Carotid Baroreflex Function in Young Men with Borderline Blood Pressure Elevation

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SUMMARY Carotid baroreflex function was assessed in 10 normotensive young men and 20 age-matched subjects with borderline hypertension (successive blood pressures above and below 140/90 mm Hg) by measuring sinus node responses to brief neck suction. Subjects with borderline hypertension were divided into two equal groups according to their average systolic arterial pressures. Baroreflex responses were reset to function at higher pressure levels than normal in subjects with mild borderline hypertension, but reflex sensitivity was normal. Responses were also reset in subjects with more severe borderline hypertension, but reflex sensitivity was subnormal. The results suggest that a gradation of baroreflex responsiveness exists among patients classified as having borderline hypertension: Subnormal responsiveness was found in those subjects whose resting average systolic arterial pressure was ≥ 140 mm Hg.

SOON AFTER THE CAROTID ARTERIAL BAROREFLEX was discovered, Koch and Mies1 and Volhard2 suggested that defective baroreflex buffering of blood pressure might cause essential hypertension. Despite numerous subsequent attempts to delineate hypertensive mechanisms, the role of the arterial baroreflex in the pathogenesis of hypertension remains an enigma. The validity of the theory of Koch and Mies and Volhard has been questioned,3 but the theory has not been discredited altogether. The study of Bristow and co-workers4 supports their postulate: In their study arterial baroreceptor-cardiac reflex responses were found to be strikingly depressed in patients with moderate (average mean arterial pressure 123 mm Hg), sustained hypertension. In these patients, baroreceptor reflex malfunction might have contributed to the development of hypertension, or it might have been a consequence of hypertension.

If a defective baroreceptor reflex mechanism causes hypertension, subnormal baroreflex responses should be found in patients with mild degrees of blood pressure elevation. Data on this issue are conflicting. Takeshita and associates5 found subnormal baroreflex responses in young men whose average blood pressure was 160/82 mm Hg, but Julius6 found normal responses in borderline hypertensive patients whose blood pressures were reported to be lower than those studied by Takeshita and co-workers. I have attempted to clarify this issue by using new techniques to measure baroreflex responses of asymptomatic young men whose blood pressures oscillate above and below 140/90 mm Hg.

Methods

Seven intensities of neck suction were delivered briefly to stretch carotid baroreceptors of young men with normal blood pressures and young men with borderline hypertension (defined as blood pressures above and below 140/90 mm Hg on successive examinations). Sinus node responses were measured.

Hypertensive and Normal Volunteers

Volunteers, ages 19–25 years, were recruited from 900 university students who had blood pressures measured during registration. Blood pressures of each volunteer were measured two to four (average 2.85) times with subjects in the sitting position, after 10 minutes of rest. Weight, height, and skinfold thickness, measured in the midline midway between the chin and the upper margin of the thyroid cartilage were also measured.
Hypertensive subjects were accepted for this study if their systolic blood pressures were 140–165 mm Hg, or their diastolic pressures were 90–110 mm Hg (only one subject, on one of three measurements, had a diastolic pressure of 110 mm Hg; all other diastolic pressures of this, and other subjects were 102 mm Hg or less); they were asymptomatic; they had no other known health problems; and they were taking no medications. All hypertensive subjects had systolic pressures above and below 140 mm Hg (15 subjects), or diastolic pressures above and below 90 mm Hg (11 subjects), when measured on different occasions, and thus satisfied one criterion for the diagnosis of borderline hypertension. Laboratory studies were not conducted to exclude secondary causes of hypertension. I assumed, on the basis of probability, that very few of the subjects studied would have secondary hypertension.

Normal volunteers were accepted if all of their blood pressure measurements were below 130/80 mm Hg; they had no known illnesses, including hypertension; and they were taking no medications. Each subject was accepted without prior knowledge of family medical history, body habitus, degree of physical fitness or cardiovascular reflex function. All volunteers gave prior written, informed consent.

Equipment

The neck chamber, pneumatic valve and digital stimulator were designed and fabricated in the laboratory. Experimental results were transcribed by an ink writing recorder; four channels were used for the ECG, beat-by-beat pulse interval, neck chamber pressure and respirations, measured with a pneumograph.

Baroreceptor Stimulation

Carotid baroreceptors were stimulated by applying suction to a neck chamber formed from an elliptical piece of sheet lead and rimmed with sponge rubber. The intensity of suction was measured with a strain gauge pressure transducer mounted upon the chamber. A commercial vacuum cleaner was used to provide a continuous vacuum source; its intensity was regulated by a rheostat. Suction was initiated electronically by rotation of a solenoid pneumatic valve which was mounted directly on the neck chamber. All stimuli were applied during held expiration.

Two types of baroreceptor stimuli were delivered:

1) Stimulus-Response Relation. Neck suction, 10–70 mm Hg, was applied for 0.6 seconds and timed to begin 0.75–0.85 seconds before the appearance of the next anticipated P wave, as described earlier. During held expiration, the heart rate is nearly constant; therefore, the timing of the next anticipated P wave could be predicted accurately on the basis of the preceding P-P interval. Prolongation of the first P-P interval after the onset of the stimulus, from the preceding P-P interval, was plotted as a function of stimulus intensity. Seven stimuli were applied at each intensity, and the average response was calculated. This method was used to derive a baroreceptor stimulus intensity-sinus node response relation.

2) Steady-State Responses. Neck suction of 50 mm Hg for 5 seconds was begun at random times in the cardiac cycle and prolongation of each P-P interval was plotted as a function of time from the onset of neck suction until the P wave concluding each successive cardiac cycle. Stimuli were applied about 25 times, and composite responses were averaged at 0.5-second intervals. This method was used to provide an estimate of the intensity of steady-state baroreflex sinus node inhibition.

Statistical Analyses

Standard tests used to determine statistical significance included the unpaired t test (weight, skin thickness, P-P intervals and saturation pressures), analysis of variance with orthogonal contrasts (figs. 1 and 2), and least squares linear regression (fig. 3). Differences were considered significant when p < 0.05.

In addition, a new technique was devised to use with the stimulus-response relation to estimate objectively the point of inflection, or the intensity of stimulation at which baroreflex responses reached their maximum levels. This method is described in the Appendix. The timing of stimuli delivered to measure the intensity-response relation was such that neck suction coincided with the natural arterial pulse. The saturation pressure was considered to be the absolute sum of the average systolic arterial pressure during the study, and neck chamber pressure at the inflection point. For example, a subject whose systolic pressure was 110 mm Hg, and whose point of inflection occurred at a neck suction intensity of 45 mm Hg, would be considered to have a saturation pressure of 155 mm Hg. Increments of

![Figure 1. Sinus node responses of subjects with normal blood pressure (circles), and milder (squares) and more severe (triangles) borderline hypertension to brief (0.6 second) neck suction. These curves depict the combined average responses of the 10 subjects in each group. Carotid distending pressure was considered to be the absolute sum of systolic arterial pressure and neck chamber pressure. Brackets indicate SEM.](http://circ.ahajournals.org/content/633/1/633/F1)
neck suction beyond this point did not provoke additional P-P interval prolongation.

**Results**

**Hypertensive and Normal Volunteers**

Ten normotensive volunteers and 20 subjects with borderline hypertension were studied. All volunteers were white. The average ages of normotensive and borderline hypertensive volunteers were similar. The average weight of hypertensive subjects was greater than that of normotensive volunteers, but there was considerable overlap, and the difference was not significant (83 ± 3 kg (SEM) vs 74 ± 2 kg, 0.10 > p > 0.05). Neck skin thickness was insignificantly greater in hypertensive subjects than in normotensive volunteers (6.2 ± 0.9 vs 4.1 ± 0.5 cm, p > 0.10).

**Blood Pressure**

Average systolic and diastolic blood pressures were 113 ± 2 and 70 ± 1 mm Hg for normotensive volunteers and 139 ± 1 and 86 ± 1 mm Hg for borderline hypertensive subjects. The average control P-P interval (measured before the onset of neck suction, after 5 seconds of held expiration) was 1001 ± 48 msec in normal volunteers, and 941 ± 26 msec in borderline hypertensive subjects (0.1 > p > 0.05). The average standard deviation of control pulse intervals was 57 msec in normotensive volunteers, and 64 msec in borderline hypertensive subjects (p > 0.2). Thus, baseline pulse interval and its variability did not discriminate between normotensive and borderline hypertensive subjects, as reported by others.

Hypertensive subjects were divided arbitrarily into two equal groups according to their average systolic blood pressures: One group had average pressures ≥ 140 mm Hg and the other had pressures < 140 mm Hg. Six of each group of 10 subjects had first-degree relatives with hypertension. The two groups also were comparable in diastolic pressure (87 ± 2 mm Hg vs 86 ± 1 mm Hg), age (22.8 ± 0.4 years vs 22.1 ± 0.7 years), and weight (88 ± 5 vs 77 ± 4 kg, p > 0.10). Three subjects in the group with average systolic pressures of 140 mm Hg or more all weighed 65 kg; their baroreflex responses were similar to those of other members of this group.

Average stimulus-response data for all subjects are depicted in figure 1. Responses of the group of borderline hypertensive subjects with lower systolic pressures (average 134 ± 1 mm Hg) were displaced to the right of responses of normal subjects, and their calculated saturation pressures were significantly (177 ± 6 vs 152 ± 6 mm Hg, p < 0.01) greater than those of normal subjects. However, the slope of the linear portion of the intensity-response relation, and the maximum level of baroreflex sinus node inhibition (average responses at the three highest intensities of neck suction) in this group were comparable with those of normal subjects.

Responses of the group of subjects who had blood pressures in the upper half of those studied (average systolic pressure 144 ± 1 mm Hg) were significantly different from those of normal volunteers and from those of subjects with more mild pressure elevations. The estimated average saturation pressure, 191 ± 4 mm Hg, was significantly higher than that of normal subjects (p < 0.001), and subjects with less severe...
borderline hypertension ($p < 0.005$). Baroreflex sensitivity (slope) and the maximum level of baroreflex sinus node inhibition were significantly lower than those of normal subjects ($p < 0.001$) and subjects with milder elevations of blood pressure ($p < 0.001$). Figure 2 shows that steady-state baroreflex responses also were depressed in this group.

Subjects with borderline hypertension also were divided into two equal groups according to their average baseline pulse intervals. Baroreflex responses were similar in the two groups; responses were not significantly less in the group with shorter baseline pulse intervals (faster resting heart rates).

Saturation pressures of all volunteers are plotted as a function of their average systolic arterial pressures in figure 3. Saturation pressure varied as a linear function ($r = 0.76$) of average systolic arterial pressure.

**Discussion**

I have evaluated arterial baroreflex function of young men whose average systolic arterial pressures were between levels accepted as normal and those regarded as hypertensive. In each borderline hypertensive subject studied, the baroreflex mechanism was shifted to function at its usual arterial pressure level. In addition, in a subset of borderline hypertensive subjects whose systolic pressures were in the upper half of those studied, acute and steady state baroreflex responses were clearly depressed.

These data clarify the relationship between baroreflex responsiveness and resting arterial pressure. Baroreflex responses have been found to be subnormal in subjects who have average systolic pressures of 177, $160^5$ and 144 mm Hg (present study), but not 134 mm Hg (present study). Thus, it appears that the decline of baroreflex responsiveness is critically related to the average level of resting arterial pressure attained.

The results of this study support recent experimental evidence which suggests an important contribution of baroreflex malfunction in the maintenance of hypertension. The antihypertensive agent clonidine, appears to lower blood pressure by enhancing the efficiency of the native baroreflex mechanism in experimental hypertension. $^{13}$ Surgical destruction of the nucleus tractus solitarius, the first medullary relay station for incoming baroreceptor information, leads to sustained, rapidly fatal hypertension in rats, $^{14}$ and to labile hypertension in cats. $^{15}$ Baroreceptor nerve responses to arterial pressure changes are subnormal in rats with spontaneous hypertension. $^{16}$

Single baroreceptor nerve fiber activity has not been measured in man. However, abnormalities of sinus node responses to baroreceptor stimulation with neck suction bear a striking qualitative similarity to abnormalities of baroreceptor nerve responses to changes of arterial pressure found in experimental animals with hypertension. $^{13, 14}$ I assume (but have not proven) that the abnormalities observed in man primarily reflect derangements at the receptor level in the reflex arc.

Whatever the cause of human hypertension, most investigators agree that secondary pathological arterial changes contribute to maintenance of pressure elevation, and also may lead to persistence of hypertension after the primary cause has been removed. Chief among these changes is the accretion of arterial smooth muscle and connective tissue $^{16, 18}$ which leads to retention of salt and water by the kidneys $^{19}$ and elevation of resting vascular resistance. $^{20}$ Baroreceptor reflex malfunction is probably a third expression of hypertensive arterial pathology. $^{16}$

The prognostic significance of depressed baroreceptor-cardiac reflex responses in patients with sustained or borderline hypertension is unknown. I postulate that borderline hypertensive subjects with depressed baroreflex responses are more likely to develop hypertensive cardiovascular disease than those with normal responses. This poorer prognosis may result from suboptimal baroreflex buffering of arterial pressure or generalized hypertensive arteriopathy, of which the depression of baroreflex responses is merely one marker. A corollary of this postulate is that baroreflex responsiveness may predict the subsequent development of hypertensive cardiovascular disease more accurately than casual blood pressure determinations.

This testable hypothesis, if valid, might have considerable public health significance. Long-term studies show that most middle-aged patients with hypertensive cardiovascular disease had borderline blood pressure elevations in youth. $^{21}$ A modification of the safe, noninvasive technique of baroreceptor stimulation described in this study might be used to discriminate between young people whose blood pressures will decline spontaneously and who require no treatment, and those whose blood pressures will probably rise more or less inexorably, and who, therefore, require careful follow-up, if not immediate, rigorous antihypertensive therapy. This delineation may be of great practical importance because of the cost of caring for hypertensive patients. Even the wealthiest societies may not have sufficient resources to provide long-term follow-up and treatment for all of their members with borderline or mild blood pressure elevations. $^{22}$

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**References**


**Appendix**

A new statistical technique was devised (in collaboration with Dr. G.G. Woodworth, Department of Statistics, University of Iowa) for use with the asymptotic stimulus-response relation (fig. 1) to provide an objective estimate of the saturation pressure, or the carotid distending pressure at which pulse interval prolongation becomes maximal. Least squares linear regression analyses were performed for each intensity-response relation. An arbitrary inflection (or bending) point was chosen, and a computer program calculated the residual sum of squares for portions of the intensity-response relation lying to the left and to the right of this point. An iterative program shifted the inflection point by increments or decrements of 1 mm Hg, and these calculations were repeated. The neck chamber pressure at which the residual sum of squares was least was taken as the inflection point. The saturation pressure was considered to be the absolute sum of the average systolic arterial pressure during the study, and neck chamber pressure at the inflection point. The method for determining the inflection point is illustrated in figure 4.

![Figure 4](http://circ.ahajournals.org/content.figures/157274/)

**FIGURE 4.** Method used to determine the inflection point of the stimulus response relation.
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