Baroreceptor Dynamics and Their Relationship to Afferent Fiber Type and Hypertension

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SUMMARY Static characteristics of baroreceptors differ depending on whether receptors are connected to myelinated or unmyelinated axons (MBs and UBs) and whether they come from normotensive or spontaneously hypertensive rats (NTRs and SHRs). Dynamic characteristics are incompletely known and were examined using an in vitro rat aortic arch-aortic nerve preparation in which static characteristics are similar to those present in vivo. Small amplitude sinusoidal pressures were applied at frequencies varying from 0.1 to 20 Hz over the range of linear responses to pressure. MBs from SHRs and NTRs show peaking in curves relating gain to frequency, gain being the ratio of sinusoidal discharge-rate amplitude and sine wave pressure amplitude. Similar curves from UBs of NTRs and SHRs are overdamped and show no such peaking. In MBs, the response phase leads initially, starts to lag around resonant frequencies, and falls behind progressively thereafter. In UBs, the phase also leads initially, then lags monotonically to about −60°. The discharge rectifies at high frequencies probably as the result of nonlinear threshold properties of the spike-initiating zone. The dynamic response curves of SHR and NTR aortas also were determined and found to be flat to much higher frequencies than those of the baroreceptors. Thus aortic wall dynamics do not limit the frequency range of the baroreceptors. There are no differences between NTRs and SHRs in the dynamics of either their aortas or their baroreceptors. The differences in dynamics between MBs and UBs may be due to differences in mechanical coupling related to structural differences between their endings.

CARDIOVASCULAR baroreceptors are connected to the central nervous system by either myelinated or unmyelinated axons. The reflexes elicited by electrical stimulation of the two groups, which will be referred to as MBs and UBs, differ quantitatively and qualitatively. Electrical excitation of unmyelinated afferents in the aortic nerve produces more profound depressor reflexes than excitation of myelinated afferents (Fig. 1 in paper by Douglas and Ritchie). Moreover, electrical excitation of myelinated cardiac vagal afferents may produce tachycardia, whereas excitation of both myelinated and unmyelinated cardiac vagal afferents elicits marked depressor effects. These results emphasize the differences in the central connections of MBs and UBs but do not address the question of the functional differences between the two groups of receptors. Recently, Thorén et al. have compared the static characteristics of aortic MBs and UBs and found that the threshold is higher and the sensitivity to suprathreshold pressures is lower in UBs. The dynamic characteristics have not been compared, however. A comparison would clearly be important since cardiovascular pressures are normally phasic and the discharge of MBs and UBs has frequency-dependent components. In addition, the dynamic characteristics of baroreceptors are largely unknown except for a few receptors which have been studied over limited frequency and pressure ranges. For these reasons, a thorough examination of the dynamic characteristics of MBs and UBs seems warranted. A comparison of the dynamic characteristics of baroreceptors from normotensive and spontaneously hypertensive rats (NTRs and SHRs, respectively) also seems desirable, since they have different static characteristics which are related to resetting and reduced sensitivity of SHR baroreceptors. This comparison might provide more insight into the mechanisms underlying hypertensive resetting. Therefore, the dynamic characteristics of MBs and UBs from NTRs and SHRs 4–6 months of age were examined using small sinusoidal pressures and small pressure steps. The suitability of the linear analysis presently used was verified. The essential observations are that the gain of MBs shows peaking and the phase a clear inflection at the resonant frequencies, whereas the gain of UBs is overdamped and the phase declines gradually. These responses are not limited by the dynamic properties of the aortic walls. There are no differences in dynamics between baroreceptors of SHRs and NTRs. The highly distinctive differences in dynamics between MBs and UBs are interpreted according to the structural differences reported for the two groups.

Methods

Experiments were performed upon male rats of the Wistar-Kyoto strain (NTRs) or Okamoto-Aoki strain (SHRs) of 4–6 months of age. The details of the preparation and recording methods have been described elsewhere, but several modifications have since been incorporated and for convenience the essentials are shown in Figure 1. The aortic segment was adjusted to approximate its in vivo position. Each receptor reported on in the present study was tested with pressure steps of 10–30 mm Hg and pressure sine waves. The sinusoidal analysis was
performed in the steady state over a range of 0.1-20 Hz at amplitudes of 10-60 mm Hg and at several mean arterial pressures. Each sinusoidal analysis was bracketed by static studies. Efforts were directed mainly toward testing the response over its linear range which was assessed from the static pressure-response curves.

Aortic segments from four NTRs and four SHRs were excised in exactly the same way as in the receptor experiments in order to examine the dynamic properties of the aortic walls. A chord of each aortic wall was measured using a piezoelectric sonomicrometer which has a measured flat (±5%) frequency response to 40 Hz. One crystal was fixed to the aortic segment at a site corresponding to the terminal nerve branches depicted schematically in Figure 1, and the other crystal was fixed directly across from it on the opposite aortic wall. The mean pressures and pulse amplitudes used as forcing functions covered the range of pressures used in the receptor experiments and included mean values between 80 and 150 mm Hg in NTRs and between 110 and 180 mm Hg in SHRs.

**Data Analysis**

The spike trains were converted to instantaneous frequencies as described before. When sinusoidal pressures were used, the instantaneous frequency curves were analyzed on a PDP 11/70 using an average frequency method which divides a sine wave into 72 bins each covering 5° of the cycle. The interspike interval in each bin is then averaged over a number of cycles. Between 10 and 20 response periods were averaged for a given stimulus x(t), and the response y(t) was fitted by the method of least mean squares error. Thus, the pertinent analytical expressions are:

\[ x(t) = p \sin (2\pi f t) + P_0 \text{ (mm Hg)} \]  
\[ y(t) = a \sin (2\pi f t + \theta) + C \text{ (impulses/sec)} \]

where \( P_0 \) = mean pressure  
\( p \) = modulation pressure amplitude  
\( C \) = mean discharge rate  
\( a \) = modulation discharge amplitude  
\( f \) = test frequency (Hz); \( f = 1/T \) with \( T \) being one cycle period (sec) and \( \theta \) is the response phase shift (phase lead when \( \theta > 0 \), phase lag when \( \theta < 0 \)) and \( K = a/p \) represents the gain of the system. \( \theta \) and \( K \) are plotted against the test frequencies in graphs describing the frequency response transfer function of the linearized system. The measurements of amplitude and phase derived from the curve-fitting program were checked with direct measurements and there was close agreement.

**Sources of Error**

Measurements of phase are less accurate than measurements of amplitude because the inaccuracies associated with assigning interspike intervals to bins seem to have larger effects on phase measurements. The delays due to conduction in unmyelinated fibers have insignificant effects upon measurements of phase even at high frequen-
cies. The filtering dynamics of the recording equipment were not limiting, since they were negligible compared to those of the baroreceptors. An absence of spikes in a part of the cycle occurred at higher frequencies and was associated with nonlinear discharge behavior termed rectification.12,13 This reduced the goodness of fit made by eye and the computer-averaged fitted functions were far more satisfactory.

Results

The baroreceptors were divided into four groups, baroreceptors from normotensive and spontaneously hypertensive rats and baroreceptors having myelinated or unmyelinated axons. Of receptors with myelinated axons, 17 were examined in 11 NTRs and 8 in 6 SHRs. Of receptors with unmyelinated axons, 4 were examined in 4 NTRs and 2 in 2 SHRs.

The mean systolic blood pressures measured by the occlusive tail cuff method6 were 110-125 mm Hg in unanesthetized NTRs and 185-200 in unanesthetized SHRs. The conduction velocities of the receptors’ axons ranged from 5 to 25 m/sec in MBs and 0.3 to 1.8 m/sec in UBs. The static characteristics of these four groups of baroreceptors have been described and are similar to those found in vivo.5-9 As we have already reported,9 fibers can be studied for as long as 6 hours without any change in their responses. Steady discharge in response to a pressure step is attained within a few seconds and persists for at least 3 minutes, which is the longest duration we have used. The major differences between SHR and NTR baroreceptors are that SHR baroreceptors have higher pressure thresholds, but threshold and maximum asymptotic discharge frequencies are similar. The major differences between MBs and UBs from either NTRs or SHRs are the UBs have higher pressure thresholds and much lower threshold and maximum asymptotic discharge frequencies.

Baroreceptor Response to Sine Waves of Pressure

Pressure sine waves applied over the linear response range elicited corresponding periodic discharge activity in MBs and UBs (Figs. 2 and 3), the UBs having lower discharge frequencies and higher static thresholds. At low stimulus frequencies, the instantaneous discharge frequen-

![Figure 2](http://circres.ahajournals.org/external版本/supplemental figures/figure2.png)

**Figure 2** Response of an NTR baroreceptor with a myelinated axon (mb) to pressure sine waves 3 mm Hg in amplitude at frequencies of 1 (A) and 6 Hz (B). The top panels show neural discharge on the top trace and pressure sine waves below. The middle panels show the instantaneous frequency which is the inverse period of the discharge (above) and pressure sine wave. Note the differences in the pressure calibrations between the two middle panels (done to avoid running the pressure wave through the instantaneous frequency points in B), and also note that frequency is the only change between the two pressure sine wave forcing functions. The bottom panels show the average frequency values obtained by adding 20 successive cycles, represented by the filled circles. The solid lines are the curves fitted to the data by the least mean squares error method using Equation 1B in the text. Note the rectification that appears at higher frequencies and the computed sine wave fit at these frequencies.
cies were sinusoidal (Fig. 2A). There was greater scatter in the UB frequencies, as was anticipated from earlier studies on their static discharge characteristics. The average values of amplitude and phase for 10–20 periods were readily fitted either by eye or by the computer. When higher frequencies were used while maintaining amplitude and mean pressures constant, the discharge no longer occurred during the falling part and nadir of the sine waves (Figs. 2B and 3B). The interruption of discharge persisted despite increases in mean pressure of 5–15 mm Hg. The effect was not related to a change in the static characteristics since the steady state pressure-response curves were identical before and after each sinusoidal analysis performed in the present experiments. This phenomenon has been reported for other mechanoreceptors and is called rectification. It reflects the nonlinear nature of neural discharge in sensory receptors that occurs when the generator potential which responds sinusoidally falls below values predicted from consideration of the static threshold. When rectification occurred, the amplitude and phase of the instantaneous frequency curves determined by eye were not as accurate as those determined by the computer.

As frequency increased, the number of impulses per cycle decreased, but the number of impulses per second remained constant for MBs and UBs in either NTRs or SHRs (Fig. 4). Again, the level of discharge is lower in UBs. Similar observations have been reported by other investigators. At very high frequencies, the number of impulses per second rose in UBs.

Linear Range of Baroreceptor Responses

The linear range of the response was estimated for each receptor from steady state pressure step-response curves (Fig. 5). Increasing the amplitudes of the steps produced linear increases in discharge over the range of pressures used for the linear analyses. The receptor discharge rose sharply in response to a step input of pressure, but with a definite time duration, and then slowly to a steady level. Although the fast phase gave rise to a pronounced overshoot, there were no detectable oscillations during the slow phase; many UBs, however, showed an irregular steady state discharge.

Linearity was also examined by measuring the receptor response to increases in amplitude of the pressure sine waves. Increases in amplitude were less than 40 mm Hg and did not pass through either threshold pressure or the pressure for maximum asymptotic discharge (saturation). Under these conditions, the amplitude of the receptor response increased linearly with increases in sine wave amplitude and there was no change in phase (Fig. 6). Similar results occurred in three baroreceptors with mye-
The effects of pressure sine wave frequencies upon baroreceptor discharge per cycle (A) and per second (B). □, MB; ○, UB. The values for \( p \) and \( p_0 \) (see Equation 1A) are 18 and 99 for the MB and 16 and 180 for the UB. There is an inverse relationship between spikes/cycle and frequency but the discharge/unit time is unchanged over most of the frequencies. The log-log scales are used for data compression.

The average values ±1 SEM for 37 runs in 17 NTR MBs and 27 runs in 8 SHR MBs are shown in Figure 7. There were no significant differences in the gain curves of SHR and NTR baroreceptors with myelinated axons. The corresponding average phase curves are shown in Figure 8. There was a small phase lead at low frequencies which converted to phase lag at the resonant frequencies and fell rapidly to values of around -120°. Again, there were no significant differences between MBs from SHRs and NTRs.

The gain curves of UBs differed quite markedly from...

**Figure 4** The effects of pressure sine wave frequencies upon baroreceptor discharge per cycle (A) and per second (B). □, MB; ○, UB. The values for \( p \) and \( p_0 \) (see Equation 1A) are 18 and 99 for the MB and 16 and 180 for the UB. There is an inverse relationship between spikes/cycle and frequency but the discharge/unit time is unchanged over most of the frequencies. The log-log scales are used for data compression.

Frequency Response Characteristics of MBs and UBs from Normotensive and Spontaneously Hypertensive Rats

Gain and phase plots for individual MBs and UBs from NTRs and SHRs were normalized for comparison. The gain of MBs increased at about 1 Hz, peaked between 5 and 9 Hz, and decreased rapidly at higher frequencies.

**Figure 5** Baroreceptor discharge in response to small pressure steps, the values of which (in mm Hg) are alongside each step response (A). The baseline pressure was 115 mm Hg. The peak, ○, and steady state, □, responses are linearly related to the amplitude of the step (B). The sine wave analyses were performed over this range of pressures.
there was no peaking and the gain started to deteriorate at frequencies above 0.1 Hz and continued to fall monotonically. There was a small phase lead at low frequencies and the phase fell continuously, reaching values of about $-60^\circ$ at the highest frequencies tested here. We have compared the gain and phase behaviors of four UBs from NTRs (nine runs) and two UBs from SHRs (six runs), and they were similar. The average gain and phase values for these six units are shown in Figure 9.

We also tested the effects of mean pressure $P_o$ on the dynamic response curves. Pressures that saturated receptor discharge or dropped it below threshold were avoided. In the linear range, changes of 20-40 mm Hg in $P_o$ had no effect on the dynamic response curves of MBs or UBs from SHRs and NTRs. Thus, as long as the operating point is within this range, it does not affect the dynamic characteristics of the baroreceptors for all cases.

**Frequency Response Characteristics of Excised Aortas**

The dynamic responses of excised aortic segments were compared in four NTRs and four SHRs. The piezoelectric crystals measured similar aortic chords in the two groups. The response of the chords to pressure sine waves ranging from 10 to 40 mm Hg in amplitude was sinusoidal and followed frequencies from 0.1 to 15 Hz with only small reductions in gain which became somewhat larger at 20 Hz (Fig. 10). The dynamic ranges have also been examined when mean pressures ranging from 80 to 150 mm Hg in NTRs and 110 to 180 mm Hg in SHRs were used, and the results were similar to those shown in Figure 10.
Discussion

The present experiments on the dynamic characteristics of baroreceptors were interpreted using linear analysis;
this is justified since a linear range of responses has been clearly identified. The approach we have taken has been only infrequently reported for baroreceptors and usually over very limited ranges of frequencies and mean and modulating pressures. Our experiments produced several new results. Baroreceptors with myelinated axons (MBs) show peaking in their gain curves, and baroreceptors with unmyelinated axons (UBs) have overdamped responses. The static characteristics of MBs and UBs also differ. In contrast, baroreceptors from normotensive and spontaneously hypertensive rats 4–6 months in age have similar dynamic characteristics, but their static characteristics are quite dissimilar. While the gain of SHRs should be less at frequencies approaching zero, our range for comparison did not extend below 0.4 Hz where differences in gain may have occurred.

The dynamic characteristics are probably due to mechanical filtering arising either from the coupling of the receptors to the vessel wall or from the receptors themselves. The dynamic ranges of the aortic wall and the receptors' axons for all four categories of baroreceptor examined presently extend beyond the limited response range of the receptors (Figs. 7, 9A, and 10). The dynamic response is also unlikely to be limited by the receptor membrane, since mechanoreceptor generator potentials following frequencies of 300 Hz have been reported.

At higher frequencies, rectification appears. As noted already, this is related to the nonlinear nature of the discharge from sensory receptors—when the generator potential falls below threshold for spike initiation, discharge ceases. Rectification may cause or contribute to the phasic discharge recorded from the entire carotid sinus nerve trunk at pressures well above threshold. An earlier interpretation of this observation, namely, that baroreceptors operate normally only at or near threshold, therefore needs to be reevaluated.

The transient response to step stimuli has an initial rise which is rapid but not instantaneous; this was either overlooked or ignored previously. The transient develops an overshoot followed by a slow relaxation to a steady state discharge. These qualitative features are similar in MBs and UBs. The slow phase is a monotonically decreasing function showing no sign of oscillation. This suggests that the slow process in MBs and UBs may not differ greatly. Quantitative assessment of the fast phase is difficult to make accurately in the time domain. The equivalent examination of frequency response data at intermediate to higher frequencies is much easier because the region of interest is expanded. Indeed, this has revealed the significant difference in the fast phase between MBs and UBs, as we have already noted. The nature of this difference poses a hypothesis that the fast phase is due to a second order filter, which again may well be common for MBs and UBs, except for its damping factor \( \xi \); i.e., \( \xi < 1 \) or underdamped for MBs and \( \xi > 1 \) or overdamped for UBs. Further quantitative study is needed to substantiate the above theory that attributes the observed dynamic difference ultimately to a single parameter \( \xi \).

**Interpretation and Significance of the Functional Differences between Baroreceptors with Myelinated or Unmyelinated Axons**

A tentative explanation of the differences in the dynamic and static characteristics of UBs and MBs may come from the structural differences between their endings. An electrophysiological explanation is unlikely, since the amount of current required to discharge a UB should be smaller, thereby reducing threshold, which is inconsistent with our observations. Complex, unencapsulated baroreceptor endings (CUE) are usually connected to axons which are myelinated in the nerve trunk (MBs) although their terminations may be unmyelinated. On the other hand, axons that are unmyelinated in the nerve trunk are usually connected to simple endings. CUEs have extensive

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**Figure 10** Dynamic characteristics of excised aortic segments from NTRs and SHRs. The gain is the ratio of the amplitude of the sinusoidal changes in chord dimensions and the amplitude of the sinusoidal pressure wave and is normalized to the lowest frequency values. Mean pressures were 130 mm Hg for the NTRs and 150 mm Hg for the SHRs, and the pressure sine wave amplitude was 20 mm Hg. Data are mean ± 1 SEM from four NTRs (A) and four SHRs (B). The dynamic range of the aortic wall is much greater than that of the aortic baroreceptors (compare with Figs. 7 and 9A). The dynamic ranges were at least as great at other mean pressures ranging from 80 to 150 mm Hg in NTRs and from 110 to 180 mm Hg in SHRs.
branching and small protrusions, free of covering Schwann cells, which are connected to the nearby elastin and collagen fibers. Thus they may be tightly coupled to the vessel wall. Whereas the details of the connections between simple endings and the vessel wall are not known, it is unlikely that they are coupled so tightly. These structural differences could be responsible for the higher static threshold, reduced sensitivity, and overdamped dynamic response found in UBs and the opposite results found in MBs. It seems intuitively reasonable to associate “tight endings” and “loose endings,” respectively, with a lower threshold and a higher one. In this regard, for instance, one can imagine a possible effect of tissue wrinkling. The structural differences also appear to support our theory which attributes the filtering difference between MBs and UBs to the damping factor $\zeta$ of the hypothetical common second order filter. This is because, compared to tight endings of MBs, loose endings of UBs should dissipate a given mechanical energy more quickly and thus result in a greater damping effect.

The physiological significance of the differences in the dynamics between MBs and UBs is not known. Some speculation seems justified, since baroreceptor discharge patterns have frequently been used to account for sinoarotic Blutdruck-characteristics. It is of interest that MBs of the rat show resonant enhancement for pressure signals at or near the heart rate usually present in these animals, namely, 4–5 Hz, and it would be interesting if a similar correlation were present in other species with different resting heart rates. The gain of MBs is 4 times that of UBs at these frequencies, and UBs clearly provide poor feedback to the central nervous system (CNS) with respect to heart rate information. The well-known frequency dependence of carotid sinus reflexes may also be related to the resonant characteristics of MBs. On the other hand, the observation that the input to the CNS per unit time is relatively unaffected over a wide range of frequencies in both UBs and MBs, despite the large differences between their dynamic responses, needs to be considered as well.

**Implications of the Dynamic and Static Characteristics of NTR and SHR Baroreceptors**

The similarities of the dynamic responses of NTR and SHR baroreceptors indicate some similarities in mechanical filtering, since the latter is probably mainly responsible for the dynamic responses we have observed. The differences in static characteristics, namely, resetting and reduced sensitivity, may also have a mechanical explanation. Thus the coupling to the aortic wall of both MBs and UBs from SHRs may be reduced equivalently. An alternative possibility, however, is that baroreceptor resetting is due to intrinsic changes in the receptors themselves. This problem will be examined further in a paper (Andersen, Kraus, and Brown, unpublished observations) which compares the static and dynamic characteristics of NTR and SHR aortas as they relate to hypertensive resetting.

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