in accordance with a thin-walled, axially symmetric vessel model. The results showed that the carotid sinus wall deformation increases almost linearly with increasing pressure, whereas the receptor output is a sigmoidal function of the wall deformation. Thus, the nonlinearity in the pressure-nerve activity relationship appeared to be due primarily to the inability of the receptor elements to respond to increasing wall strain.

The purpose of the present study was to partition similarly the baroreceptor process in the chronic phase of one-kidney Goldblatt renal hypertension and to determine whether the "resetting" of the baroreceptors is due to an altered distensibility of the wall or to changes in the properties of the receptor elements, or both. An alteration in the pressure-strain energy density relationship would implicate the wall elements as the locus of baroreceptor resetting, whereas an alteration in the strain energy density-nerve activity relationship would implicate the receptor elements as the locus of baroreceptor resetting.

Methods

Surgical Preparation

Healthy female mongrel dogs were divided into two groups. Group I, consisting of six dogs, was made hypertensive under aseptic conditions by partial constriction of the left renal artery with a Goldblatt clamp, followed by a right nephrectomy one week later. The Goldblatt clamp was adjusted so as to reduce renal blood flow by about 50%, as determined by a Statham model SP 2202 electromagnetic blood flowmeter. Group II, consisting of five dogs, was subjected to the same surgical procedures except for placing the Goldblatt clamp loosely around the left renal artery.

Five to nine weeks after right nephrectomy, the baroreceptor process in the isolated carotid sinus was studied under acute conditions as described below. Arterial blood pressure measured at this time showed a 27 to 36% increase in the mean pressure. However, systolic blood pressure was the only component which was positively correlated to the duration of time post-nephrectomy.

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Under sodium pentobarbital anesthesia (30 mg/kg, iv), the right carotid sinus area was exposed by cautery and blunt dissection. Under a Zeiss operating microscope, the baroreceptor branch of the carotid sinus nerve was located; it was identified by monitoring the relationship of the spike frequency to the pressure pulse. Except for placing on the electrode, the nerve was not subjected to any additional handling and the nerve sheath was left intact (Koushanpour and McGee, 1969). In this manner, insofar as possible, the physiological integrity of the gross baroreceptor nerve was preserved.

Following identification of the nerve, the carotid sinus was functionally isolated from the circulation as follows. The occipital artery, the ascending pharyngeal artery, and all collateral arteries except the common carotid, the lingual, the internal carotid, and the external carotid were tied and cut. This surgical procedure allowed the carotid sinus to be perfused only by the common carotid artery and to be drained by the internal and external carotids and the lingual arteries. The intrasinus pressure was measured via a polyethylene catheter (PE90) inserted into the lingual artery and connected to a Statham model P23Dd pressure transducer. The isolated carotid sinus was forced via a polyethylene catheter (PE 320) inserted into the external carotid artery and connected to a pressure bottle. During forcing, the common carotid and the internal carotid arteries were clamped, and the desired pressure forcings were applied to the carotid sinus.

Data Acquisition and Analysis

The experimental protocol consisted of recording the baroreceptor nerve activity and measuring the carotid sinus wall deformation in response to equally spaced steps in static pressure between zero and 300 mm Hg. The pressure forcings were carried out sequentially starting at an intrasinus pressure of zero mm Hg, proceeding in 25 mm Hg increments to a pressure of 300 mm Hg, and returning in 25 mm Hg decrements to zero mm Hg.

Gross baroreceptor nerve action potentials were measured by placing the intact nerve across a pair of platinum electrodes spaced 2 mm apart. The nerve signal was then amplified successively by an Argonaut LRA 042 differential amplifier with a passband of 100–1,600 Hz and a Tektronix FM 122 differential amplifier with a passband of 80–10,000 Hz. The amplified signal provided a suitable input voltage for recording the nerve action potentials along with the applied pressure forcing on a Sanborn model 3907A FM analog tape recorder at a speed of 15 inches/sec.

It is generally accepted that the frequency of impulses traveling along a single baroreceptor nerve fiber is the most significant measure of nerve activity. In this study, where action potentials were recorded from a multifiber preparation, we calculated the "time-averaged frequency" of the gross baroreceptor nerve signal as a measure of nerve activity, assuming that it is a linear function of the individual fiber impulse frequencies (Katz, 1966). The calculation was based on a method described previously (Koushanpour and Kelso, 1972) using the following equation:

\[
\text{Time-averaged frequency} = \frac{1}{T} \int_{0}^{T} v \, dt \quad (1)
\]

where \( T \) is the period (usually 1 minute) over which the nerve signal is averaged, \( R \) is the interelectrode resistance, \( A \) is the number of joules of energy contained in each action potential, and \( v \) is the potential difference measured by the electrode.

The amplified nerve signal was digitized at a rate of 20,000 data points/sec by the analog-to-digital conversion unit of a PDP-12A digital computer. This sampling rate was quite sufficient for resolving each action potential. The digitized values were then used to integrate Equation 1 numerically, using Simpson's integration rule (Carnahan et al., 1969).

The carotid sinus wall deformation was measured from still photographs taken during the pressure forcings by the method described previously (Koushanpour and Kelso, 1972). Briefly, from these photographs, two indices of carotid sinus wall deformation, namely, longitudinal strain, \( \varepsilon_l = (\ell - \ell_0) / \ell_0 \), and circumferential strain, \( \varepsilon_c = (d - d_0) / d_0 \), were calculated. \( \ell_0 \) and \( d_0 \) are the measured length and diameter of the carotid sinus at an intrasinus pressure forcing of 50 mm Hg (representing zero strain), and \( \ell \) and \( d \) are the measured length and diameter of the carotid sinus at any other intrasinus pressure forcings. Since both longitudinal and circumferential strains are vector quantities, they were combined in accordance with a thin-walled axially symmetric model to obtain a scalar quantity, namely, the strain-energy density (SED) using the following equation:

\[
\text{SED} = \frac{1}{2} \left[ \left( \frac{P_r}{h \cos \theta} \right) (\varepsilon_c + 1) + \frac{h}{r} \cos \theta \left( \varepsilon_l + 1 \right) + \frac{h}{r} \sin \theta \left( \varepsilon_l + 1 \right) \right] \quad (2)
\]
where $r_i$ and $r_e$ are the internal and external radii of the carotid sinus, respectively. The wall thickness, $h = (r_e - r_i)$, was then determined from the weight of the excised carotid sinus ($W_c$), using a density of 1.06 (McDonald, 1974). Substituting the volume of the carotid sinus by weight measurement $V_w = W_c/1.06$ for $V_s$ in Equation 2, and rearranging terms, we get:

$$ r_i = \left( r_e^3 - \frac{0.7076}{\pi} W_c \right)^{1/3}. \quad (3) $$

The only unknown in this equation is $r_e$, which was measured on the surface of the photographs. The wall thickness thus measured was compared with that obtained from histological sections of the carotid sinus. We found a reasonable agreement between the two methods.

**Results**

**Pressure-Nerve Activity Relationship**

Figure 1 shows the plots of the pooled, normalized baroreceptor nerve activity as a function of the applied intrasinus pressure forcings for the normotensive and hypertensive dogs. Based on a previous mathematical analysis of the baroreceptor process in the carotid sinus (Koushanpour, 1973), we found that the pressure-nerve activity data can best be fitted to an exponential equation of the form:

$$ N = A - \frac{A - B}{1 + e^{-(C+DP)}} \quad (4) $$

where $N$ is the predicted nerve activity, $P$ is the applied intrasinus pressure, $A$ and $B$ are the maximum and minimum measured nerve activities, and $C$ and $D$ are the coefficients of the exponential term. Using the standard least-squares technique (Draper and Smith, 1966), the paired digitized pressure and nerve data were fitted to the above equation, and the coefficients $A$, $B$, $C$, and $D$ were estimated by a curve-fitting program (Marini and Perry, 1979) written for the PROPHET computer system (Raub, 1974). Table 1 presents a summary of the pertinent statistical results.

The pressure-nerve activity relationship for the normotensive dogs generally was similar to the sigmoidal relationships obtained previously in this laboratory and those reported by other investigators (Kirchheim, 1976). The baroreceptor nerve activity increases linearly as the intrasinus pressure rises from 100 to about 180 mm Hg. Thereafter, nerve activity approaches an asymptote as the intrasinus pressure exceeds 200 mm Hg. In the case of hypertensive dogs, although the pressure-nerve activity relationship follows a sigmoidal pattern, the curve is significantly shifted toward the pressure axis. As shown in Figure 1, the threshold pressure was somewhat lower, but not significantly different, in the normotensive as compared to the hypertensive dogs. Also, the maximal baroreceptor response was significantly lower in the hypertensive as compared to the normotensive group ($P < 0.01$).

The downward shift of the pressure-nerve activity relationship for hypertensive dogs suggests a significant reduction in the sensitivity of the baroreceptors to respond to increasing levels of intrasinus pressures. Thus, a higher intrasinus pressure is required to generate the same degree of nerve output, as compared with the normotensive dogs. The marked reduction in baroreceptor nerve output with increasing intrasinus pressure shown in Figure 1 provides quantitative evidence for the "resetting" of the carotid sinus baroreceptors in one-kidney Goldblatt hypertensive dogs. This finding confirms previous observations in rabbit (Angell-James, 1973), rat (Krieger, 1970), and dog (Sleight et al., 1975).

Although most investigators agree that the baroreceptors are reset in the chronic state of hypertension, there is no general consensus regarding the mechanisms, nature, or locus of the baroreceptor

**Table 1** Calculated Coefficients of Equation 4 Fitted to Normotensive and Hypertensive Pressure-Nerve Data

<table>
<thead>
<tr>
<th></th>
<th>Normotensive (n = 5)</th>
<th>Hypertensive (n = 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.825062 ± 0.01829541</td>
<td>1.319077 ± 0.02018954</td>
</tr>
<tr>
<td>B</td>
<td>0.9154496 ± 0.01998614</td>
<td>0.9657798 ± 0.01550515</td>
</tr>
<tr>
<td>C</td>
<td>5.660437 ± 1.225583</td>
<td>-0.03466594 ± 0.007592093</td>
</tr>
<tr>
<td>D</td>
<td>-0.06379001 ± 0.00751567</td>
<td>-0.06379001 ± 0.00751567</td>
</tr>
</tbody>
</table>

Values are means ± sd. Fitted coefficients were significant at $P < 0.01$ level.
resetting. The aim of this study was to determine the mechanisms of baroreceptor resetting by partitioning the pressure-nerve activity relationship between its two components, namely, pressure-deformation and deformation-nerve activity relationships.

**Pressure-Deformation Relationship**

Figure 2 compares the plots of strain-energy density (SED) as a function of applied pressure forcings between normotensive and hypertensive groups. The data for both groups were fitted to a third degree polynomial of the form:

\[
\text{SED} = \beta_0 + \beta_1 P + \beta_2 P^2 + \beta_3 P^3
\]

where SED is the predicted strain-energy density and P is the applied intrasinus pressure. The coefficients \(\beta_0\), \(\beta_1\), \(\beta_2\), and \(\beta_3\) were estimated by least squares method, using the same curve-fitting programs mentioned above. The degree of the polynomial was estimated by choosing the lowest order polynomial which had no bias at the 5% level of significance and whose lack-of-fit sum of squares was not decreased significantly by adding a higher order term. This estimation was accomplished by calculating the difference between the lack-of-fit sum of squares for k and k + 1 degree polynomial and then dividing it by the mean square error. This ratio then was compared with the corresponding value in Snedecor's F-distribution table (Snedecor, 1962) for the appropriate degrees of freedom at the 5% level of significance. Table 2 presents a summary of the pertinent statistical results.

The most striking feature of these plots is that, in both the normotensive and hypertensive groups, strain-energy density increases rather linearly with increasing pressure, with no evidence of saturation. This was surprising, in view of the fact that both circumferential and longitudinal strains were positive monotonic functions of applied pressure, approaching an asymptote as the intrasinus pressure exceeded 200 mm Hg. However, for reasons stated elsewhere (Koushanpour and Kelso, 1972), we have chosen the strain-energy density because it includes deformation in all directions and is not dependent upon a particular reference choice.

The pressure-SED plots shown in Figure 2 further reveal that at every applied intrasinus pressure there is significantly greater wall deformation in the hypertensive group as compared to normotensive dogs. This apparent increase in the distensibility of the carotid sinus in hypertension, rather than the expected stiffening of the wall, was supported further by wall thickness measurements. We found no significant difference between the carotid sinus wall thickness in the hypertensive (0.9928 ± 0.0355 mm) and the normotensive (1.0132 ± 0.0865 mm) animals. Furthermore, standard histological staining did not show a systematic difference in the structure of the wall or in the distribution of the collagen and elastin components of the wall between the hypertensive and normotensive groups. The pressure-SED relationship and the wall thickness measurements cited above, coupled with the significant reduction in the baroreceptor nerve activity at increasing levels of intrasinus pressure (Fig. 1), suggest that the locus of baroreceptor resetting may be due to an alteration in the properties of the receptor elements rather than to an alteration in the mechanical properties of the wall. To explore this further, we next compared the deformation-nerve activity relationship between the normotensive and hypertensive groups.

**Deformation-Nerve Activity Relationship**

The least squares fitted Equations 2 and 3 for pressure-nerve activity and pressure-SED relationships were solved simultaneously for pressure values ranging from zero to 300 mm Hg, in 25 mm Hg increments. Figure 3 compares the plots of normal-
BARORECEPTOR RESPONSE IN HYPERTENSION/Koushanpour and Kenfield

Comparison of hypertensive and normotensive responses

Figure 3 Comparison of strain energy density-normalized nerve activity relationships for normotensive (unfilled circles) and renal hypertensive (filled triangles) dogs. The solid lines connecting the data were drawn by the computer.

Discussion

The purpose of this study was 2-fold: first, to quantify the carotid sinus baroreceptor response in one-kidney Goldblatt hypertension and to define the extent of resetting of baroreceptors in this model of hypertension, and second, to delineate the locus of resetting in the baroreceptor response by partitioning the pressure-nerve activity relationship between the mechanical properties of the sinus wall (pressure-deformation relationship) and the receptor elements (deformation-nerve activity relationship).

The pressure-nerve activity relationships (transfer function) were found to be sigmoidal for both normotensive and hypertensive animals (Fig. 1). However, the relationship for hypertensive dogs was characterized by a shift of the response curve toward the pressure-axis, and a lower asymptote at higher pressures. The transfer function for normotensive dogs also followed a sigmoidal curve, but had a much steeper slope, with baroreceptor response approaching an asymptote at an intrasinus pressure of 175 mm Hg. In contrast, the transfer function for hypertensive dogs followed a sigmoidal curve, having a much flatter slope, with baroreceptor response approaching an asymptote at an intrasinus pressure exceeding 225 mm Hg. The slopes of the transfer functions were significantly different at intrasinus pressures exceeding 100 mm Hg. The baroreceptor responses for both groups were virtually identical at intrasinus pressures below 100 mm Hg. The percent increase in nerve activity with the increase in pressure from 75 to 175 mm Hg was about 114% for the normotensive group, as compared to only 20% for the hypertensive group.

In both normotensive and hypertensive groups, the strain-energy density was found to be a linear function of pressure, as the intrasinus pressure increased above 75 mm Hg (Fig. 2). However, for the hypertensive group, the curve was shifted significantly toward the SED-axis, suggesting that at each pressure forcing above 75 mm Hg, the carotid sinus from the hypertensive dog shows a greater volume expansion as compared to normal. Otherwise, both curves appear to be similar in pattern, and neither reaches an asymptote as the intrasinus pressure is increased to high levels. This finding strongly implicates the receptor elements and their associated mechanical linkages as the probable limiting factor in the baroreceptor response in hypertension, a suggestion supported by recent findings of Andersen et al. (1978). Thus, it appears that a major factor contributing to the baroreceptor resetting in hypertension is a pathophysiological alteration in the function of the receptor elements and perhaps, to a lesser extent, the altered mechanical properties of the carotid sinus wall. This question was explored further by comparing the transfer function for the receptor elements of the hypertensive and normotensive groups.

Comparison of the relationship of the normalized nerve response against the strain-energy density between normotensive and hypertensive dogs (Fig. 3) reveals that the hypertensive baroreceptor response reaches a maximum firing rate below that of the normotensive receptor, even though the expansion of the carotid sinus (increase in SED) continues to increase. Thus, the hypertensive baroreceptor nerve appears to be less responsive to changes in intrasinus pressure than is the normotensive baroreceptor nerve at identical intrasinus pressure forcings.

Figure 4 compares the partitioning of the carotid sinus baroreceptor process for the hypertensive and normotensive dogs and summarizes our results. The normotensive relationships are shown by the continuous lines, and the hypertensive relationships are represented by the dashed lines. The shape of the overall pressure-nerve transfer function remains sigmoidal in hypertension, but is shifted toward the pressure-axis, so that for any intrasinus pressure greater than 125 mm Hg, the nerve output is sig-
The present method of partitioning of the carotid sinus baroreceptor process between the mechanical properties of the wall and the neural receptor elements reveals that the pressure-deformation relationship of hypertensive dogs is shifted toward the deformation axis. This finding does not support the concept of a "stiffening" of the carotid sinus wall as the contributing factor to the resetting of the baroreceptor process. Although contrary to the results reported in the literature for other areas of the vascular tree in hypertension, our finding is supported by observations of Asteroth and Kreuziger (1951), who found that distensibility of the carotid sinus wall does not decrease in patients with renal hypertension.

Graphical analysis of the normalized nerve output as a function of the strain-energy density showed that the shapes of the normotensive and hypertensive curves approximated those of the pressure-nerve relationships, with the hypertensive curve shifted toward the deformation axis. Thus, on the basis of this method of partitioning of the baroreceptor process, the locus of "resetting" of the baroreceptor response appears to be primarily within the neural receptor response to deformation, which shows a significant decrease in sensitivity in chronic renal hypertension. The alteration of the nerve response to deformation in hypertension may be due to (1) an adaptive change in the receptor elements, (2) a pathological degeneration of nerve endings, or (3) a change in the mechanical properties of the coupling of the receptor elements to the wall components. Hilgenberg (1959) has reported degenerative changes in, and complete destruction of, some afferent nerve endings, in the carotid sinus area of hypertensive humans. It is not possible to define at this point which of the three possibilities mentioned above may be responsible for the observed resetting of the baroreceptor process. Our studies implicate the receptor elements, rather than the wall elements, as the locus of baroreceptor resetting.

Our findings regarding the locus of the baroreceptor resetting are at variance with two previous studies on the aortic arch baroreceptor resetting in renal hypertensive rabbits (Aars, 1969; Angell-James, 1973). However, our results are supported by two other studies which examined the distensibility characteristics of the carotid artery in renal and DOCA hypertensive rats (Cox, 1977) and of the aortic arch in spontaneously hypertensive rats (SHR) (Andersen et al., 1978). A number of factors could have contributed to the differences in the reported results. Of these, four factors deserve some consideration. First, there are considerable differences between the mechanical properties and structure of the carotid sinus and aortic arch (Dobrin, 1978). In view of this, it is unrealistic to assume that changes in the mechanical and structural properties of the carotid sinus should be analogous to those seen in the rest of the vascular tree, such as the aortic arch. Second, the technique used to measure the distensibility of the aortic arch was different from that used in the present study. Aars (1969) determined aortic arch distensibility from links of changes in the diastolic diameter of the aorta (measured by two piezo-electric crystals) as a function of changes in diastolic aortic pressure (produced by hemorrhage and blood reinfusion). A critical examination of his original data reveals considerable variations and overlaps between the normotensive and hypertensive plots, thereby rendering his conclusion statistically untenable. In contrast, both Angell-James (1973) and Andersen et al., (1978) quantified the aortic arch distensibility from pressure-volume plots obtained by injecting a known volume of fluid into the isolated aortic arch and recording the resulting pressure. Angell-James (1973) found a definite shift of the volume vs pressure curve toward the pressure-axis for the hypertensive group, as compared to the normotensive group, suggesting a reduction in the distensibility of the aorta in renal hypertension, particularly at the higher pressure range. Andersen et al. (1978), however, found that at 10 weeks, aortas from the normotensive rats (NTR) and SHR were equally distensible but, at 20 weeks, aortas from NTR had become more distensible. On the basis of these findings, Andersen and co-workers (1978) attributed the baroreceptor resetting to a defect in the receptors themselves, rather than to a change in the structural characteristics of the wall. Cox (1977) has used yet another method to quantify the passive mechanical properties and connective tissue composition of the carotid artery in renal and DOCA hypertensive rats. He found that the tangential stress-strain relationship was shifted toward the strain-axis, in both hypertensive groups, suggesting...
an increase in the distensibility of the carotid artery in these two types of hypertension. Our finding for the hypertensive canine carotid sinus is in full agreement with that for the carotid artery in the hypertensive rat. Third, the hypertension models in the studies cited above all are different, a fact that must have some as yet unknown effect on the mechanical properties of the vessel wall containing the baroreceptors as well as the receptor elements and their functions. Finally, there may be species differences in the response to hypertension as well as in the mechanical properties and structure of the vascular tree. The above-mentioned differences in methodology, hypertension models, and animal species used may, in part, explain the differences in the findings reviewed briefly above. However, it is reasonable to expect that, because the carotid sinus is the most distensible arterial segment known, the functional and/or structural properties of the wall could be altered in a unique way by the effect of pathologically high intrasinus pressures of chronic renal hypertension.

In summary, the results of the present study show that, although the carotid sinus wall distensibility does not decrease during renal hypertension, the nerve output, which depends upon stretching of the wall elements to stimulate the receptors, does decrease at the same pressures. Therefore, it appears that the receptors have become less responsive to the same stimulus. This observation may be explained by (1) an adaptive change in receptor sensitivity consequent to hypertension, (2) a pathological degeneration of the receptor nerve endings, or (3) an uncoupling of the wall and neural elements consequent to hypertension. Thus, the locus of the baroreceptor resetting appears to be in the receptor elements, which show significant alterations in their functional characteristics determined by the present methods.

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