Prevention or Attenuation of Baroreceptor Resetting by Pulsatility During Elevated Pressure

MARK W. CHAPLEAU, CHERYL M. HEESCH, AND FRANCOIS M. ABBoud

SUMMARY Acute static elevation of arterial pressure increases the pressure threshold for activation of baroreceptors (acute resetting). The purpose of this study was to test the hypothesis that pulsatility during acute elevation of pressure modifies this acute resetting. Activity was recorded in 21 single baroreceptor units from the isolated carotid sinuses of dogs anesthetized with chloralose. Single-unit pressure thresholds were determined with a slow ramp increase in pressure. After a control period of static pressure at 25 to 50 mm Hg, the pressure threshold averaged 69 ± 4 (SE) mm Hg. Three graded levels of static pressure were held for 5 to 15 minutes. The levels averaged 76 ± 4, 115 ± 6, and 170 ± 6 mm Hg. The corresponding nerve activity during these periods was 0, 44 ± 6, and 63 ± 6 spikes per second, and the resulting increases in pressure threshold averaged 10 ± 1, 17 ± 2, and 26 ± 3 mm Hg, respectively. In contrast, during equivalent elevations of pulsatile pressure, nerve activity averaged 20 ± 3, 37 ± 4, and 61 ± 5 spikes per second, and the increases in pressure threshold averaged 0 ± 4, 14 ± 2, and 24 ± 2 mm Hg, respectively. In some units, the pressure threshold decreased following elevation of pulsatile pressure. The results indicate that: 1) pulsatility during elevation in pressure prevents or attenuates the acute baroreceptor resetting except at maximal pressure; 2) upward resetting occurs with elevation of static pressure even when there is no nerve activity during the period of elevated pressure; in contrast, with equivalent elevation of pulsatile pressure, resetting does not occur and occasionally the single-unit pressure threshold is reduced despite a significant increase in nerve activity during the period of pulsatile pressure. (Hypertension 9 [Suppl III]: III-137–III-141, 1987)

KEY WORDS • pulsatility • acute resetting • blood pressure regulation • mechanoreceptors • dogs
Methods

Mongrel dogs (16 to 24 kg) were anesthetized with thiopental sodium (30 mg/kg, i.v.) and α-chloralose (80 mg/kg, i.v.). Supplemenetal doses of α-chloralose were administered hourly. The dogs were intubated and mechanically ventilated with room air supplemented with oxygen. Arterial pH and partial pressure of carbon dioxide (P\textsubscript{CO\textsubscript{2}}) 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 pressure measurements and α-chloralose administration, respectively.

Isolated Carotid Sinus Preparation

The isolated carotid sinus and baroreceptor recording techniques have been described elsewhere\textsuperscript{1,2} and will be described here 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 salt solution equilibrated with 95% O\textsubscript{2}-5% CO\textsubscript{2} and warmed to 37°C. The sinus was connected to a pressure reservoir and carotid sinus pressure (CSP) was measured through the external carotid catheter by a Statham transducer (Model P23AA, Statham, Hato Rey, Puerto Rico).

The mean level of CSP was controlled by adjusting a regulator valve connected to a pressurized air source. A voltage waveform generator fed sine wave pulses into an electromagnent pressure converter (Millar, Houston, TX, USA) that was connected to the reservoir. Pulse rate and pulse pressure were set at 90 to 130 pulses/min and 30 to 40 mm Hg, respectively, and were maintained constant whenever pulsatile pressure was utilized. This pressure generating system made it possible to instantly convert static to pulsatile pressure and vice versa without changing the mean CSP.

Carotid Sinus Nerve Recordings

The carotid sinus nerve was cut near its junction with the glossopharyngeal nerve, placed on a dissecting stage, covered with paraffin oil, and desheathed. The vago-sympathetic 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, Quincy, MA, USA) and amplified by a Grass (P511) bandpass amplifier (high frequency cuttoff 3000 to 10,000 Hz; low frequency cuttoff 30 Hz). Nerve traffic was visualized on a dual-beam storage oscilloscope (Model 5113, Tektronix, Beaverton, OR, USA) and listened to through a loudspeaker.

A nerve traffic analyzer that counts spikes exceeding a preselected voltage at 115 ± 6 mm Hg, and 170 ± 6 mm Hg to levels of 76 ± 4 mm Hg, respectively (Figures 1 and 2). In contrast, pulsatile pressure at equivalent mean pressures resulted in increases in P\textsubscript{a} averaging 0 ± 4, 14 ± 2, and 24 ± 2 mm Hg, respectively (see Figure 2). In four of nine receptors, there was a decrease in the P\textsubscript{a} after the first level of elevated pulsatile pressure (see Figure 1, lower half). Thus, resetting was prevented by pulsatile pressure at 76 mm Hg and was attenuated at 115 mm Hg (see Figure 2).

Baroreceptor activity was absent during static pressure at 76 ± 4 mm Hg but was increased (20 ± 3 spikes/sec) during pulsatile pressure at the same level. Activity was greater during static than during pulsatile pressure at 115 ± 6 mm Hg, and equal during

Results

Increases in static pressure from less than 50 mm Hg to levels of 76 ± 4, 115 ± 6, and 170 ± 6 mm Hg increased P\textsubscript{a} by 10 ± 1, 17 ± 2, and 26 ± 3 mm Hg, respectively (Figures 1 and 2). In contrast, pulsatile pressure at equivalent mean pressures resulted in increases in P\textsubscript{a} averaging 0 ± 4, 14 ± 2, and 24 ± 2 mm Hg, respectively (see Figure 2). In four of nine receptors, there was a decrease in the P\textsubscript{a} after the first level of elevated pulsatile pressure (see Figure 1, lower half). Thus, resetting was prevented by pulsatile pressure at 76 mm Hg and was attenuated at 115 mm Hg (see Figure 2).

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FIGURE 1. Nerve activity during a pressure ramp in a single carotid baroreceptor unit before and after two periods of elevated pressure, one static (upper half) and one pulsatile (lower half). Acute elevation of static pressure to a level insufficient to cause sustained activation of the unit caused an increase in pressure threshold (P_{th}) from 83 to 97 mm Hg. The diameter at threshold (D_{th}) was also increased by 10%. Conversely, acute elevation of pulsatile pressure to an equivalent level activated the unit, but the P_{th} dropped to 71 mm Hg and D_{th} was essentially back to the control level. Thus, pulsatile elevation in pressure not only prevented resetting but markedly decreased the P_{th} and wall tension at threshold in this experiment.

Static and pulsatile pressures at 170 ± 6 mm Hg (see Figure 2).

Five single units did not reset upward after elevation of static pressure from 28 ± 2 to 108 ± 7 mm Hg. In these units, exposure to high pulsatile pressure reduced P_{th} significantly (Figure 3).

Discussion

The results indicate the following. First, an acute increase in carotid sinus pressure from low levels of static pressure to three graded higher levels of static pressure causes graded upward resetting of single units of baroreceptor afferents. Resetting is defined in these experiments as an increase in the P_{th} or the pressure at which a single unit begins to fire during a slow ramp of carotid sinus pressure at a rate of less than 3 mm Hg/sec. This acute resetting can occur within minutes of a sustained elevation of pressure and has been described previously by Coleridge, Brown, Krieger, Korner, and their collaborators, as well as by our group.

Second, the step increase in static pressure to 76 ± 4 mm Hg was not sufficient to cause sustained activity, yet it caused acute resetting. This has also been observed previously. Acute resetting has been attributed in part to an ionic mechanism. It has been proposed that the influx of Na^+ into baroreceptor nerve terminals during elevated pressure causes depolarization of the generator potential, which in turn may activate Na^+,K^+-ATPase. The Na^+ pump-induced extrusion of Na^+ leads to hyperpolarization of the neuron and renders it less excitable. Indirect evidence support-
ing this concept was obtained in baroreceptors. The same concept applies even at subthreshold levels of elevated pressure, where depolarization of the generator potential insufficient to trigger the spike-initiating zone of the axon may still result in activation of Na⁺,K⁺-ATPase, decreased excitability, and increased P.2,9

Third, in contrast to the effect of elevation of pressure to high static levels, which increases P, elevation to high pulsatile pressures either does not increase P or attenuates the increase noted after equivalent static pressure. In fact in several units, elevation to a pulsatile pressure decreased the P. This is the major new finding in this study.

Several explanations for this third finding were considered. First, the magnitude of baroreceptor resetting following elevated pressure has been related to the degree of depolarization and Na⁺ pump activation that occurs during the elevated pressure. Although the mean level of pressure was equivalent during elevated static versus pulsatile pressure in this study, the degree of depolarization may not have been equal. The fact that baroreceptor activity was less during pulsatile pressure compared to static pressure at 115 ± 6 mm Hg suggests lesser depolarization during pulsatile pressure and therefore may explain the attenuated resetting. This hypothesis is not supported by the results obtained at a mean holding pressure of 76 ± 4 mm Hg. At that level, the baroreceptors were firing during pulsatile pressure but were silent during static pressure. If anything, one would expect greater depolarization and greater resetting during pulsatile pressure. This was opposite to what was observed.

The second possibility is that a change in carotid sinus compliance after repetitive pulsatile deformation could have altered the mechanical stimulus to the receptors. We have not examined the compliance systematically in these studies, but we doubt that this is the explanation. Previously we have shown that an increase in compliance accompanies acute upward resetting of baroreceptors but that compliance remains elevated even after resetting has been reversed after exposure to a low distending pressure. In other words, there is no consistent correlation between changes in compliance and changes in P. In addition, in one experiment in which carotid sinus diameter was measured with sonomicrometry during the pressure ramps both before and after elevated pulsatile versus static pressure, the threshold diameter was much lower after the exposure to pulsatile pressure and thus the wall tension at threshold was greatly reduced (see Figure 1, right panels).

A third explanation for the prevention or reversal of acute upward resetting with pulsatility is speculative. It is known that pulsatile stretch or strain may cause the release of vasoactive substances such as prostacyclin or other endothelium-dependent factors. These factors may sensitize the baroreceptors and offset the upward resetting. Preliminary studies from our laboratory provide indirect support for this possibility.

The physiological significance of this finding may relate to the buffering capacity of the arterial baroreceptor reflex. Acute upward resetting of baroreceptors during a rise in pressure reduces the buffering capacity of the reflex and offsets to some degree this compensatory mechanism. On the other hand, if acute resetting is minimized or reversed with pulsatile elevation in blood pressure, it would tend to preserve or enhance the buffering capacity of the reflex during sustained elevations of pressure.

Important questions still remain to be answered in this regard. Although we have shown that an increase from low static to elevated pulsatile pressure prevents or attenuates acute resetting, we do not know whether upward resetting occurs with an increase from low pulsatile to high pulsatile pressure in single units with constant frequency, pulse pressure, and rate of change of pressure. If this is true, the physiological significance of the phenomenon of acute resetting will require reevaluation.

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M W Chapleau, C M Heesch and F M Abboud

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