PATHOPHYSIOLOGY AND NATURAL HISTORY

HYPERTENSION

Arterial baroreflex control of sympathetic nerve activity during elevation of blood pressure in normal man: dominance of aortic baroreflexes

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ABSTRACT Arterial baroreceptors in the carotid sinus (CBR) and aortic arch (ABR) regions exert important control over heart rate and peripheral vascular responses to changes in arterial pressure. The relative roles of these two baroreflex pathways on control of sympathetic nerve activity during sustained elevation of arterial pressure in man is unknown. We therefore studied the relative contributions of the carotid versus the aortic baroreflexes on the control of muscle sympathetic nerve activity (MSNA) during elevation of arterial pressure in normal human subjects. In eight normal men (group I), we measured MSNA (microneurography) during sustained elevation of arterial pressure produced by intravenous infusion of phenylephrine (PE) alone (combined ABR and CBR activation) versus during PE infusion with superimposed application of sustained external neck pressure (NP). NP was applied during sustained PE infusion to eliminate the increase in transmural carotid sinus pressure and thereby causing ABR stimulation alone. Mean arterial pressure was measured directly, central venous pressure was held constant during PE infusion, and MSNA was measured as total activity (burst frequency × amplitude) and expressed as units. Infusion of PE (ABR and CBR activation) increased mean arterial pressure from 87.2 ± 2.8 to 94.9 ± 2.9 mm Hg (±SE, p < .001). This was accompanied by a decrease in heart rate from 65.8 ± 3.4 to 56.1 ± 3.3 beats/min (p < .001) and a decrease in MSNA from 236.2 ± 47.5 to 84.5 ± 19.3 units (p < .001). During infusion of PE with superimposed NP (ABR activation alone), mean arterial pressure increased further to 101.2 ± 2.9 mm Hg (p < .001 versus control or PE alone), and heart rate returned to control levels of 62.9 ± 2.0 beats/min (p = NS vs control; p < .01 PE vs PE plus NP), but MSNA remained reduced at 48.6 ± 9.2 units (p < .01 vs control; p = NS vs PE alone). Thus, combined activation of ABR and CBR resulted in a 65 ± 5% attenuation of MSNA, while activation of ABR alone resulted in a 73 ± 7% attenuation of MSNA. In a separate series of experiments in seven subjects (group II) we used sustained external neck suction alone to activate the CBR (leaving the ABR either unchanged or minimally deactivated) and studied the MSNA responses to this CBR activation. Application of −17.5 ± 1.3 mm Hg of neck suction resulted in a decrease in mean arterial pressure from 83.9 ± 2.7 to 78.7 ± 3.5 mm Hg (p < .01). This was associated with a tendency for a decrease in heart rate from 62.0 ± 2.0 to 58.2 ± 2.3 beats/min (p = .05). This activation of CBR by external neck suction was not associated with a sustained decrease in MSNA (NS control = 188.9 ± 50.1 units vs MSNA during NS = 168.3 ± 44.3 units, p = NS). These results demonstrate that the aortic baroreflexes alone do not produce a significant sustained inhibition of MSNA.


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Supported by NHLBI grants HL-14388 and HL-24962, General Clinics grant RR-59, National Institutes of Health, and research funds from the Veterans Administration. Dr. Ferguson is a recipient of New Investigator Award HL-39340-01 from the National Institutes of Health (1987-90).

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Received July 21, 1987; revision accepted Oct. 29, 1987.

REFLEX REGULATION of the circulation involving afferent nerves within the cardiovascular system has been recognized since the original description of the depressor nerve by Cyon and Ludwig in 1866. While the presence of cardiodepressor nerves arising from the regions of the aortic arch and origin of the great vessels was demonstrated by Koster and Tschermak in 1903, the carotid sinus region has been the primary focus for most studies of arterial baroreflex control of the cir-
calculation in both animals and humans. Not until recent decades have there been investigations aimed at distinguishing the relative contributions of the aortic and carotid baroreflex pathways on the control of heart rate and vascular tone during alterations in blood pressure.

Animal studies have suggested that these two baroreflex pathways differ in important respects. In dogs, studies by Donald and Edis \(^{3}\) and Pelletier et al. \(^{4}\) showed that the carotid and aortic baroreflexes differ in both threshold and sensitivity. Likewise, Dampney et al. \(^{5}\) showed that while the time courses of the aortic and carotid baroreflex control of hindlimb vascular resistance in dogs were similar, the aortic baroreflex appeared to be about half as sensitive as the carotid baroreflex in control of vascular resistance.

The relative roles of the aortic and carotid baroreflexes on control of heart rate during elevation of arterial pressure in animals have been extensively studied, but the results have been contradictory. \(^{6-10}\) Prior studies of normal human subjects in our laboratory \(^{11}\) and by Mancia et al. \(^{12}\) have indicated that the aortic baroreceptors have a greater role than the carotid baroreceptors on heart rate control during dynamic increases in arterial pressure. However, it is clear from both animal and limited human studies that arterial baroreflex control of heart rate (predominantly a parasympathetic mechanism) does not necessarily imply parallel control of systemic vascular resistance (predominantly a sympathetic mechanism). \(^{9,11}\) The relative influence of carotid versus aortic baroreflex control of sympathetic nerve activity in man remains undefined. Bath et al. \(^{13}\) recently suggested that the aortic baroreflexes may participate in the control of sympathetic nerve activity in man under physiologic ranges of alteration of blood pressure.

We report a series of studies designed to determine the relative contribution of the carotid and aortic baroreflexes on control of sympathetic nerve activity in normal man during sustained increases in arterial pressure. The unique features of these studies are the utilization of direct measurements of sympathetic nerve activity and a strategy to provide stimulation of both the carotid (CBR) and extracarotid baroreceptors together versus stimulation of either one alone. We believe it is reasonable to assume that the extracarotid receptors stimulated are primarily, if not solely, the aortic arch baroreceptors (ABR). Using these approaches, we evaluated the relative contribution of carotid and aortic baroreflexes on control of sympathetic nerve responses to sustained elevation of arterial blood pressure in normal human subjects.

**Methods**

**Subjects.** We studied 14 normal human subjects. Eight healthy male subjects, 20 to 32 years old (subjects 1 to 8, group I) were studied with the use of phenylephrine (PE) and neck pressure (NP). Seven subjects, 19 to 32 years old (including one of the initial eight) were studied with the use of neck suction (NS). This group (subjects 6 and 9 to 14, group 2) included two female and five male participants. All subjects were studied without sedation in the supine, postabsorptive state and were free of cardiovascular and other systemic disease based on a medical history and physical examination. The subjects were not receiving any medication. Written informed consent was obtained from all subjects before the study and the study protocol was approved by the Human Subjects Review Committee of the University of Iowa.

**Measurements.** A direct-writing multichannel physiologic recorder was used to simultaneously record systolic arterial pressure (SAP, mm Hg), mean arterial pressure (MAP, mm Hg), central venous pressure (CVP, mm Hg), heart rate (beats/min), respiratory activity, level of external NP (mm Hg) or NS (mm Hg), and sympathetic nerve activity to muscle (MSNA, bursts/min). Arterial pressure was measured directly with a Statham P231D pressure transducer through an indwelling No. 5F polyethylene catheter inserted percutaneously in a brachial artery under local anesthesia. MAP was obtained by an electrical mean signal. An 18.5-gauge polyethylene catheter was inserted percutaneously under local anesthesia into a median antecubital vein and advanced to an intrathoracic position for measurement of CVP. Heart rate and rhythm were recorded continuously by an electrocardiogram and respiratory activity was recorded by a strain-gauge pneumograph applied lightly over the lower thoracic cage. Zero pressure reference point was defined as the midaxillary position in these supine subjects.

**Procedures for changing pressure at arterial baroreceptors.** Several experimental techniques were used for stimulation of ABR and CBR together and separately. Steady-state elevation of arterial pressure was used in studies of group I subjects to simultaneously activate both CBR and ABR. This was achieved by the administration of a continuous intravenous infusion of PE. The infusion of PE was rapidly titrated to, and then maintained as a steady-state infusion at a dose that produced an adequate increase in MAP and a resulting discernible attenuation of MSNA. The dose of PE averaged 81.3 ± 6.6 μg/min and produced a 4 to 14 mm Hg increase in MAP. Subsequently, during continued steady-state infusion of PE, sustained external NP was applied to the region of the carotid sinuses with the use of a malleable neck collar, as previously described. \(^{14}\) This external NP removed the transmural gradient across the carotid sinus wall produced by the rise in arterial pressure and returned the carotid sinus distending pressure equal to or less than control levels, while the aortic pressure remained elevated. Thus, during combined infusion of PE with superimposed application of NP, we achieved primarily a selective stimulation of ABR alone.

Prior studies in our laboratory have suggested that infusion of PE to normal subjects results in an increase in CVP. Therefore, during the infusion of PE, CVP was maintained constant by the application of low levels of lower body negative pressure (LBNP) with the use of a chamber placed over the subject’s body below the iliac crest. \(^{15}\) The level of LBNP applied was adjusted manually to maintain CVP at control levels.

In a separate series of experiments on seven subjects (group II), activation of CBR alone, or with a resultant minimal deactivation of ABR, was achieved by the application of sustained external NS with the use of the same neck collar apparatus described above. \(^{14}\) Application of NS results in a distention of the carotid sinuses, thereby activating the CBR. The tendency
for a resultant fall in arterial pressure might have partially deactivates the ABR during this sustained NS.

Microangiographic recording of sympathetic nerve activity. Multiunit recordings of postganglionic MSNA were obtained from a muscle nerve fascicle in the right peroneal nerve posterior to the fibular head. The recordings were made after the percutaneous insertion of tungsten microelectrodes with a 200 μm insulated shaft diameter tapering to an uninsulated tip of 1 to 5 μm. A reference electrode was inserted subcutaneously 1 to 3 cm from the recording electrode. The electrodes were connected to a preamplifier with a gain of 1000 and an amplifier with a gain of 50-fold. The neural activity was then fed through a bandpass filter with a bandwidth of 700 to 2000 Hz. For monitoring during the experiment, the filtered neurogram was routed through an amplitude discriminator to a storage oscilloscope and a loudspeaker. For recording and analysis, the filtered neurogram was fed through a resistance-capacitance integrating network (time constant, 0.1 sec) to obtain a mean voltage display of the neural activity.

There were three criteria for an acceptable recording of MSNA. First, weak electrical stimulation (1 to 3 V; 0.2 msec; 1 Hz) through the electrode in the peroneal nerve elicited involuntary muscle contraction (muscle nerve fascicle) but not paresthesia (cutaneous nerve fascicle). Second, tapping or stretching the muscles or tendons supplied by the impaled fascicle elicited afferent mechanoreceptor discharges, whereas stroking the skin in the distribution of the peroneal nerve did not evoke afferent discharges. Third, the neurogram revealed spontaneous, intermittent, pulse-synchronous bursts that increased during held expiration and phases 2 and 3 of a Valsalva maneuver, characteristic of MSNA. Evidence that such activity represents efferent sympathetic activity has been provided by earlier studies and includes (1) interruption of the activity by local nerve block proximal but not distal to the recording site, (2) elimination of the activity by ganglionic blockade, and (3) conduction velocity approximating 1 m/sec.16, 17 Neurograms that revealed spontaneous activity characteristic of cutaneous sympathetic activity were not accepted. Inadvertent contraction of the leg muscles adjacent to the recording electrode produces electromyographic activity, which causes a sudden rise in baseline noise level on the mean voltage neurogram and produces a characteristic repetitive firing that is evident on both the filtered neurogram and the audio display. These electromyographic artifacts were readily distinguished from sympathetic bursts. Resting nerve activity was measured for 6 to 10 min before the experiments were begun to ensure that a stable baseline level of nerve activity had been obtained.

Sympathetic bursts were identified by inspection of the mean voltage neurogram and expressed as bursts per minute (burst frequency). Individual burst amplitude was measured and total MSNA was calculated as the total sum of burst amplitudes per minute and expressed as arbitrary units. Prior studies in our laboratory have determined an intraobserver variability in identifying bursts of 5%, with an interobserver variability of less than 10% in this expression of MSNA.18

Protocol. The subjects were familiarized with the techniques and procedures before the study began. A 20 min rest period followed the insertion of all intravenous catheters and the location of a satisfactory recording site for MSNA. In all subjects, control measurements of SAP, MAP, CVP, heart rate, and MSNA were recorded over a continuous 3 min period.

In group I subjects, after control measurements were obtained, incremental intravenous doses of PE were administered until a steady-state dose was identified that produced a discernible attenuation of MSNA. Repeat measurements of all variables were then obtained over a consecutive 3 minute period of infusion of PE alone (combined CBR and ABR activation). Imme-

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TABLE 1

does to the sustained infusion of PE alone and during superimposed NP

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>SAP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>HR (bpm)</th>
<th>MSNA (bursts/min)</th>
</tr>
</thead>
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<tr>
<td></td>
<td>C</td>
<td>PE</td>
<td>PE/NP</td>
<td>C</td>
</tr>
<tr>
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<td>124.6</td>
<td>133.3</td>
<td>137.3</td>
<td>96.0</td>
</tr>
<tr>
<td>2</td>
<td>136.7</td>
<td>140.7</td>
<td>144.0</td>
<td>86.0</td>
</tr>
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<td>114.7</td>
<td>125.3</td>
<td>131.3</td>
<td>81.3</td>
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</tr>
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<td>123.3</td>
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<td>87.3</td>
</tr>
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<td>135.7</td>
<td>146.0</td>
<td>96.0</td>
</tr>
<tr>
<td>8</td>
<td>137.3</td>
<td>142.6</td>
<td>148.0</td>
<td>94.0</td>
</tr>
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<td>Mean</td>
<td>123.2</td>
<td>131.0</td>
<td>136.9</td>
<td>87.2</td>
</tr>
</tbody>
</table>

± SEM: ± 3.7 ± 3.5^A ± 3.6^B ± 2.8 ± 2.9^A ± 2.9^B ± 3.4 ± 3.3^A ± 2.0 ± 2.8 ± 1.9^A ± 1.4^A

C = control; HR = heart rate; NP/dMAP = ratio of external NP applied to PE-induced change in MAP.

^p < .01 vs control; °p < .01 PE vs PE/NP.

alization of the MAP as a guide and was maintained at a level that would more than compensate for the increased transmural carotid pressure. This allowed for either activation of the ABR alone, or perhaps in some individuals, activation of ABR and minimal deactivation of the CBR. The increase in MAP over the control value during infusion of PE with superimposed application of NP averaged 13.9 ± 1.2 mm Hg, while the level of NP applied was 21.2 ± 2.0 mm Hg, resulting in a NP change in MAP ratio of 1.6 ± 0.1. This level of NP should have been adequate to compensate for the increased carotid sinus distending pressure, taking into account the incomplete transmission of NP in human subjects.19

Figures 1 and 2 and table 1 summarize the responses of the group I subjects to continued infusion of PE with superimposed application of NP. During combined PE and NP, SAP increased further to 136.9 ± 3.6 mm Hg (p < .01 vs control or PE alone) and MAP increased further to 101.2 ± 2.9 mm Hg (p < .01 vs control or PE alone). This was associated with a return of heart rate to control levels = 62.9 ± 2.0 beats/min (p = NS vs control, p < .01 vs PE). Again, CVP was held constant by application of graded levels of LBNP (CVP during combined PE and NP = 3.1 ± 1.1 mm Hg, p = NS vs control or PE). During this combined infusion of PE and application of NP, MSNA tended to be further inhibited with MSNA burst frequency = 7.9 ± 1.4 bursts/min (p < .01 vs control) and total MSNA = 48.6 ± 9.2 units (p < .01 vs control), but the decrease was not statistically significantly greater during combined PE and NP than during PE alone (figure 2).

Figure 3 shows portions of the recordings from subject 4 during control, PE, and PE plus superimposed NP intervention periods. PE infusion (combined ABR

**FIGURE 1.** Hemodynamic effects of combined ABR and CBR stimulation produced by steady-state infusion of PE alone versus activation of aortic baroreceptors alone during continued infusion of PE with superimposed application of NP (PE+NP). There were significant increases in both systolic and mean arterial pressures from control to PE, and from PE to PE+NP interventions. Heart rate decreased significantly during PE, but returned to baseline levels during combined PE+NP. CVP was maintained constant throughout by application of LBNP during infusion of PE. Values are mean ± SEM for n = 8. C = control. *p < .01 vs control; °p < .01 PE vs PE plus NP.

**FIGURE 2.** MSNA responses to combined ABR and CBR stimulation produced by steady-state infusion of PE alone versus during selective activation of ABR produced by continued infusion of PE with superimposed NP (PE+NP). There was a marked attenuation of MSNA during combined stimulation of the arterial baroreceptors, which was not different from that during stimulation of the ABR alone. Values are mean ± SEM for n = 8. C = control. *p < .01 vs control.
and CBR stimulation) increased MAP from 74 to 80 mm Hg, with a resultant decrease in heart rate from 62 to 52 beats/min and a marked attenuation of MSNA from 505 to 141 units/min. CVP was maintained constant at 7.0 mm Hg with application of low levels of LBNP. With the superimposition of NP during continued infusion of PE (ABR activation, CBR negation, or deactivation), MAP increased to 90 mm Hg, heart rate was 55 beats/min, and MSNA remained markedly attenuated at 55 units/min.

Responses to neck suction (CBR activation with possible ABR deactivation). The hemodynamic and MSNA responses of group II subjects to application of external NS are summarized in table 2 and figures 4 and 5. NS was applied at levels of \(-17.5 \pm 1.3\) mm Hg. This decreased MAP from 83.9 \pm 2.7 to 78.7 \pm 3.5 mm Hg (p<.01) and tended to decrease SAP. NS was associated with a tendency for a decrease in heart rate from 62.0 \pm 2.0 to 58.2 \pm 2.3 beats/min (p = .05), while CVP remained constant (CVP = 2.0 \pm 0.4 before vs 2.2 \pm 0.5 mm Hg during NS, p = NS). As seen in figure 4, despite the activation of the CBR (as evidenced by the fall in MAP and heart rate after application of NS), there was no significant change in MSNA. MSNA burst activity was 19.9 \pm 2.9 bursts/min before vs 17.3 \pm 2.0 bursts/min during NS (p = NS). Similarly, total MSNA activity was 188.9 \pm 50.1 units before vs 168.3 \pm 44.3 units during NS (p = NS).

Discussion

In these studies, we used experimental strategies to allow selective and combined activation of the aortic and carotid arterial baroreceptors to determine their relative influence on the control of efferent sympathetic nerve activity and heart rate during steady-state elevation of arterial pressure in normal human subjects. From these studies, we conclude the following: (1) the aortic baroreflex exerts the dominant arterial baroreflex role on inhibition of MSNA during elevation of blood pressure in normal man and (2) the carotid baroreflex appears to be important in reflex cardiac slowing after steady-state increases in arterial pressure. These findings emphasize the dissociation of arterial baroreflex control of heart rate and MSNA in humans.

The discussion focuses on the following topics: (1) the unique aspects of the experimental design, (2) evidence for ABR dominance on control of MSNA responses to elevation of arterial pressure, (3) relative role of ABR and CBR in control of heart rate and MSNA, and (4) potential limitations of the study.

Experimental design. The most common approach to the study of arterial baroreflex control of the circulation in humans has been to alter arterial pressure with vasoactive pharmacologic agents and observe the resulting reflex changes in heart rate and vascular resis-
TABLE 2
Hemodynamic and MSNA responses to sustained NS

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>SAP (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>HR (bpm)</th>
<th>MSNA (bursts/min)</th>
<th>MSNA (units)</th>
<th>NS level (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>NS</td>
<td>C</td>
<td>NS</td>
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<td>NS</td>
</tr>
<tr>
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<td>84.7</td>
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<td>68.3</td>
</tr>
<tr>
<td>9</td>
<td>108.7</td>
<td>106.0</td>
<td>90.0</td>
<td>87.3</td>
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</tr>
<tr>
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<td>106.7</td>
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<td>58.0</td>
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<td>11</td>
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<td>12</td>
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<td>88.0</td>
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</tbody>
</table>

Mean ± SEM: ±3.6 ±2.8 ±2.7 ±3.5 ±2.0 ±2.3 ±2.9 ±2.0 ±50.1 ±44.3 ±1.3

Abbreviations are as in table 1.

*p < .01 vs control.

The heart rate changes are known to be due primarily to parasympathetic efferent mechanisms, while the vascular responses are believed to be due to alteration in efferent sympathetic tone. However, since many of these vasoactive agents have direct vascular effects on peripheral organ beds, extrapolation of findings related to changes in vascular resistance to the presumed underlying mechanism of changes in sympathetic efferent tone are potentially misleading. In addition, it has been clearly shown in both animal and human studies that reflex changes in heart rate cannot be used as a reliable index of baroreflex-mediated changes in control of the total circulation. A distinct advantage of the present study is the utilization of microneurography to directly measure efferent MSNA and thus allow simultaneous study of heart rate and MSNA responses to selective perturbations of the arterial baroreceptors.

The strategy used in these studies was to compare MSNA and heart rate responses to combined versus selective activation of the ABR and CBR. Combined activation of these two arterial mechanoreceptors was achieved by producing steady-state elevation of arterial pressure by intravenous infusion of the vasopressor PE. Evidence that we achieved effective arterial baroreflex activation is shown by the significant decrease in heart rate and MSNA after the PE-induced increase in arterial pressure. Following this, we employed the use of superimposed sustained external NP to negate the increase in carotid sinus distending pressure, thereby allowing selective stimulation of the aortic baroreceptors alone.

To achieve this negation of CBR activation during continued PE infusion, we used a modified neck chamber apparatus that has been described previously. Since this method of the use of alterations in pnuematic pressure within a sealed neck chamber surrounding the neck was first described by Ernsting and Parry, the neck chamber technique has been systematically evaluated with regard to the quality and quantity of pressure transmission to the region of the carotid sinus in human subjects. Kober and Arndt have shown that positive NP results in a reduction of diameter of the common
carotid arteries, thus validating the premise on which the technique is based. Eckberg and Ludbrook and their colleagues\textsuperscript{14, 19} have shown that application of positive external NP is transmitted to the internal jugular vein (a vessel adjacent to the carotid artery) with negligible delay. However, it is thought that this transmission is not perfect. Using a catheter inserted percutaneously into the tissues of the neck immediately surrounding the carotid sheath, Ludbrook et al.\textsuperscript{19} showed that the tissue pressure varied in a reliable and linear fashion with the level of externally applied NP. They found that 86 ± 2% of applied NP was transmitted to the pericarotid region and that pressure transmission was independent of the shape or thickness of the subject’s neck. Assuming 86 ± 2% transmission of external NP, one would calculate that to achieve the desired negation of CBR activation during PE infusion in our studies, a level of NP would need to be applied that equals 1.2 times the elevation of arterial pressure over control levels. In these studies, we used a neck pressure apparatus somewhat different from that studied by Ludbrook, and therefore applied NP at an average level that equaled 1.6 times the increase in MAP. We believe that we may safely assume that the activation of CBR was successfully negated at this level of NP. This assumption is supported by the finding that arterial pressure increased after the application of NP due to a deactivation of the CBR. Since the exact level of pressure transmission to the carotid sinus was not known precisely in these subjects (due to limitations of invasive studies in human subjects) we may have either completely negated the PE-induced activation of the CBR or actually achieved deactivation of the CBR with the combination of PE and superimposed NP. In either case, the ABR were being selectively activated and therefore the conclusions from this study remain intact.

Evidence for aortic baroreflex dominance in control of MSNA. The finding of a relative dominance of the aortic baroreflex as compared with the carotid sinus baroreflex in control of MSNA after elevation of arterial pressure derives from observations in both group I and group II subjects. In group I subjects, infusion of PE resulted in an increase in arterial pressure, with consequent stimulation of both ABR and CBR. In response to this stimulation, there was a significant decrease in both heart rate and MSNA. This attenuation of heart rate and MSNA could have resulted from an increased tonic inhibitory influence on the brainstem vasomotor centers of the CBR, the ABR, or a combination of the enhanced inhibition of both sets of afferent reflex pathways. Subsequently, superimposition of NP at levels greater than the increase in arterial pressure was used to negate the influence of the CBR. Because the level of NP applied in group I subjects was likely of a magnitude to more than compensate for the total increase in carotid transmural pressure during PE infusion with superimposed NP, we suspect that the CBR were likely partially deactivated as compared with under control conditions. In other words, under the experimental condition of PE plus NP, the group I subjects’ CBR and ABR were exposed to disparate stimuli (CBR-hypotension, ABR-hypertension). This is supported by the finding of a continued increase in arterial pressure during the application of NP. Despite this presumed CBR negation or deactivation, which would have been expected to result in an increase in efferent sympathetic tone, MSNA remained significantly attenuated during this phase of the experiment. These findings are consistent with a dominant influence of the aortic baroreflex over that of the carotid baroreflex on the regulation of MSNA responses to elevation of arterial pressure. Such a response is in accordance with other studies in human subjects by Bath et al.\textsuperscript{13} In those studies, application of sinusoidal NS at cycle lengths of 30 sec duration resulted in changes in carotid transmural pressure (CBR activation) that were almost completely out of phase with changes in arterial pressure (ABR activation). Under those circumstances, it was found that MSNA correlated better with arterial (i.e., aortic) than with carotid transmural pressure. Bath et al.\textsuperscript{13} concluded that the ABR had significant control over MSNA at normal levels of arterial pressure in man and that the ABR influence predominated over that of the CBR.

Similarly, the studies reported here in group II subjects with application of sustained NS also support a dominating role of the ABR on control of MSNA. In these experiments, application of NS was used to selectively activate the CBR by increasing the carotid transmural distending pressure. The resultant small but significant fall in MAP supports CBR activation and also likely resulted in partial ABR deactivation. However, despite CBR activation this external application of NS was not associated with any significant change in MSNA. Thus, direct activation of the carotid baroreflex, while causing a decrease in heart rate, did not attenuate efferent sympathetic nerve responses in these normal subjects. We suggest that this was due to a deactivation of the dominant ABR, with compensatory maintenance of MSNA at control levels.

In the studies involving group II subjects, we used relatively low levels of NS in an effort to match the increase in MAP obtained during the combined PE and NP interventions in group I subjects. Other investiga-
tors, using higher levels of NS, have also failed to see a sustained inhibition of MSNA in normal human subjects.\textsuperscript{13, 23}

**Relative roles of ABR and CBR in control of heart rate and MSNA responses.** Animal and limited human studies to date have suggested that the ABR and CBR may have different roles in the control of heart rate and peripheral vascular resistance in response to changes in arterial pressure. In animals, studies that have examined the relative influence of CBR versus ABR on heart rate during changes in arterial pressure have been contradictory. Vatner et al.\textsuperscript{6} suggested from studies in awake dogs that the ABR were more effective than the CBR in controlling heart rate. Similar findings in the dog were reported by Ito and Scher,\textsuperscript{7, 8} whose chronic denervation experiments suggested that reflex heart rate responses are impaired to a greater extent by aortic baroreflex denervation than by carotid denervation. In contrast, Guo et al.\textsuperscript{9} have shown that the CBR and ABR exert similar degrees of vagally mediated heart rate control in anesthetized rabbits during PE-induced hypertension. Furthermore, their studies suggested that there was essentially no redundancy of carotid and aortic baroreceptor afferents with regard to activation of vagal neurons, but that there was essentially “total redundancy” of these arterial baroreceptors with respect to inhibition of sympathetic efferent neurons. The picture is complicated by the suggestion of Kendrick et al.\textsuperscript{10} that there is a mutual facilitatory interaction of carotid and aortic baroreflexes in the control of heart rate in the dog. They showed that combined stimulation of both ipsilateral aortic and carotid sinus nerves resulted in cardiac slowing that was significantly greater than the respective sum of the responses to separate stimulation of these nerves.

Prior studies in man have demonstrated that the carotid baroreflexes contribute importantly to the control of heart rate.\textsuperscript{21, 24–27} Recent studies by Mancia et al.\textsuperscript{12} suggested that the extracarotid baroreflexes, presumably aortic, played a more important role than the carotid baroreflexes on heart rate control. Similarly, recent studies from our laboratory\textsuperscript{11} indicate that while both the carotid and aortic baroreflexes appear to participate in heart rate control during dynamic and steady-state elevation of arterial pressure, the aortic baroreflexes appear to have the greater role in control of heart rate during dynamic increases in blood pressure.

There is increasing evidence from studies in both animals and humans that a dissociation sometimes exists between arterial baroreflex control of heart rate and that of vascular resistance after alterations in arterial pressure.\textsuperscript{9, 11, 12} Therefore, one cannot assume that alterations in control of heart rate are paralleled by alterations in control of efferent sympathetic tone to the peripheral vasculature. The present study in normal humans supports this concept of a dissociation between arterial baroreflex control of heart rate and MSNA. Heart rate responses to elevation of arterial pressure are primarily a parasympathetic efferent response, while vascular responses are primarily mediated by sympathetic efferent mechanisms. In our subjects, the profound attenuation of MSNA seen during PE-induced hypertension (combined CBR and ABR activation) was maintained during deactivation of the CBR with the superimposition of NP. In contrast, the reflex bradycardiac response to PE infusion was abolished when CBR stimulation was eliminated.

The studies using NS are also consistent with this concept. If the incomplete transmission of externally applied NS (approximately 64%) to the carotid sinus is taken into account,\textsuperscript{19} the stimulus to the CBR during NS (–17.5 ± 1.3 mm Hg) in group II subjects was similar to the CBR stimulation during infusion of PE (increase in MAP = 7.6 ± 1.0 mm Hg) in group I subjects. During NS, MAP and heart rate decreased, consistent with CBR activation. However MSNA did not change during NS, in contrast to the profound attenuation of MSNA during the infusion of PE. ABR stimulation during NS was presumably unchanged or slightly decreased, while during PE the ABR were being activated along with the CBR. Thus, CBR stimulation alone resulted in reflex bradycardia but had no significant effect on inhibition of MSNA, probably due to the opposing influence of the ABR. Wallin and Eckberg\textsuperscript{22} have shown inhibition of MSNA with application of NS at –30 mm Hg, but this effect is very transient. The brevity in sympathetic responses to sustained CBR stimulation may be due to central adaptation to baroreceptor input,\textsuperscript{28} but is more likely secondary to the associated decrease in arterial pressure with resultant ABR deactivation. Although our subjects were subjected to lower levels of NS, they tended to have decreased levels of MSNA during the first minute compared with the third and this was associated with a progressive decrease in arterial pressure over the 3 min. While the sympathetic responses to NS in Wallin’s study were transient (1 to 2 sec), the reflex bradycardia showed minimal adaptation and in our subjects the relative slowing of heart rate was maintained throughout NS.

**Potential limitations of the study.** Several potential limitations in the design and interpretation of this study are recognized. First, the increases in arterial pressure produced by PE were only of a moderate degree, rang-
ing from 4 to 14 mm Hg. We were constrained from producing larger increases in pressure by a concern about producing pronounced bradycardia in these normal young subjects. Nevertheless, this degree of elevation of blood pressure was adequate to produce prompt and reproducible changes in MSNA and heart rate. It is, however, possible that the relative influence of the CBR and ABR on these responses might be different at higher levels of blood pressure.

A second caution that must be applied in the interpretation of these data is that all studies were performed in subjects in the supine position. This was necessitated by the inability to achieve adequate fitting of the neck collar in upright subjects. In addition, we wished to minimize the possibility that alterations in cardiac filling pressure, and resultant changes in cardiopulmonary baroreceptor influences, would alter the observations on the arterial baroreflex mechanisms (see below). We cannot exclude the possibility that differences in arterial hydrodynamics in the upright position might produce a different balance between the carotid and aortic baroreflex influence on MSNA and heart rate control.

A third caution relates to the potential for the cardiopulmonary baroreceptors, another group of tonically active inhibitory mechanoreceptors, to have been influenced by the techniques used in these studies. In particular, we were concerned that the administration of the vasopressor PE, by nature of its α-adrenoceptor-mediated effects on both resistance and capacitance vessels, might increase cardiac filling pressure as well as ventricular systolic pressure. Cardiac preload is the predominant determinant of the activity of these cardiopulmonary receptors, while ventricular systolic pressure is also of some importance. Therefore, we used the gradual application of LBNP to maintain central venous pressure at control levels throughout all phases of the experiments. In studies of sinoaortic denervated rabbits, Guo et al. found that administration of PE did not appear to engage cardiac vagal afferents until the PE produced very marked increases in systolic pressure. In our studies, the increase in arterial pressure only ranged from 4 to 14 mm Hg. Likewise, a recent study in our laboratory of a patient with sinoaortic denervation but preserved cardiopulmonary afferent responses demonstrated no attenuation of MSNA responses during the infusion of PE. We believe, therefore, that cardiopulmonary baroreceptor activity was most likely not altered by the experimental interventions used in these studies. A fourth concern relates to the lack of precise quantitation of the level of carotid sinus transmural pressure during the various phases of the experiments due to a lack of knowledge regarding precise pressure transmission characteristics of the neck collar used in these experiments. This results from constraints on human experimentation, preventing us from detailed analysis of pressure transmission through the neck tissues down to and within the carotid sheath. However, by extrapolating from the studies of a similar pneumatic neck device used by other investigators, we believe that we have achieved reasonable levels of both NP and NS to alter the CBR, as detailed in the discussion above.

Because of the limitations imposed by studies in intact human subjects, we were unable to selectively activate the carotid baroreceptors during infusion of PE in a manner analogous to the selective activation of the aortic baroreceptors during PE with superimposed NP. However, we believe the carotid baroreceptors were selectively activated during the NS protocol, which would not be associated with activation of aortic baroreceptors. However, even this activation of the carotid baroreceptors alone failed to inhibit MSNA.

Finally, in the performance of these studies we have used recordings of efferent sympathetic nerve activity from only one site, the peroneal nerve. It is known that there are profound differences in the control of sympathetic nerve activity to various tissue and vascular beds. Nonetheless, in normal subjects, spontaneously occurring fluctuations in muscle sympathetic activity are similar in different extremity nerves. In these studies, all MSNA responses were compared with a stable control recording of MSNA. Thus, while we cannot generalize to total or other organ-specific sympathetic responses, the intradividual comparisons of peroneal MSNA responses remain valid.

In summary, using experimental strategies to selectively perturb the aortic and carotid sinus baroreflexes in normal man, we directly measured heart rate and efferent sympathetic nerve responses to assess the relative contribution of these two reflex pathways to cardiovascular mechanisms in normal human subjects. The results suggest that the aortic baroreflex is the dominant regulator of efferent sympathetic nerve responses to steady-state elevation of arterial pressure.

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Circulation. 1988;77:279-288
doi: 10.1161/01.CIR.77.2.279

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1988 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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