Short- and Long-Term Determinants of Baroreceptor Function in Aged Normotensive and Spontaneously Hypertensive Rats

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SUMMARY. In a variety of animal models, baroreceptor resetting during chronic hypertension has been correlated to vessel wall hypertrophy and decreased distensibility. In one possible mechanism of chronic resetting, termed the splinting hypothesis here, it has been suggested that a stiffer vessel wall might increase the minimum pressure required for activation of these mechanoceptors (pressure threshold) and decrease suprathreshold pressure sensitivity. Lower vessel distensibility would alter baroreceptor function by preventing equivalent pressures from producing equivalent vessel distensions and, thus, receptor distortions. Recent studies have also suggested that the pressure threshold is strongly influenced by the most recent (minutes) history of blood pressure exposure during a process termed rapid resetting. Hypertension and advanced aging are associated with distensibility changes. The present study examines pressure and equivalent mechanical response characteristics of aortic baroreceptors from aged normotensive Wistar-Kyoto and spontaneously hypertensive rats. An in vitro aortic arch-aortic nerve preparation was used to assess the discharge properties from a number of baroreceptors and the pressure-diameter relationship of each aorta. Both control and rapid resetting protocols were used to study the baroreceptor characteristics. Aged normotensive rats were normotensive and averaged 115 weeks of age. Aged spontaneously hypertensive rats had systolic tail pressures of 187 mm Hg and averaged 76 weeks of age. Although aortic distensibility of aged WKys was much lower than previously found in younger animals, the pressure threshold was unchanged. Aged spontaneously hypertensive rat receptors were chronically reset in proportion to their blood pressure. Decreased distensibility did not alter the rapid resetting process. It is concluded that baroreceptor pressure sensitivity is more closely related to aortic distensibility under several conditions altering vessel stiffness, whereas, the pressure threshold may be regulated additionally by mechanisms independent of distensibility. The results are inconsistent with the splinting hypothesis. (Circ Res 54: 750–759, 1984)

During chronic hypertension in humans and in animals, the characteristics of both the baroreceptors and baroreflexes are shifted to operate over a higher pressure range, and thus require higher than normal pressures for threshold activation and greater increments in pressure for further increments in activity (see Folkow, 1982). In a variety of animal models, this chronic hypertensive resetting process has been repeatedly correlated with the development of the marked vessel wall hypertrophy and decreased distensibility which accompanies the elevated blood pressures (e.g., Aars, 1969). Thus, in one suggested mechanism of chronic baroreceptor resetting, the decreased distensibility might influence the baroreceptor transduction process at the point where transmural pressure is transformed into receptor-activating vessel distortion (Brown, 1980). During chronic hypertension, a stiffer vessel would require greater pressures to distend the vessel and, therefore, to stimulate the receptors (Gribbin et al., 1971; Angell-James, 1973). This can be termed the splinting hypothesis of chronic baroreceptor resetting. In normotensive developing rats and in spontaneously hypertensive rats (SHR), the splinting hypothesis does not account for changes in aortic baroreceptor threshold and suprathreshold sensitivity during changes in vessel wall distensibility (Andresen et al., 1980).

Recent work has established that baroreceptors are also subject to the relatively short-term influence of the prevailing blood pressure (Coleridge et al., 1981; Dorward et al., 1982; Krieger et al., 1982; Munch et al., 1983). These studies have shown that baroreceptor pressure threshold shifts in the direction of a change in the prevailing mean arterial pressure within 15 minutes, and the new threshold does not change further for at least the next hour. Suprathreshold pressure sensitivity is unchanged during rapid resetting. The reversible shifts in threshold are always quantitatively less than the change in mean arterial pressure. Thus, short-term factors have an important part in the setting of baroreceptor response characteristics.

Vascular distensibility even in normotensives is
Measurement of Baroreceptor Discharge

All aortic arch preparations were exposed to a fixed control temperature regulated peripherally, the ascending aorta, left common carotid, and left innominate an in vitro aortic arch-aortic nerve preparation was used. Metal cannulas were placed in the innominate and vessel region between the ligatures, and the trimmed baroreceptor characteristics were measured. cMAP of 80 mm Hg after mounting in the perfusion apparatus. A minimum of 1 hour of perfusion at 80 mm Hg occurred before isolation of the first single-fiber baroreceptor, and generally this period was closer to 3 hours. When the nerve was divided to a single active baroreceptor, perfusion was halted and MAP abruptly reduced to 20 mm Hg. After 30 seconds at 20 mm Hg, the aortic arch was subjected to a slow ramp of increasing pressure using the shaker driver-bellows system (Brown et al., 1976). The ramp rate never exceeded 2 mm Hg/sec and generally included the range of pressures from 20 to 220 mm Hg. Responses measured with these slow ramp inputs are very similar to the responses measured after 30 seconds of adaptation to various levels of step inputs (Andresen et al., 1979). From these ramp responses, a pressure-discharge relationship was constructed for each baroreceptor. Typically, these relationships have a distinct minimum pressure at which discharge begins (Pth) and a suprathreshold region in which increases in discharge are quite linearly related to increases in pressure in the range of 50-60 mm Hg above Pth, or up to frequencies equal to one-half the difference between the threshold and maximal discharge rates (Andresen et al., 1980; Munch et al., 1983). The slope of this linear suprathreshold region was used as an index of receptor gain or sensitivity to pressure (Sth). Pth and Sth were used as the basic parameters for comparison of baroreceptors.

Generally, if the responses of more than five unitary baroreceptors were successfully recorded in an individual rat, then the final baroreceptor fiber isolated was subjected to a rapid resetting protocol (Munch et al., 1983). The rapid resetting portions of these experiments were begun with a series of test ramps given over a minimum of 20 minutes at the control cMAP. cMAP then was stepped away from the control perfusion pressure of 80 mm Hg for periods of 20-60 minutes. Initially, 60-minute periods were used to monitor the stability of the rapid resetting, but in later experiments, this was reduced to 20 minutes when no changes were found over the extended tests. At intervals following this change in cMAP, a pressure ramp was given to reassess baroreceptor properties. Thus, both the time course and magnitude of the rapid resetting process could be examined. The steps in cMAP usually included both suprathreshold and subthreshold perfusion pressures. The periodic step changes in cMAP were continued as long as the unitary action potentials could be reliability recorded—the longest case for this phase of these experiments involved 6 hours of measurements.

Vessel Wall Mechanics

At the end of each experiment, the pressure-diameter relationship of the aortic arch preparation was measured in the region of baroreceptor innervation. The ocular micrometer method of diameter measurement has been previously described (Andresen et al., 1978, 1980). This method has a resolution of 1% for diameter measurements. Briefly, the diameter was measured 30 seconds following a step change in pressure. Pressure was randomly varied from 0 to 220 mm Hg at 20 mm Hg intervals. Finally, the aortic segment was trimmed to include only the vessel region between the ligatures, and the trimmed aortic arch was patted dry and weighed. Thus, mechanical data were obtained from the same rats from which the baroreceptor characteristics were measured.

Several parameters were calculated from the aortic diameter and segment weight measurements to quantify the

Methods

Twenty-five normotensive male rats (WKY) 40 weeks of age and 25 male SHR (Okamoto-Aoki strain) 15 weeks of age were obtained from Laboratory Supply, Inc. Both groups were housed in the same room and fed the same pelleted rat chow diet. Of the original 25 SHRs, 12 survived to be studied during the period from 65 to 90 weeks of age (mean age: 76 weeks). In contrast, only five fatalities occurred in the WKY study group through the ages from 100 to 125 weeks (mean age: 115 weeks). The tail blood pressure of each rat was measured on the day of the experiment by the indirect tail cuff method. Single day measurements have been found to agree with repeated experiment by the indirect tail cuff method. For both baroreceptor and vessel measurements, an in vitro aortic arch-aortic nerve preparation was used (Brown et al., 1976). Briefly, under pentobarbital anesthesia (30-50 mg/kg), the aortic arch and nerve were exposed. Metal cannulas were placed in the innominate artery and the descending aorta and ligatures were placed on the ascending aorta, left common carotid, and left subclavian arteries. The aortic arch and nerve then were removed and transferred to a temperature-regulated perfusion bath where the vessel was fixed to approximate its in situ length and shape. The lumen of the aortic arch was perfused with Krebs-Henseleit solution, and the preparation covered with warm mineral oil (Andresen et al., 1979).

Measurement of Baroreceptor Discharge Characteristics

The baroreceptor pressure threshold (Pth), the minimum pressure at which the receptor discharges, is very dependent on the most recent conditioning pressure (cMAP) to which it is exposed (Coleridge et al., 1981; Dorward et al., 1982; Krieger et al., 1982; Munch et al., 1983). Therefore, all aortic arch preparations were exposed to a fixed control
static vessel wall mechanics. Based on an assumption of constant vessel wall volume, the inner radius of the vessel wall (Ri) was calculated from the following expression:

$$R_i = \left[ R_e^2 - \left( \frac{w}{\pi d} \right) \right]^{1/2}$$

where $R_e$ is the measured external aortic radius, $w$ is the vessel segment weight, $d$ is the tissue density of 1.06 (McDonald, 1974) and $l$ is the length of the vessel segment. The wall thickness, $h$, could then be calculated as the difference between $R_e$ and $R_i$.

Circumferential wall strain $\varepsilon$ is considered to be a good index of vessel mechanical properties (Fronek and Fung, 1980), and was used to quantify vessel distortion calculated as:

$$\varepsilon = \frac{R_p - R_o}{R_o}$$

where $R_p$ is the midwall radius at a given pressure and $R_o$ is the unstressed, usually minimum midwall radius. In addition, to express distensibility, the incremental elastic modulus of Bergel (1961a) was calculated as:

$$E_{inc} = \frac{(\Delta P/\Delta R)(1 - \theta^2)R_o/R_i^2}{R_e^2 - R_o^2}$$

where $\theta$, the Poisson ratio was assumed to be 0.5.

Statistical Treatments

Unpaired t-test and ANOVA were used for comparisons of general baroreceptor and wall properties between the two groups (Sokal and Rohlf, 1969). Linear regressions of the relationship between $P_{th}$ and cMAP were used to fit rapid resetting data, by the least squares method. A significance level of $P < 0.05$ was used throughout.

Results

Tail systolic blood pressure was significantly elevated in the nine SHRs in which baroreceptor measurements were successfully made (Table 1) and averaged 187 mm Hg (WKY: $n = 15$, BP = 130 mm Hg). Earlier studies on survival rates and longevity of normal and SHR rats suggest that the animals in this study were nearing the end of their normal lifespans (Nagaoka et al., 1972; Freis and Ragan, 1976). Freis and Ragan (1976) reported an 80% mortality in untreated SHRs by 100 weeks of age.

Baroreceptor Pressure Characteristics

Only regularly discharging, single baroreceptors were included in this study and, although conduction velocities were not measured, these are probably all from the class of baroreceptors with myelinated axons (Thoren et al., 1977; Andresen et al., 1980). The pressure characteristics of aged SHR baroreceptors (Table 1) showed the classic hallmarks of chronic hypertensive resetting with thresholds significantly elevated above the WKY average (SHR: $n = 42$, $P_{th} = 110$ mm Hg and WKY: $n = 41$, $P_{th} = 86$ mm Hg). Baroreceptor pressure sensitivity was also significantly lower in SHRs (SHR: $S_{th} = 0.78$ spikes/sec per mm Hg and WKY: $S_{th} = 1.13$ spikes/sec per mm Hg). There is a considerable overlap in the distributions of $P_{th}$ and $S_{th}$ in the SHR and WKY baroreceptor populations (Fig. 1). The shapes of the $P_{th}$ distributions appear quite similar between SHRs and WKYS, but with the SHR distribution shifted to higher pressures. Although the mean $S_{th}$ was significantly lower in SHRs, the distributions are dissimilar, with large numbers of SHR baroreceptors with very low sensitivity.

Aortic Vessel Wall Properties

The average vessel wall mechanics showed marked differences between the aortas of aged WKYS and aged SHRs, but considering the great differences in blood pressure, there were also several surprising similarities. The relative wall thickness at 100 mm Hg (the ratio of wall thickness to external

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Summary of Baroreceptor Properties of Aged WKY and Aged SHR</th>
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<tr>
<td></td>
<td>WKY</td>
</tr>
<tr>
<td>Animals</td>
<td></td>
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<tr>
<td>$n$ receptors (rats)</td>
<td>41 (15)</td>
</tr>
<tr>
<td>Age (wks)</td>
<td>115.3 ± 1.8</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
<td>130.0 ± 0.1</td>
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<tr>
<td>Pressure</td>
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<tr>
<td>Threshold $P_{th}$ (mm Hg)</td>
<td>85.7 ± 2.5</td>
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<tr>
<td>Sensitivity $S_{th}$ (spikes/sec per mm Hg)</td>
<td>1.13 ± 0.07</td>
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<tr>
<td>Distortion</td>
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<tr>
<td>Threshold $S_{th}$</td>
<td>0.37 ± 0.01</td>
</tr>
<tr>
<td>Sensitivity $S_{th}$ (spikes/sec per 1% $\varepsilon$)</td>
<td>2.70 ± 0.17</td>
</tr>
<tr>
<td>Vessel wall</td>
<td></td>
</tr>
<tr>
<td>Relative thickness $^\dagger$</td>
<td>0.088 ± 0.007</td>
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<tr>
<td>Strain$^{100}$</td>
<td>$r_{th}$</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SE. NS = not significant

$^*$ Significant difference ($P < 0.05$)

$^\dagger$ Ratio of wall thickness at 100 mm Hg to the external radius at 100 mm Hg
radius) was somewhat less in the aortas of the normotensive WKYs, but this difference was not significant (WKY: 0.088; SHR: 0.101, Table 1). SHR aortas had significantly larger radii at low pressures, but with increases in transmural pressure, SHR radius increased much less than the radius in WKY aortas (Fig. 2, upper panel). These differences in distensibility are shown quite clearly when expressed as the incremental elastic modulus ($E_{inc}$), an index of vessel stiffness (Fig. 2, lower panel). The minimum in $E_{inc}$ for SHR aortas was significantly greater than for WKY aortas (Fig. 2), and the curve was shifted along the pressure axis to levels 40 mm Hg greater than the curve for WKY aortas. This shift to higher pressures is an amount roughly equal to the differences in systolic blood pressure between the two groups, and $E_{inc}$ was 30% greater for SHR aortas at the prevailing systolic blood pressure. Thus, WKY aortas were distended to a much greater extent (developed higher wall strains) at equivalent pressures, e.g., $\epsilon_{100}$: 0.44 WKY, and 0.25 SHR. At pressures above 120 mm Hg, the WKY pressure-radius curve became inflected, showing the beginnings of the limits to distension, and $E_{inc}$ rose concomitantly (Fig. 2). This inflection occurred at much higher pressures in the SHR aortas; a pattern observed in earlier studies of WKYs and SHRs up to 30 weeks of age (Andresen et al., 1980). Thus, the aged WKY aortas appeared functionally adapted to a much lower pressure range than SHR aortas (Cox, 1979a).

**Baroreceptor Mechanical Characteristics**

Previous studies lumped several individual animals together to form an average view both of the aortic wall properties and of the baroreceptor properties for that group (Andresen et al., 1978, 1980). For this study, baroreceptor pressure characteristics, $P_{th}$ and $S_{th}$, were converted to terms of the equivalent mechanical characteristics based on the pressure-diameter measurements of the individual aortic segments in which the receptors were tested. Thus, $P_{th}$ was converted to the equivalent circumferential wall strain at that pressure and became $\epsilon_{th}$, the threshold strain. Likewise, $S_{th}$ was converted to $S_{e}$.
the strain sensitivity to suprathreshold distortions. \( e_{th} \) was significantly lower in SHR baroreceptors (SHR: \( e_{th} = 0.26 \) and WKY: \( e_{th} = 0.37 \)), so that WKY baroreceptors required more vessel wall distortion to become excited than did SHR baroreceptors (Table 1). The population distributions of \( e_{th} \) were very different in shape, with SHRs having a very broad, uniform distribution of thresholds and WKYS having a relatively narrow peak at higher strains (Fig. 3). \( S_e \), however, was not different between the two groups (SHR: \( S_e = 2.59 \) spikes/sec per 1% \( e \), and WKY: \( S_e = 2.70 \) spikes/sec per 1% \( e \), Table 1) and the histogram distributions were flat and featureless for both groups.

Strain-Discharge Relationships in Individual Baroreceptors

Our earlier work showed that the population averages of the baroreceptor discharge relationships were much more linear when plotted against the mean circumferential wall strain than against pressure or wall stress (see Figs. 7 and 9, from Andresen et al., 1978). This suggested that discharge is more directly related to \( e \) than to pressure as the receptor input. To test this idea further, and to see how well-correlated \( e \) and discharge are, in individual baroreceptors, we plotted discharge relationships of several single baroreceptors from the same animal, first against pressure, and then against \( e \) over a wide input range, usually 0-220 mm Hg (Fig. 4). The pressure-discharge relationships were predominantly linear in the pressure range from \( P_{th} \) to 50-60 mm Hg above \( P_{th} \). At progressively higher pressures, discharge increased more slowly for most receptors until, at the highest pressures, either a maximum discharge frequency was attained or, in some cases, there was even a small decrease in discharge rate. SHR receptors tend to start discharging at higher pressures and have somewhat lower pressure-discharge slopes than WKY receptors. Overlap of these characteristics between the two rat strains, however, is quite apparent, and certainly some SHR baroreceptors have quite similar pressure-discharge characteristics to some WKY baroreceptors, especially in these aged groups.

The strain transformation did not result in uniformly linear input-discharge relationships. For aortic arches in which multiple baroreceptors were tested in each aorta, about one-third of the individual baroreceptors had input-discharge relationships which were very linearly related to \( e \) throughout the range of inputs and had correlation coefficients greater than 0.95. Nearly an equal number showed no qualitative change in the shape of the input-output relationship when expressed as \( e \). The \( e \) transformation in the remainder, however, resulted in a reduction in the range of input levels over which the input-output relationship of individual baroreceptors was linear. No differences were found in the relative prevalence of these transformations of the \( e \)-discharge relationships between aged WKY and SHR. Whereas the baroreceptors appear to be largely circumferentially oriented in the vessel wall (Krauhs, 1979), one possible explanation for nonlinear strain responses could be simply differences in this receptor orientation away from circumferential or irregularities in the receptive field. Despite individual deviations from complete linearity, when discharge relationships of all the baroreceptors from a given aorta were averaged together, the overall input-output relationship was generally linear over a wider range of inputs when plotted against \( e \) than when plotted against pressure (Fig. 5), as suggested by the earlier analysis (Andresen et al., 1978).

Rapid Resetting of Aged Baroreceptors

In eight animals, it was possible to study the ability of these aged baroreceptors to reset rapidly. All protocols began at a perfusion cMAP of 80 mm Hg, which was subthreshold for all but one of the baroreceptors studied. In all cases, receptors were tested at cMAPs both above and below threshold, and thus with and without receptor discharge, during the conditioning period. In two receptors, a cMAP step was successfully and reversibly made within the region of asymptotic discharge where the step increase in cMAP resulted in no further increase in the discharge rate but resulted in a further increment in resetting. As found in previous reports in
younger, normotensive animals (Dorward et al., 1982; Munch et al., 1983), this process in the aged animals reached a stable level within 10–15 minutes and was completely reversible. No further changes were observed after 15 minutes. Thus, when cMAP was changed, $P_{th}$ measured at 5-minute intervals was rapidly shifted in the direction of the change in cMAP. $P_{th}$ was selectively affected, with $S_{th}$ unaltered by the resetting process. The shift in $P_{th}$ was always less than the change in cMAP. Thus, in these aged animals with markedly lower aortic distensibilities, the rapid resetting process was qualitatively similar to that of younger animals (Munch et al., 1983).

Quantitatively, the rapid resetting process can be represented through a range of pressures as a continuous relationship between $P_{th}$ and cMAP (Fig. 6). Earlier work has shown that these relationships are remarkably linear throughout the range of cMAPs tested, both for baroreceptors in the intact animal (Dorward et al., 1982), and in vitro (Munch et al., 1983). The slopes of these relationships can serve as an index of the extent of or capacity for rapid resetting. As in these earlier studies, the slopes of the $P_{th}$-cMAP relationships were not different among the different receptors, so that all relationships were generally linear and parallel in the baroreceptors of aged rats (Fig. 6). Note that this equivalence of slopes occurs despite substantial differences in $S_{th}$ among receptors. WKY slopes ranged from 0.20 to 0.33 mm Hg $P_{th}$ shift per one mm Hg change in cMAP (mean slope: 0.26). The two SHR relationships had slopes of 0.34 and 0.27, very similar to those for aged WKYs, and well within the range encountered in the more extensive baroreceptor studies in younger WKYs (Munch et al., 1983). SHR baroreceptors were clearly capable of reversible resetting in a manner similar to WKY baroreceptors. The relationships for both SHR receptors were displaced vertically along the $P_{th}$ axis (Fig. 6), reflecting the chronic differences in $P_{th}$ (Fig. 1). Based on this limited sample, it appears that, at least within the time frame of rapid resetting (on the order of minutes to hours), WKY baroreceptors would not be shifted to functional pressure ranges similar to SHR baroreceptors despite similar elevations in pressure. This offset may, therefore, represent a chronic resetting factor as a consequence of either the differ-
FIGURE 5. Example of a family average of input-output relationships for six baroreceptors from a single SHR aortic arch. Data for individual receptors are shown in Figure 4. Pressure-discharge points are plotted unfilled, and generally lie to the left of the equivalent strain-discharge values shown with filled points. Discharge was normalized as a percentage of the maximum discharge rate for each unit baroreceptor. Solid line is a least squares linear regression fit to the strain data. Correlation coefficient, r = 0.984.

Discussion

Chronic Baroreceptor Resetting—The Splinting Hypothesis

The first direct electrophysiological recordings from baroreceptors during chronic hypertension showed relatively normal activity patterns at the elevated resting pressure (McCubbin et al., 1956). Since then, one of the most widely held explanations for this resetting to higher operating pressures has been that decreased vascular distensibility reduces the amount of receptor distortion at given pressure (e.g., Bader, 1967) and results in a resetting of the baroreceptor response characteristics: an increased pressure threshold (Pth) and a decreased suprathreshold pressure sensitivity (Sth). Many different groups of investigators using different models of experimental hypertension have found chronic barorecep-
Baroreceptors from aged SHRs had elevated P_th and S_th did not change concomitantly under these chronic conditions. Data consistent with this corollary have been reported by Bergel et al. (1981), who showed that, during renal hypertension in the greyhound, no differences in mechanical thresholds could be detected in carotid sinus baroreceptors. Thus, the splinting hypothesis suggests that distensibility is the major, if not the sole, determinant of baroreceptor properties.

For both normotensive (WKY) and hypertensive (SHR) rats, this splinting hypothesis does not appear to hold true in at least three instances of changing aortic distensibility: (1) during early WKY development, (2) during development to maturity in SHR, and (3) during advanced age in normotensive WKYS. As normotensive rats grow to maturity, the vessel wall in the region of the aortic baroreceptors increases substantially, both in diameter and in distensibility (Andresen et al., 1980). The splinting hypothesis predicts that increased distortion would be transmitted to baroreceptors at a given pressure when aortic stiffness declined, thus decreasing P_th. Instead, P_th was remarkably constant, as was blood pressure. During hypertension in case 2 (Andresen et al., 1980), SHRs developed both lower aortic distensibility and elevated P_th values relative to WKY, in apparent agreement with the splinting hypothesis. However, analysis of receptor mechanical properties showed that SHR baroreceptors were actually more stimulated than WKY baroreceptors at equivalent circumferential wall strains (SHR e_th > WKY e_th). This, again, is in contradiction to the splinting hypothesis, which requires unchanging e_th. Thus, the splinting hypothesis of chronic baroreceptor resetting does not appear to account for the lack of resetting during the substantial increases in vascular distensibility during normal development, or appropriately account for the changes in mechanical thresholds during SHR hypertension.

The results presented in this paper demonstrate that the splinting hypothesis fails to account for the data in a third instance—the decline in aortic distensibility found in aged normal rats. Decreased aortic distensibility and increased relative wall thickness in aged WKYS were not associated with a higher P_th than observed in the younger, more distensible WKY aortas of previous studies (Andresen et al., 1978, 1980). The decreased aortic distensibility in aged WKYS was, however, accompanied by a substantially lower S_th for baroreceptors than found at 30 weeks of age (Andresen et al., 1980) (aged = 1.13 spikes/sec per mm Hg; 30 weeks = 2.01 spikes/sec per mm Hg; P < 0.05). Thus, P_th and S_th did not change concomitantly under these chronic conditions. Baroreceptors from aged SHRs had elevated P_th, coupled with a depression of S_th during chronic hypertension, as found by many others (Sapru and Wang, 1976; Aars, 1969; Angell-James, 1973). The average mechanical threshold (e_th) of the aged WKY baroreceptors (115 weeks old) was somewhat lower than the value found at 30 weeks (Andresen et al., 1980) (aged = 0.37; 30 weeks = 0.43; P < 0.05). At the same time, suprathreshold mechanical sensitivity, S_m, was also lower than values for the 30-week age group (aged = 2.70 spikes/sec per 1% e; 30 weeks = 3.48 spikes/sec per 1% e, P < 0.05). Thus, both the mechanical and pressure characteristics of the aged WKY baroreceptors show that, although the minimum input required for activation is reduced with age, the overall suprathreshold sensitivity is depressed. In man, a general decline in vessel distensibility with age has been observed (Abboud and Huston, 1961a, 1961b). This has led to the suggestion (Bader, 1967) that essential hypertensives might reflect a subgroup of the general population whose baroreceptors were less able to adapt to the stiffening of vessel walls with age and, thus, might contribute to an elevated blood pressure. However, much controversy surrounds this potential neurogenic contribution to essential hypertension (Fol-kow, 1982).

Rapid Baroreceptor Resetting

Surprisingly, the rapid resetting process in the baroreceptors of these aged rats was not different from that found in much younger rats (Munch et al., 1983). This is in spite of the fact that aortic distensibility was frankly decreased, and baroreceptor suprathreshold pressure sensitivities were compromised. This study does establish that both aged WKY and aged SHR baroreceptors are certainly capable of reversible rapid resetting in a manner generally similar to earlier studies in young rats (Munch et al., 1983). Thus, little interaction could be detected between the chronic mechanical factors influencing receptor discharge characteristics and the rapid resetting process. These conclusions are based on a small sample, however, and are complicated by the fact that baroreceptor P_th and S_th are not identical across the receptor population, even of an individual animal (Fig. 4). Larger samples might have revealed subtle differences with age or between WKY and SHR. Interestingly, however, other studies with much larger samples, have also found no tendency for the degree of rapid resetting to be correlated with the initial or 'offset' threshold value (Dorward et al., 1982; Munch et al., 1983).

The mechanism of rapid baroreceptor resetting is poorly understood and a number of mechanisms have been suggested. Clearly, it does not require neurohumoral modulation, since resetting occurs in vitro (Munch et al., 1983) and is so similar to that found in the intact animal (Coleridge et al., 1981; Dorward et al., 1982). The extent of rapid resetting remains linear for most baroreceptors in regions of...
the pressure-discharge relationship where no discharge or no increment in discharge occurs with a change in cMAP—namely, at subthreshold and supra-asymptotic pressures (Fig. 6). This suggests that action potentials or changes in their rate are not required for rapid resetting to occur. Thus, unlike postexcitatory depression (Saum et al., 1976), rapid resetting cannot be related directly to activation of an electrogenic ion pump by sodium entering the receptor during an action potential. These observations do not exclude possible activation of an electrogenic ion pump by other possible mechanisms, such as sodium entry during the receptor current (Kunze, 1981), and a number of other membrane mechanisms for resetting are possible (Brown, 1980). Alternatively, a stress relaxation/wall creep mechanism has been suggested for rapid resetting which would involve the viscoelastic properties of the vessel wall (Coleridge et al., 1981). Several characteristics of rapid resetting appear inconsistent with a viscoelastic mechanism. First, viscoelastic behavior is quantitatively very nonlinearly related to length and, therefore, is dependent on the pressure range, with accelerated stress relaxation found at increasing lengths (Cox, 1979b). In contrast, rapid baroreceptor resetting is quite linearly related to pressure over a large range of pressures (and, therefore, lengths), and no changes in time course have been found at various cMAPs. Several groups have found no correlated changes in the vessel pressure-diameter relationships during the time course of the rapid resetting protocol (Bell et al., 1983; Munch and Brown, 1983; Heesch and Thames, 1983). During normal development, aging, or hypertension, the composition of the vessel wall and its static mechanical properties change dramatically (Andresen et al., 1980; Cox, 1983), and although stress relaxation has not been measured in this study, arterial viscoelastic properties would be expected to change substantially with these age-related changes in vascular composition (Leary and Taylor, 1966; Bergel, 1961b). Again, rapid resetting was not affected by these chronic changes in aortic wall properties. Thus the mechanism for rapid resetting remains an open question.

Integration of Long- and Short-Term Factors

Baroreceptor characteristics at any point in time and conditions are the summed influences of a number of factors. Steady state vessel wall mechanical properties seem to contribute to the overall shape of the pressure-discharge curve, and probably account for the limitation of discharge at high pressures (Figs. 4 and 5). In the present study, the limits of the circumferential wall strain of a particular aortic arch very precisely predicted the discharge limits of many individual and most families of baroreceptors. Similar results were reported in the greyhound for carotid sinus baroreceptors (Bergel et al., 1976). It should be emphasized, however, that these conclusions may apply only to the regularly discharging, presumably myelinated, class of baroreceptor afferents which transduce pressure with high fidelity and that C-fiber baroreceptors have very different discharge properties (Thoren et al., 1977, 1983). These same mechanical properties of the vessel wall appear to dominate the baroreceptor suprathreshold sensitivity over both the long and short term. Hence, the long-term decreases in distensibility found in the present study resulted in declines in S_th, but the rapid resetting process does not affect S_th while substantially shifting P_th.

Obviously, vessel wall mechanics make a substantial contribution to P_th. Additional and apparently nonmechanical mechanisms contribute strongly to the measured P_th. A major factor is, of course, the rapid resetting phenomenon which appears to be similar in various baroreceptors despite great differences in age, distensibility, S_th, or initial P_th. It should be noted that resetting, whether rapid or chronic, has rarely been reported to approach "complete" resetting where the shift in P_th is equal to the change in cMAP (see Table I in Munch et al., 1983). Even at constant cMAPs of long duration, P_th values remain distributed across pressure in any given animal (Fig. 1).

These observations and logic suggest that there must be some mechanical bounds to the rapid resetting process. The nonmechanical mechanisms must operate within limits imposed by vessel wall composition, architecture, and mechanics. Rapid resetting acts operationally as an offset. Overall, the pressure-discharge curve is molded by the vessel wall, and this curve can be offset—selectively translated along the pressure axis—by the rapid resetting mechanism, with no effect on S_th, or the form of the curve. As the control data at cMAP of 80 mm Hg suggest, there remains a substantial chronic contribution to P_th, which cannot be offset completely by rapid resetting. Thus, P_th results from the sum of long-term and short-term (rapid resetting) factors. The aged WKY data suggests that, as with rapid resetting, the long-term component is not necessarily changed following substantial changes in distensibility, and seems most closely linked with blood pressure. This differential association—P_th linked to blood pressure and S_th linked to distensibility—suggests that P_th and S_th may be independently regulated. The link between blood pressure and P_th and a regulation of P_th independent of S_th may both result from a common mechanism, possibly a membrane mechanism within the neural component of the baroreceptor complex (Brown, 1980).

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Chronic vs. Rapid Baroreceptor Resetting

References


Bergel DH (1961b) The dynamic elastic properties of arterial wall J Physiol (Lond) 156: 458-469


INDEX TERMS: Baroreceptor • Hypertension • Development • Age • Blood pressure • Distensibility • Threshold • Sensitivity • Resetting
Short- and long-term determinants of baroreceptor function in aged normotensive and spontaneously hypertensive rats.

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