Determinants of Sensitization of Carotid Baroreceptors by Pulsatile Pressure in Dogs

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The threshold pressure of single baroreceptor units is decreased after compared with before exposure to pulsatile pressure according to previous studies in our laboratory. The purpose of the present study is to characterize the determinants of sensitization of arterial baroreceptors by pulsatile pressure. Carotid sinus nerve activity was recorded in dogs anesthetized with chloralose. Two indexes of baroreceptor "sensitivity" were obtained by comparing nerve activity before and immediately after exposure of the isolated carotid sinus to pulsatile pressure for periods up to 10 minutes. Sensitization occurred 1) when the threshold pressure of single baroreceptor units determined with a slow nonpulsatile ramp decreased after as compared with before pulsing and 2) when multiple unit activity increased after as compared with before pulsing at various mean levels of static pressure. Sensitization was evident after pulsing at mean pressures of 50 and 100 mm Hg, but not at 150 and 200 mm Hg, and was caused by the pulsatile change in diameter or deformation and not by the pulsatile change in wall tension. The magnitude of the effect was directly related to the duration of the pulsing period and to the frequency and amplitude of the pressure pulses. The sensitization could not be explained by increased diameter (sonomicrometers) or strain of the carotid sinus at the same pressure after pulsing; thus, there was an increase in "strain sensitivity" that outlasted the period of pulsing by up to several minutes. In most experiments the shift from static to pulsatile pressure at 50 and 100 mm Hg caused an increase in nerve activity, yet sensitization occurred after pulsing when one would have expected postexcitatory hyperpolarization or depression of activity upon return to static pressure. The sensitization was not caused by the release of prostacyclin from the endothelium since it was not reduced after endothelial denudation or inhibition of cyclooxygenase with indomethacin (30-80 \( \mu \)M) or ibuprofen (250 \( \mu \)M). We speculate that sensitization of baroreceptors by pulsatile pressure may contribute to the decreased sympathetic activity after periods of elevated pulse pressure (e.g., after exercise). We also propose that the decreased sensitivity of baroreceptors after acute elevation of arterial pressure (acute resetting) may be offset in part by the sensitizing effect of increased pulsatile stretch. (Circulation Research 1989;65:566-577)
elevated pressure was pulsatile. This finding suggested that the baroreceptors are sensitized by exposure to PP and that the increased sensitivity persists after the pulsing period.

The purpose of this study was twofold. First, we sought to determine the degree to which "post-PP sensitization" can alter the amount of baroreceptor activity recorded from the whole carotid sinus nerve. In this way, the effect of pulsing on the magnitude of augmentation of baroreceptor afferent activity relayed to the central nervous system could be estimated. Second, we wished to define the determinants of the sensitization. Specifically, the following determinants were examined:

1) Do increases in the duration of pulsing or the amplitude or frequency of the pressure pulses augment the sensitization?

2) Is sensitization related to the magnitude of pulsatile deformation or stretch rather than pulsatile tension? We suspected that deformation might have a predominant influence because in our earlier study the sensitization after pulsing was more evident at low to moderate distending pressures where dynamic vascular compliance is known to be greater than at high pressures.

3) Is the increased pressure sensitivity caused simply by increased diameter or strain at the same pressure or by a true increase in sensitivity of receptors, that is, increased strain sensitivity?

4) Does a negative correlation exist between the change in nerve activity during the shift from static to PP and the magnitude of "post-PP sensitization"? Increased activity (i.e., frequency of depolarization) as a result of the shift from static to PP might be expected to cause decreased sensitivity upon return to static pressure because of "postexcitatory depression." Conversely, decreased activity as a result of the shift from static to PP might cause a postpulsing excitation.

5) Does endothelial denudation or inhibition of cyclooxygenase alter the degree of sensitization? Prostacyclin released from the endothelium during pulsatile stretch may activate baroreceptors.

Materials and Methods

Mongrel dogs (16–24 kg) were anesthetized with thiopental sodium (30 mg/kg i.v.) and α-chloralose (80 mg/kg i.v.). Supplemental doses of chloralose were administered on a regular basis as needed. The dogs were intubated and mechanically ventilated with room air supplemented with oxygen. Arterial pH and PCO₂ were maintained within normal limits by adjusting the ventilation and administering sodium bicarbonate when necessary. Catheters were placed in a femoral artery and vein for measurement of arterial pressure and administration of chloralose, respectively.

Isolated Carotid Sinus Preparation

The isolated carotid sinus and baroreceptor recording techniques have been described elsewhere and will be explained briefly. The left carotid sinus was surgically exposed, and all arteries in the vicinity of the sinus were ligated. Catheters were placed in the common and external carotid arteries. The isolated sinus was flushed and filled with a physiological saline solution equilibrated with 95% O₂–5% CO₂ and warmed to 37°C. The solution contained the following substances in their respective concentrations (mM): CaCl₂:H₂O 2.5, KCl 4.7, MgSO₄ 1.2, KH₂PO₄ 1.1, CH₃COONa·3H₂O 20, NaCl 98.0, glucose 10.0, and NaHCO₃ 24.0. The Po₂, PCO₂, and pH of the solution in the sinus were 150–250 mm Hg, 35–45 mm Hg, and 7.3–7.4, respectively, and remained within these ranges throughout the experiment. The sinus was connected to a pressure reservoir via the common carotid artery, and carotid sinus pressure was measured through the external carotid catheter by a Statham transducer (model P23AA, Hato Rey, Puerto Rico). The undamped natural frequency of the catheter-manometer system was 38 Hz, and the frequency response was flat to greater than 10 Hz.

The mean level of pressure was controlled by adjusting a regulator valve connected to a pressurized air source. A voltage waveform generator fed sine-wave pulses into an electromagnetic pressure converter (model MPG-30, Millar, Houston, Texas) that was connected to the reservoir. In experiments designed to assess the effect of pulsatility at various levels of mean pressure, pulse frequency and pulse amplitude were set at the beginning of each experiment and maintained throughout. The ranges were 1.5–2.2 Hz (90–130 pulses/min) and 25–50 mm Hg. In other experiments, pulse frequency was varied while maintaining pulse amplitude constant, or pulse amplitude was varied while maintaining frequency constant in order to assess the effects of pulse frequency and amplitude on the "post-PP sensitization."

Carotid Sinus Nerve Recordings

During the preparation of the sinus nerve for recordings, the isolated carotid sinus pressure was held at a static pressure between 25 and 50 mm Hg, and the sinus was flushed approximately every 1–2 hours with freshly oxygenated saline solution. The nerve was cut near its junction with the glossopharyngeal nerve, placed on a dissection stage, covered with paraffin oil, and desheathed. The vagosympathetic trunk and other nerves innervating the sinus region were sectioned. Baroreceptor activity was recorded with a bipolar platinum electrode connected to a Grass high-impedance probe (model HIP 511E, Grass Instrument, Quincy, Massachusetts) and amplified by a Grass (P511) bandpass amplifier (high frequency cutoff, 3,000–10,000 Hz; low frequency cutoff, 30 Hz). Nerve traffic was...
visualized on a dual-beam storage oscilloscope (model 5113, Tektronix, Beaverton, Oregon) and heard on a loudspeaker. A nerve traffic analyzer that counted spikes that exceeded a selected voltage was used to quantify nerve activity.

Multiple unit activity was recorded from large strands of the sinus nerve or from the whole nerve in 47 dogs. Single unit activity was recorded from seven fibers in seven additional dogs. Single units were identified by repeatedly splitting the sinus nerve until a fine strand was obtained that exhibited the following characteristics: 1) increased activity of uniform spike height in response to increases in pressure, 2) relatively constant interspike interval during maintained static pressure, and 3) lack of activity from other units above the preselected voltage.

Decamethonium bromide, 0.3 mg/kg, was administered to each dog to prevent muscular movement while nerve activity was recorded. The gas tensions and pH of the physiological saline solution and arterial blood minimized chemoreceptor activity.

**Measurement of Carotid Sinus Diameter**

The diameter of the carotid sinus was measured with sonomicrometers. Two 7-MHz piezoelectric crystals were mounted on the opposite tips of a low resistance stainless steel clip with a frequency response of 35 Hz. The clip was placed around the carotid sinus. The crystals were aligned across the sinus and secured by suturing one side of the clip to the tissue around the carotid sinus. The clip enabled the placement of the crystals with minimal trauma to the wall of the sinus and did not significantly influence the pressure-diameter relation of the sinus over a pressure range of 25–200 mm Hg. This was shown in preliminary experiments by direct microscopic visualization of the sinus and image enhancement with a television camera and monitor before and after placement of the clip. The electrical signal was monitored on a Tektronix oscilloscope. Carotid sinus diameter, carotid sinus pressure, integrated baroreceptor activity, mean baroreceptor activity, and systemic arterial pressure were displayed on a recorder (model R411, Beckman, Schiller Park, Illinois).

**Endothelial Denudation and Inhibition of Cyclooxygenase**

Removal of the endothelium was accomplished in some experiments by inserting an embolectomy balloon catheter (2–4F; Edwards Laboratories, Santa Ana, California) into the isolated carotid sinus, inflating the balloon until the vessel was distended by 25–50%, and withdrawing the catheter slowly. The procedure was repeated three to four times. The ability of this technique to remove endothelium has been demonstrated in our laboratory by scanning electron microscopy and by elimination of acetylcholine-induced vasodilatation of the carotid sinus. The production of prostacyclin and other cyclooxygenase metabolites was inhibited with intraluminal exposure of the carotid sinus to either indomethacin or ibuprofen.

**Definition of Sensitization of Baroreceptors**

Sensitivity of baroreceptors is generally described as the slope of the baroreceptor pressure-activity relation. However, for the purposes of this study we define increased sensitivity or sensitization as a decrease in Pth of single units as determined with a slow nonpulsatile pressure ramp or increased multiple unit activity at equivalent static pressures after as compared with before the periods of pulsing.

**Protocols**

Several protocols were performed, and in all of them the carotid sinus was exposed first to a certain level of static pressure for 5–15 minutes to allow for acute resetting before introducing the PP. PP was introduced at a mean level equivalent to static pressure for up to 10 minutes, and then static pressure was restored.

The Pth of single baroreceptor units was determined with a slow ramp increase in static pressure (less than 3 mm Hg/sec) immediately before and after the pulsing periods. In other experiments, the activity of single or multiple units was recorded continuously before, during, and after the pulsing periods without changing the level of mean carotid sinus pressure.

**Single unit activity before and after the pulsing period.** In five experiments the influence of the pulsing period on the Pth of single units was tested at three levels of mean pressure: 50, 100, and 150 mm Hg. The order of the mean pressure levels was reversed in two of the five experiments. The duration of pulsing at each level of pressure was 1 minute in all five experiments. Because Pth did not decrease after pulsing at high pressure (150 mm Hg), longer periods of pulsing at each level of pressure were tested also: 5 minutes in two experiments and 10 minutes in two others.

In three of the experiments described above and two additional ones, static pressure was held just below Pth. Then PP was applied for periods ranging from 5 seconds to 10 minutes, and static pressure was restored. The duration of sustained activity after return to static pressure was then related to the duration of the pulsing period.

**Multiple unit activity before and after the pulsing period.** In one group (n=8), we determined the influence of mean pressure level (50, 100, 150, and 200 mm Hg) on the change in baroreceptor activity measured after compared with before pulsing. The duration of pulsing at each level of mean pressure was 10 minutes.

The influence of the duration of pulsing was tested at one level of mean pressure where increased activity was observed after the pulsing period (100 mm Hg in seven experiments and 50 mm Hg in one experiment). The durations of pulsing were 1, 5, and 10 minutes. Responses that we observed in an
earlier study⁴ are now reported (n=9). The duration of pulsing was very short (15–30 seconds) at a mean pressure of 100 mm Hg, and the pulse amplitude (30–50 mm Hg) and frequency (1.5–2.2 Hz) were not significantly different than those used in the present study.

In a second group (n=13), we determined the influence of pulse amplitude (range 10–55 mm Hg, n=9) at constant frequency (2.1±0.0 Hz) and pulse frequency (range 0.18–3.87 Hz, n=9) at constant amplitude (29±2 mm Hg) on the magnitude of increased activity after 5-minute periods of pulsing at a mean pressure of 94±3 mm Hg. The data were grouped according to four levels of amplitude: less than 15 (n=8), 15–30 (n=7), 30–45 (n=8), and 45–55 (n=9) mm Hg; data were also grouped according to four levels of frequency: less than 1 (n=9), 1–2 (n=8), 2–3 (n=9), and 3–4 (n=8) Hz.

In a third group (n=15), we determined if the increased baroreceptor activity after pulsing could be explained by increased diameter and strain of the carotid sinus. Both baroreceptor activity and carotid sinus diameter were measured at the same level of static pressure before and after the pulsing period.

Finally, in a fourth group (n=17), we examined whether the increased activity after pulsing might be related to the production of cyclooxygenase metabolites from the endothelium. Baroreceptor activity measured after versus before pulsing was compared both before and 1–2 hours after endothelial denudation (n=6) and before and during inhibition of cyclooxygenase with indomethacin (30–80 μM, n=8) or ibuprofen (250 μM, n=4).

Correlation of “post-PP sensitization” with the pulsatile change in diameter or tension during pulsing. Carotid sinus diameter was measured in 12 isolated carotid sinuses. Mean pressure was 50, 100, 150, and 200 mm Hg. We were able to keep pulse pressure constant during each experiment at mean pressure levels of 50, 100, and 150 mm Hg, but it declined at 200 mm Hg. The dynamic compliance of the carotid sinus was calculated by dividing the pulse diameter (systolic–diastolic diameter) by the pulse pressure. The magnitude of increase in sinus diameter during pulsing (pulse diameter) and the corresponding increase in pulse tension [(pulse pressure × radius)sysolic−(pulse pressure × radius)diastolic] were calculated at each level of mean pressure. These values were correlated with the magnitude of reduction in the Pth of single baroreceptor units.

Analysis of Data

All data are expressed as the mean±SEM. The paired t test (one-tailed) was used to compare Pth and nerve activity measurements obtained after versus before the pulsing periods. The effects of the mean pressure level on the magnitude of the increase in activity and the decrease in Pth following PP were analyzed with a one-way analysis of variance (ANOVA) and Bonferroni's multicomparison test.²³,²⁴

The effect of the duration of the pulsing period on the duration of sustained single unit activity after the pulsing period was determined with linear regression and correlation analysis in individual experiments.²³,²⁴

An unpaired t test (one-tailed) was used to compare the magnitudes of increased activity after pulsing for short durations (15–30 seconds) versus long durations (10 minutes), with small pulse amplitudes (<15 mm Hg) versus large amplitudes (45–55 mm Hg), with low frequencies (<1 Hz) versus high frequencies (3–4 Hz), and before denudation or cyclooxygenase inhibition versus after denudation or cyclooxygenase inhibition.

The mechanical characteristics of the carotid sinus during pulsing (i.e., pulse diameter and pulse tension) were contrasted at each level of pressure by ANOVA and Bonferroni’s test.²³,²⁴

The data relating changes in pulse diameter to the magnitude of the “post-PP sensitization” (percent decrease in Pth after versus before PP) were fit to a third order polynomial equation. Significance was defined at the p≤0.05 level.
Results

Single Unit Activity Before and After the Pulsing Period

Effect of the level of mean pressure during pulsing on the decrease in Pth after pulsing. Pth decreased significantly from 86±9 before to 75±6 mm Hg after exposure to PP at a low mean pressure (50 mm Hg) and from 100±7 before to 88±6 mm Hg after pulsing at a moderate mean pressure (100 mm Hg) (Figures 1 and 2). The decrease in Pth was reversed after return to the original static pressure within 5–15 minutes (not shown). At a high mean pressure (150 mm Hg), pulsing did not alter Pth (108±6 before vs. 109±5 mm Hg after PP) even when the duration of pulsing was maintained for up to 5 and 10 minutes (Figure 2).

Effect of the duration of pulsing on the duration of post-PP sensitization. Static pressure was held just 1–3 mm Hg below Pth for 5–15 minutes, and there was no activity; activity was then initiated with PP and was often sustained for a time after return to the original static pressure (Figure 3). This reflects the decreased Pth after pulsing. The duration of sustained activity after return to the original static pressure was correlated with the duration of pulsing periods (Figure 3). After the 5-second pulsing period, activity was present in only two of five fibers and lasted 28 and 104 seconds. After the 30-second and the 5-minute pulsing periods, activity was present in all five fibers lasting an average of 40±16 seconds and 75±37 seconds, respectively. The relation between the duration of pulsing and the duration of sustained activity after PP was positive in all five fibers (+0.15±0.10, r=0.76±0.16), but there was a wide range of responses.

The magnitude of the abrupt increase in activity does not necessarily reflect sensitization because activity of myelinated single units rises sharply or falls abruptly by 15–40 impulses/sec when the static pressure ramp exceeds or drops below Pth, respectively (Figure 1). The abrupt fall in activity of the single units...
to zero represents the rise in Pth back to the control level that was just above the holding static pressure.

**Multiple Unit Activity Before and After the Pulsing Period**

Effect of the level of mean pressure during pulsing on the increase in activity after pulsing. At low (50 mm Hg) and moderate (100 mm Hg) levels of mean pressure, baroreceptor activity was significantly greater after the period of pulsing (153±66 and 462±84 spikes/sec) as compared with before pulsing (114±49 and 330±83 spikes/sec) (n=8; Figure 4). Activity was not increased after the pulsing periods at the high pressures of 150 mm Hg (612±106 after vs. 598±104 spikes/sec before PP) and 200 mm Hg (609±118 after vs. 625±106 spikes/sec before PP).

Most of the increased activity after the exposure to PP dissipated within 1–4 minutes, but in four of the eight preparations, activity remained elevated for 12–28 minutes.

Effect of the duration of pulsing on the increase in activity after pulsing. Activity was not increased after brief pulsing periods of 15–30 seconds (253±56 after vs. 267±58 spikes/sec before pulsing, Figure 5, n=9). After 1-, 5-, and 10-minute pulsing periods, activity was increased significantly by 113±19, 130±36, and 154±39 spikes/sec (Figure 5, n=8). Activity was greater after 10 minutes versus 5 minutes of pulsing in seven of the eight preparations.

Effects of pulse amplitude and frequency on the increase in activity after pulsing. Baroreceptor activity did not increase after the 5-minute pulsing periods when the pulse amplitude was less than 15 mm Hg. After pulsing with increasing amplitudes of 24±1 mm Hg (15–30 mm Hg), 42±1 mm Hg (30–45 mm Hg), and 48±1 mm Hg (45–55 mm Hg), activity increased significantly, and the greatest increase was after the largest pulse amplitude (45–55 mm Hg) (Figures 6 and 7).

After pulsing with frequencies of 0.30±0.03 Hz (<1 Hz), 1.50±0.04 Hz (1–2 Hz), 2.38±0.09 Hz (2–3 Hz), and 3.63±0.11 Hz (3–4 Hz), activity increased significantly, and the magnitude of increased activity was significantly greater after high frequencies of pulsation (3.63±0.11 Hz) than after low frequencies of pulsation (0.30±0.03 Hz) (Figure 7).

Increased activity after pulsing was not caused by increased diameter or strain. In 15 experiments where activity was significantly greater after the pulsing period (190±39 spikes/sec) as compared with before pulsing (138±35 spikes/sec) at the same level of static pressure (81±4 mm Hg), there was no significant increase in diameter after pulsing (3,861±399 before vs. 3,891±399 μm after PP). There was also no correlation between the magnitude of increased activity and the change in diameter in individual experiments (r=0.34, p>0.2). Thus, sensitization reflected an increased strain sensitivity.

**Level of nerve activity during pulsing**. The change in level of nerve activity as a result of the shift from...
static to PP could conceivably influence the excitability of the baroreceptors upon return to static pressure after the pulsing period. Therefore, it was noted whether the shift from static to PP increased, decreased, or did not change baroreceptor activity, and an attempt was made to relate this change to the increased baroreceptor activity after the pulsing period. Activity increased after pulsing regardless of whether the activity during pulsing was higher, lower, or the same as that during static pressure (Figure 8). There was no correlation ($r=0.24$) between the change in nerve activity during the shift from static to PP and the degree of "post-PP sensitization."

Furthermore, we compared baroreceptor activity during the first and last minutes of a 10-minute pulsing period in the 22 preparations that demonstrated increased activity after pulsing at either 100 or 125 mm Hg. In this way we could determine if sensitization becomes evident during the period of pulsing. Activity increased to a variable but significant extent in 18 of the 22 experiments from $343\pm24$ spikes/sec during the first minute of pulsing to $359\pm27$ spikes/sec during the tenth minute of pulsing ($n=22$, see Figure 6).

**Effect of endothelial denudation and inhibition of cyclooxygenase on increased activity after pulsing.** The increased baroreceptor activity measured after compared with before a period of pulsing was not reduced significantly by endothelial denudation or by inhibition of cyclooxygenase with indomethacin or ibuprofen (Table 1).

**Post-PP Sensitization Correlates With the Magnitude of Pulse Diameter but Not Pulse Tension**

The dynamic compliance of the carotid sinus (pulse diameter/pulse pressure) decreased as mean

**Figure 6.** Tracings showing effect of pulse amplitude on the increase in activity after pulsing. The magnitude of the increase in activity after compared with before a pulsing period of 5 minutes was directly related to the amplitude of the pressure pulse (PP). Activity in this preparation did not increase after pulsing with an amplitude of 12 mm Hg (Panel A) but increased progressively after pulsing with amplitudes of 30 and 50 mm Hg (Panels B and C).

**Figure 7.** Bar graphs showing relations between magnitude of sensitization of baroreceptors after pulsing and the amplitude and frequency of pulsation. The degree of sensitization (i.e., the increase in activity after compared with before 5-minute periods of pulsing) was related to the amplitude (left panel, $n=9$) and frequency of pulsation (right panel, $n=9$). PP, pulsatile pressure. Initial activities before pulsing at the four different pulse amplitudes were $270\pm90$, $259\pm96$, $256\pm88$, and $225\pm76$ spikes/sec, and the initial activities before pulsing at the four different pulse frequencies were $268\pm77$, $296\pm90$, $278\pm85$, and $247\pm88$ spikes/sec, respectively. *Increase in activity after compared with before pulsing was significant at $p<0.05$. †Significantly greater increase in activity ($p<0.05$) after pulsing at the highest amplitude or frequency tested when compared with the response obtained with the lowest amplitude ($<15$ mm Hg) or frequency ($<1$ Hz), respectively.
Experiment #1

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Experiment #2

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FIGURE 8. Tracings showing sensitization after the period of pulsing in two experiments. In one (upper panel), multiple unit activity was decreased during the pulsing period whereas in the other (lower panel), activity was increased during the pulsing period. (Note: paper speed was reduced during the pulsing periods.)

pressure increased (Figure 9, Table 2). Consequently, the pulse diameter of the carotid sinus decreased progressively as mean pressure increased from 50 to 200 mm Hg. A decrease in pulse pressure contributed in part to the smaller pulse diameter at 200 mm Hg (Table 2). Pulse tension, on the other hand, increased as mean pressure increased from 50 to 100 mm Hg, did not change with the increase to 150 mm Hg, and decreased at 200 mm Hg (Table 2).

A significant relation (third-order polynomial) between the pulse diameter and the percent decrease in Pth was obtained ($p=0.05$; Figure 10). The magnitude of the pulse tension, however, did not correlate with the decrease in Pth (Figure 10).

<table>
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<tr>
<th>TABLE 1. Effects of Endothelial Denudation, Indomethacin, and Ibuprofen on the Magnitude of the Increase in Baroreceptor Activity After Exposure to Pulsatile Pressure</th>
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Values are mean±SEM.
PP, pulsatile pressure.

*Significant increase in activity after compared with before the pulsing period, $p<0.05$. NS, no significant difference between the control and experimental groups.

Discussion

We reported recently that the Pth of single baroreceptor units often decreases after a brief exposure to PP. The purpose of the present study was, first, to determine the degree to which post-PP sensitization alters the amount of baroreceptor activity recorded from the whole carotid sinus nerve and, second, to define the determinants of this phenomenon. The findings confirm that the Pth of single units is decreased after exposure to PP. In addition, the results indicate that 1) baroreceptor activity at a constant distending pressure increases after pulsing at low and moderate mean arterial pressures but not after pulsing at high pressures, 2) the magnitude of the increase in activity after pulsing is related to the duration of the pulsing period and to the amplitude and frequency of the pressure pulses, 3) the magnitude of the sensitization after pulsing is directly related to the pulsatile change in diameter but not to the pulsatile change in wall tension nor to the amount of nerve activity during the pulsing period, 4) increased activity after pulsing is not caused by increased diameter or strain of the carotid sinus, and 5) it is not dependent on intact endothelium and cyclooxygenase metabolites. The discussion will focus first on the relation of these results to previous reports regarding the effect of PP on arterial baroreceptors, second on the magnitude of and possible mechanisms responsible for the sensitization after PP, and third on the physiological implications of the observations.

Pulsatility and Baroreceptor Activity

PP has been considered a more effective stimulus of arterial baroreceptors than static pressure based on studies of baroreflexes and recordings of afferent nerve activity. Most of the previous studies including ours focused on the baroreflex or on baroreceptor activity during exposure to PP as compared with static pressure. Three factors appear to be largely responsible for the immediate influence of pulsatility on baroreceptor activity. First,
during PP the rise in systolic pressure may exceed the Pth of receptors that are silent during static pressure and lead to increased activity due to recruitment.\(^1\),\(^4\),\(^6\) Second, the rapid upstroke in pressure during systole causes receptors to begin firing at lower pressures and at higher frequencies; these effects are attributed to the responsiveness of the receptors to positive dP/dt.\(^1\),\(^4\),\(^9\),\(^10\) Third, a significant reduction in nerve activity or even silence takes place during diastole at pressure levels higher than threshold. We found that this could result in a significant decrease in nerve activity per unit time of single as well as multiple units with pulsing at mean pressure levels above 100 mm Hg.\(^4\) Thus, when we compared the pressure-activity curves during pulsing and during static pressure, the curve was sigmoid during static and linear during PP, and the two curves intersected at approximately 100 mm Hg.\(^4\) Because of the change in magnitude of the stimulus and its phasicity with pulsing, it is very difficult to determine whether the effect of pulsatile compared with static pressure is related to a change in sensitivity of the baroreceptors to the same stimulus or a change in the magnitude of the stimulus. For this reason, we explored the influence of pulsatility by examining the sensitivity of baroreceptors at the same level of static pressure before and immediately after pulsing. We found that pulsing does indeed sensitize baroreceptors,\(^5\) and we refer to the phenomenon as "post-PP sensitization" of baroreceptors although it must indeed contribute to the activity during pulsing.

**Magnitude of Sensitization**

Our results indicate that after a period of pulsation, the Pth of single units decreases by approxi-
mately 13%, and the frequency of impulses in multiunits increases by approximately 40% as compared with before pulsing at equivalent levels of static pressure and diameter. This sensitization may outlast the period of pulsation by 1 to several minutes.

There is evidence that the sensitization takes place during pulsing because activity during the tenth minute of pulsation is greater than during the first minute (Figure 6), but the magnitude of increase was variable and usually small compared with the increase seen immediately after return to static pressure. The reason why the sensitization was more apparent after than during the pulsing period may reflect the steeper slope of the pressure-activity curve during static compared with PP. If the sustained exposure to PP caused a similar shift to the left of both the static and pulsatile pressure-activity curves, the increase in activity at the same mean pressure would be much greater for static than for PP. Other investigators may not have noticed this phenomenon previously because of the very brief exposures to PP that were used or the failure to measure Pth or activity at an equivalent static pressure soon after the pulsing period. In fact, in our previous study when we contrasted effects of pulsatile and static pressure, we did not notice any sensitization when we restored static pressure after a period of pulsing, but the periods of pulsing were less than 30 seconds. We had not reported in our earlier paper the activity immediately after these brief pulsing periods. We are now reporting in this paper those values to contrast them with the results obtained after the more prolonged pulsing periods. In addition, the sensitization is not evident at high distending pressures, which might have resulted in failure to recognize the phenomenon if a systematic measurement at various levels of distending pressure had not been carried out.

**Mechanism of Post-PP Sensitization**

Several factors were explored. First, changes in viscoelastic properties of the sinus during PP could produce a vasodilatation that is sustained after PP. In our study, an increase in carotid sinus diameter after PP could not explain the magnitude of increase in baroreceptor activity. In some experiments, baroreceptor activity increased after PP when diameter was actually decreased. Although mechanical changes at the receptor level cannot be entirely discounted on the basis of absence of a change in diameter, the results indicate that after exposure to PP there is an increase in "strain sensitivity" of the baroreceptors; that is, activity increases not only at the same pressure but also at the same diameter or strain.

A second factor that could have accounted for the sensitization is a decrease in the activity of Na+,K+-ATPase after the pulsing period. This decrease in Na+,K+-ATPase activity may occur when baroreceptor activity is reduced during the pulsing period. However, baroreceptor activity was actually increased during PP rather than decreased in many instances where the "post-PP sensitization" occurred (Figure 8). Further, the sensitization was directly related to the duration of pulsing. More baroreceptor activity for a longer period should stimulate the Na+ pump and lead to postexcitatory hyperpolarization and decreased baroreceptor activity after PP instead of increased activity. Although changes in Na+ pump activity may not explain the sensitization, other ionic changes may still play a role. For example, repetitive nerve stimulation can lead to increased concentration of extracellular potassium that may depolarize sensory nerves.

An additional mechanism that we have considered is the release of an endothelial factor during PP that may influence baroreceptor activity by altering vasomotor tone or by acting directly on the nerve endings. PP stimulates the vascular endothelium to release prostacyclin and endothelium-derived relaxing factor. Prostacyclin and various prostaglandins activate sensory receptors located in the heart and lungs. We considered that these substances may contribute to the increased baroreceptor sensitivity after PP. We had obtained evidence suggesting that prostacyclin contributes to baroreceptor activation during increases in static carotid sinus pressure in rabbits, but the present findings indicate that removal of the endothelium or blockade of prostaglandin synthesis in the carotid sinus of dogs does not prevent the "post-PP sensitization" of baroreceptors (Table 1).

Whatever the mechanism responsible for the sensitization, it is related to the magnitude of the pulsatile change in diameter or "stretch" during the period of pulsing rather than to the magnitude of the pulsatile change in wall tension or force sustained by the vessel wall during pulsing (Figure 10). The dependency on pulse diameter was apparent both when pulse diameter was varied by pulsing at different mean pressures (Figure 10) or varied by changing the amplitude of the pulse pressure (Figures 6 and 7). Perhaps changes in shear stress associated with pulsatile stretch are transduced to increases in nerve activity. We have shown recently that increases in carotid sinus nerve activity correlate well with the calculated shear stress during graded changes in flow at constant non-PP in the isolated carotid sinus of dogs.

**Physiological Significance**

Two points are made concerning the physiological implications. One relates to the wide pulse pressure and high heart rates that occur during exercise, and the second relates to acute resetting or adaptation of baroreceptors.

"Post-PP sensitization" of baroreceptors was related in a graded manner to the pulse pressure amplitude (Figures 6 and 7) and the pulsatile change in diameter (Figure 10) and outlasted the period of pulsatility by several minutes. Increases in pulse...
frequency also enhanced the "post-PP sensitization" of baroreceptors (Figure 7). We speculate that "post-PP sensitization" of baroreceptors may contribute to the decreased sympathetic activity and blood pressure that has been observed after exercise.38,39 Indeed, the slowing of heart rate in response to baroreceptor stimulation has been reported to be enhanced after exercise.40

The sensitization of baroreceptors that occurs after exposure to increases in pulse pressure described in this report contrasts markedly with the adaptation or resetting of baroreceptors that is observed after acute elevations in mean arterial pressure.5,12,20–22 This resetting of baroreceptors after acute elevation of arterial pressure allows them to respond effectively to fluctuations in arterial pressure and thus buffer such fluctuations; however, the decreased baroreceptor activity may contribute to maintenance of the elevated arterial pressure. Most other sensory receptors also adapt or reset during a constant increased stimulus although some receptors can be sensitized after repetitive stimulation.41 We propose that the degree of resetting or adaptation that occurs during elevations in mean pressure may be offset when the rise in pressure is accompanied by an increased pulse pressure. As a result, baroreflex-mediated suppression of sympathetic activity may be sustained over an extended period of time when pulse pressure is elevated. The concept that pulsatility may modulate acute resetting of baroreceptors has important implications concerning the neural adjustment of the circulation during hypertension.

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