Relative contribution of aortic and carotid baroreflexes to heart rate control in man during steady state and dynamic increases in arterial pressure.

D W Ferguson, … , F M Abboud, A L Mark

J Clin Invest. 1985;76(6):2265-2274. https://doi.org/10.1172/JCI112236.

Research Article

We studied the contribution of carotid vs. extracarotid baroreceptors in control of heart rate in normal humans. We measured heart interval (HI) and arterial pressure during steady-state infusion of phenylephrine (PE). PE increased mean arterial pressure (MAP) by 13 +/- 2 mmHg (mean +/- SEM; n = 10) and thus stimulated both carotid and aortic baroreceptors. Neck pressure (NP) was applied during PE infusion to counter the increase in transmural carotid sinus pressure, thus leaving only aortic baroreceptors stimulated by the increase in arterial pressure. PE infusion alone prolonged HI by 230 +/- 24 ms (P less than 0.05). Application of NP attenuated the HI response to 65 +/- 22 ms above control (P less than 0.05 vs. PE alone). During these steady-state increases in arterial pressure, elimination of the carotid baroreflex contribution reduced the HI prolongation by 41-70% in five subjects and by greater than 93% in five subjects. We also measured the HI response to dynamic ramp elevation of systolic arterial pressure (SAP) using bolus administrations of PE. Baroreflex control was calculated from the slope of the regression correlating SAP to succeeding HI for PE alone (carotid and aortic baroreceptor activation) and for PE plus superimposed dynamic NP at levels equal to the increases in SAP (aortic baroreceptor activation). During PE alone, the baroreflex slope was 20.2 +/- […]

Relative Contribution of Aortic and Carotid Baroreflexes to Heart Rate Control in Man during Steady State and Dynamic Increases in Arterial Pressure

David W. Ferguson, Francois M. Abboud, and Allyn L. Mark
Cardiovascular Center and Department of Internal Medicine, College of Medicine, University of Iowa Hospitals and Clinics, and Veterans Administration Medical Center, Iowa City, Iowa 52242

Abstract

We studied the contribution of carotid vs. extracarotid baroreceptors in control of heart rate in normal humans. We measured heart interval (HI) and arterial pressure during steady-state infusion of phenylephrine (PE). PE increased mean arterial pressure (MAP) by 13±2 mmHg (mean±SEM; $n = 10$) and thus stimulated both carotid and aortic baroreceptors. Neck pressure (NP) was applied during PE infusion to counter the increase in transmural carotid sinus pressure, thus leaving only aortic baroreceptors stimulated by the increase in arterial pressure. PE infusion alone prolonged HI by 230±24 ms ($P < 0.05$). Application of NP attenuated the HI response to 65±22 ms above control ($P < 0.05$ vs. PE alone). During these steady-state increases in arterial pressure, elimination of the carotid baroreflex contribution reduced the HI prolongation by 41–70% in five subjects and by >93% in five subjects.

We also measured the HI response to dynamic ramp elevation of systolic arterial pressure (SAP) using bolus administrations of PE. Baroreflex control was calculated from the slope of the regression correlating SAP to succeeding HI for PE alone (carotid and aortic baroreceptor activation) and for PE plus superimposed dynamic NP at levels equal to the increases in SAP (aortic baroreceptor activation). During PE alone, the baroreflex slope was 20.2±2.9 ms/mmHg ($n = 10$). During PE plus NP, the baroreflex slope was reduced by 30% to 14.1±2.8 ms/mmHg ($P < 0.02$ vs. during PE alone). Thus, during dynamic increases in arterial pressure, eliminating the carotid baroreflex contribution reduced the HI response by 30%.

These studies indicate that extracarotid (presumably aortic) and carotid baroreflexes both participate in control of heart rate in humans. Extracarotid (aortic) baroreflexes appear to have the greater role in control of heart rate during dynamic increases in arterial pressure.

Introduction

Arterial baroreflexes exert an important control on heart rate during changes in arterial pressure. The afferent limb of these reflexes originates in the aortic and carotid sinus regions. In animals, studies that have examined the relative influence of carotid vs. aortic baroreceptors on heart rate during changes in arterial pressure have been contradictory. Vatner et al. (1) suggested from studies in awake dogs that the aortic baroreceptors were more effective than the carotid baroreceptors in controlling heart rate. Similar findings in the dog were reported by Ito and Scher (2, 3) in which 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. (4) have shown the carotid and aortic baroreceptors exert similar degrees of vagally mediated heart rate control in anesthetized rabbits during phenylephrine (PE)–induced[1] 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. (5) 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 (6–10). However, the role of the aortic baroreflexes in man remains unclear. Studies by Abboud et al. (10) indicated that during systemic hypotension caused by pooling of blood in the lower extremities, activation of carotid baroreceptors with neck suction eliminates the reflex tachycardia, which suggests a significant influence of the carotid baroreflexes on heart rate control. However, Mancia et al. (11) have recently suggested that the extracarotid baroreflexes play a more important role than the carotid baroreflexes in control of heart rate in man. The relative contribution of aortic and carotid baroreceptors to control of heart rate in man thus remains unclear, this lack of clarity being due in part to the inability to selectively perturb the aortic baroreceptors in human subjects.

We have recently devised strategies to differentiate the effect of stimulating the carotid and extracarotid baroreceptors in man from that of stimulating the extracarotid receptors alone. We believe it reasonable to assume that the extracarotid receptors stimulated are primarily, if not solely, the aortic arch baroreceptors. Using these approaches, we evaluated the relative contribution of carotid and aortic baroreflexes on control of heart

Dr. Ferguson's present address is University of Vermont College of Medicine, Division of Cardiology, Medical Center Hospital of Vermont, Burlington, VT 05401. Address reprint requests to Dr. Ferguson, or to Dr. Mark, Department of Internal Medicine, Cardiovascular Division, University of Iowa Hospitals, Iowa City, IO 52242.

Received for publication 1 August 1984 and in revised form 28 June 1985.

J. Clin. Invest.

0021-9738/85/12/2265/10 $1.00
Volume 76, December 1985, 2265–2274

1. *Abbreviations used in this paper:* HI, heart interval; MAP, mean arterial pressure; NP, neck chamber pressure; PE, phenylephrine; SAP, systolic arterial pressure.

rate during both steady-state and dynamic increases of arterial pressure.

Methods

Subjects

20 healthy male subjects, age 20–33 yr, were studied without sedation in the supine postabsorptive state. All subjects were free of cardiovascular disease based on a medical history and physical examination and were not receiving any medication. Written informed consent was obtained from all subjects before the study and the protocol was approved by the Human Subjects Review Committee of the University of Iowa.

Measurements

A direct-writing physiologic recorder was used to simultaneously record heart interval (HI), arterial pressure, respiratory activity, and neck chamber pressure (NP). HI (R-R interval) and rhythm were obtained from an electrocardiogram that was monitored continuously with lead selection chosen so that the P or atrial wave and QRS or ventricular complex were clearly defined. All subjects remained in sinus rhythm with a fairly constant R-R interval. HI was measured in milliseconds between consecutive R wave peaks with the recording performed at a paper speed of 25 mm/s. Control values for HI were taken as the average of three consecutive cardiac cycles immediately preceding the onset of a stimulus. Systemic arterial pressure was measured directly with a Statham P23ID pressure transducer through an indwelling arterial catheter inserted percutaneously under local anesthesia (1% Xylocaine, 0.5 ml) in the left brachial or radial artery of each subject. Systolic arterial pressure (SAP) and diastolic arterial pressure were obtained directly and the mean arterial pressure (MAP) was calculated as diastolic plus one-third pulse pressure in mmHg. Respirations were timed with a strain gauge pneumograph applied lightly over the lower thoracic cage. The level of NP was measured in mmHg by a Statham P23ID pressure transducer inserted into the malleable neck collar.

Procedures for changing pressure at arterial baroreceptors

Two experimental procedures were employed in two series of experiments to evaluate arterial baroreceptor control of heart rate during steady state and then during dynamic (ramp) elevation of arterial pressure. Steady-state elevation of arterial pressure was employed in subjects 1–10 as shown schematically in Fig. 1. In the control state (Fig. 1, left panel), aortic and carotid baroreceptors are under the influence of the prevailing arterial pressure (X), resulting in the control HI. Steady-state infusion of the vasopressor agent phenylephrine (PE) (Fig. 1, middle panel) increases the arterial pressure and stimulates both carotid and aortic baroreceptors, which results in an increase in HI (braycardia). A steady-state increment in arterial pressure of 15 mmHg was maintained by continuous infusion of PE. During sustained administration of the pressor agent, brief-timed positive NP (designated "Y") was applied with the neck collar at a level of 1.2 times the incremental increase in MAP produced by the sustained infusion of PE, assuming an 86% transmission of the NP to the carotid region as described by Ludbrook et al. (12). This external pressure removed the transmural gradient across the carotid sinus wall produced by the PE-induced rise in arterial pressure and returned the carotid sinus distending pressure to normal, while the aortic transmural pressure remained elevated. This permitted study of the effects of selective stimulation of aortic baroreceptors on heart rate. By measuring the prolongation of HI produced by PE (carotid and aortic baroreflex stimulation) and then that produced by PE infusion plus superimposed NP (aortic baroreflex stimulation), we studied the relative contribution of the aortic vs. the carotid baroreflexes on heart rate control during steady-state elevation of arterial pressure.

Dynamic perturbation of arterial baroreceptors was performed in the next 10 subjects (Nos. 11–20) by acute administration of an intravenous bolus of PE. In the first part of these studies, each R-R interval, beginning with the rise of SAP folowing PE bolus, was plotted as a function of the preceding SAP. Three consecutive trials were performed for each subject

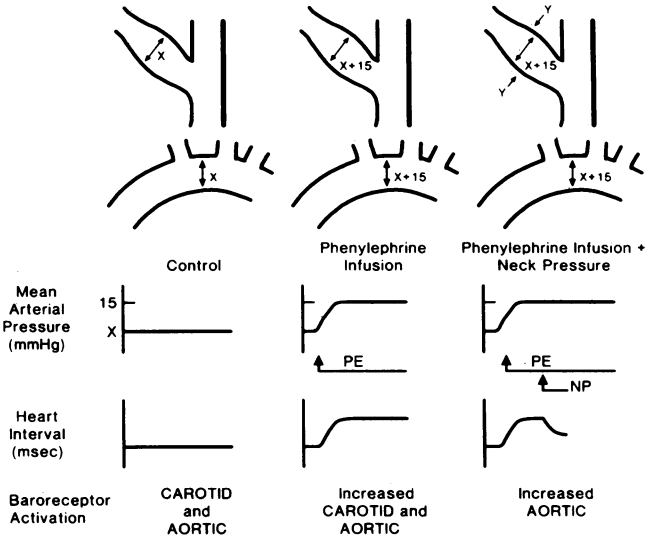

Figure 1. Schematic diagram of experimental strategy. (*Left*) Carotid and aortic baroreceptors under constant activation by prevailing level of arterial pressure (X) with resultant HI. (*Middle*) PE infusion increases arterial pressure by arbitrary 15 mmHg and increases activation of both carotid and aortic baroreceptors with resultant slowing of heart rate (increase in HI). (*Right*) Brief-timed NP applied at level (Y) to match increase in arterial pressure and prevent the increased activation of carotid baroreceptors. Thus, HI prolongation during PE plus NP reflects increased activation of aortic baroreceptors.

and the average values for each SAP and corresponding HI were correlated by using linear regression analysis. The baroreflex control of HI was expressed as the slope of this regression line (19). This slope was accepted for subsequent analysis only if the correlation coefficient was >0.80 and the P value <0.01. A 5-min recovery period followed each trial to allow a return to baseline state. In the second part of these experiments, ramp elevation of SAP was again produced by the same bolus dose injection of PE, but this time simultaneous application of NP was used to mimic the increase in SAP above control values. We were able to achieve nearly perfect correlation of NP level to change in SAP from control as expressed by the linear regression equation, $NP = -0.94 + 1.12 \times \Delta SAP_c$ ($r = 0.996$, $P < 0.001$), where NP equals the level of neck pressure and ΔSAP_c equals the change of systemic arterial pressure over control after PE intravenous bolus injection.

In both series of experiments, carotid baroreceptors were inhibited through the application of brief-timed NP applied with a malleable neck collar as previously described (13). NP was applied for 5–10 s during held end-expiration with the onset timed to occur 750–850 ms before the next anticipated P wave using the protocol of Eckberg (14). The subjects were taught to avoid a Valsalva maneuver during NP.

Protocol

Subjects 1–10 (steady-state protocol). The subjects were familiarized with the techniques and procedures before beginning the study. Baseline measurements of HI and arterial pressure were obtained under resting conditions. After this, a stimulus response relationship was derived for each subject for peak HI change during incremental levels of brief-timed NP at +5, +10, +15, +20, and +30 mmHg. HI responses to each level of NP was assessed four to five times consecutively and the average response was determined. There was a 2-min rest period between each level of NP. The subjects were then given gradually increasing doses of intravenous PE (Neo-Synephrine [Winthrop Laboratories, New York, NY]) via continuous infusion to increase arterial pressure and activate aortic and carotid baroreceptors. The dose ranged from 0.125 to 1.0 μg/kg per min (0.7±0.1, mean±SE) and was adjusted to increase MAP by ~10–20 mmHg until a bradycardia occurred. This dose was selected to be in

a range that is safe for human subjects. Heart rate slowed an average of 18% from 56 to 46 beats/min. Once the desired increment in MAP and the resulting bradycardia were achieved, a steady-state condition was obtained for at least 10 min and control HI and systemic arterial pressure again determined. Subsequently, during this sustained infusion of PE, the subjects again underwent incremental levels of brief-timed NP and maximal changes in HI were obtained and compared to the HI during PE infusion alone. Careful assessment of beat-to-beat arterial pressure was obtained during the application of NP.

Subjects 11–20 (dynamic protocol). In each of these subjects, bolus injections of PE were administered in 150–300-μg doses (205±22, mean±SE) and each R-R interval (HI), beginning with the rise of arterial pressure, was plotted as a function of the preceding SAP. Three consecutive trials were performed for each subject, the results averaged for SAP and HI, and an average baroreflex slope determined. This slope represented the collective influence of perturbation of both carotid and aortic baroreceptors. Subsequently, three more trials were performed with the same bolus dose of PE administered, and once SAP began to rise, simultaneous dynamic NP was applied at an increasing level to mimic the change in SAP from control. The control SAP was the average of the three systolic pressures before the onset of rise in pressure following PE administration. The NP was applied at a level equal to the change in SAP over control to negate the influence of this pressure change on the carotid baroreceptors. A second baroreflex slope was then determined for the average of these three trials that represented the influence of selective perturbation of aortic baroreceptors alone. Comparison of baroreflex slopes following PE bolus alone and PE bolus with superimposed dynamic NP were performed over the same range of SAP change.

Vehicle and time effects were assessed in subjects 11–20 by performance of two placebo trials in each subject using bolus administration of the vehicle (5% dextrose in water). No change in HI or SAP were observed during held expiration for the first 16 cardiac cycles following "onset" of placebo. All HI and SAP measurements mentioned above were therefore obtained during the first 13 cardiac cycles following the onset of rise in arterial pressure after PE bolus injection.

Statistical analysis

Baseline values of HI and systemic arterial pressure before and during sustained PE infusion were compared by paired *t* tests as were the responses of HI during steady-state PE infusion alone and combined with NP. Sequential comparisons of MAP, SAP, and HI before and on a beat-to-beat basis following application of brief-timed NP were performed by a two-way analysis of variance. Correlation of HI and SAP after bolus PE injection was performed by linear regression analysis. Values for SAP, HI, and baroreflex slope after PE bolus alone and after PE bolus plus dynamic NP were compared by paired *t* tests.

Data are presented in the text, tables, and figures as mean±SE. Statistical significance was defined as $P < 0.05$.

Results

Responses to NP (carotid baroreceptor inhibition) alone. The stimulus response relationship for graded levels of brief-timed NP in subjects 1–10 is shown in Fig. 2. A progressive shortening of HI occurred with increasing levels of NP from +5 to +30 mmHg ($n = 6$) (Fig. 2, left panel). The right panel of Fig. 2 demonstrates the time course of this HI response to brief-timed NP. The peak response in HI shortening occurred within the first three cardiac cycles following the application of NP. Thus, application of this stimulus resulted in a rapid graded decrease in HI.

Responses to steady-state PE infusion alone and during superimposed NP. Fig. 3 and Table I summarize the responses of subjects 1–10 to sustained intravenous infusions of PE. Steady-state infusion of PE increased MAP from 86.5±2.2 to 99.0±1.8 mmHg ($P < 0.05$) (see Table I), which was associated with a

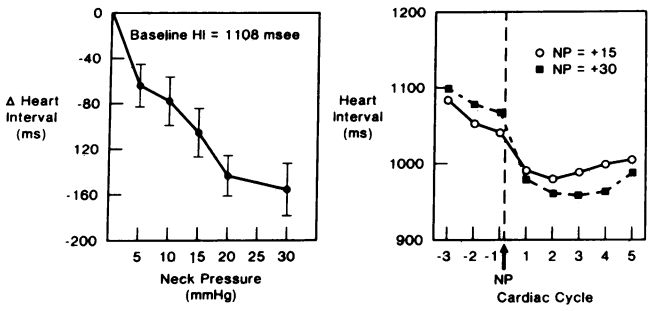

Figure 2. Responses to NP (carotid baroreceptor inhibition) alone. Increasing levels of NP result in progressive shortening of the HI (*left*). The peak response in HI occurred within two to three cardiac cycles following onset of the NP (*right*). Entries are mean±SE for $n = 6$ (*left*) and $n = 10$ (*right*). Base-line HI = 1,108 ms for data in left panel.

prolongation of HI from 1,068±58 to 1,297±69 ms ($P < 0.05$). This was an average gain in HI of 27.7 ms/mmHg increase in MAP. Fig. 3 shows the HI in the control state, during sustained infusions of PE, and then the peak change in HI produced by brief-timed NP applied during PE infusion.

NP was applied at 15.5±2.2 mmHg to counteract the 12.5±1.9 mmHg increase in MAP produced by PE. This resulted in an HI during NP superimposed on PE infusion of 1,133±55 ms ($P < 0.05$ was compared to HI during PE alone). This peak HI change occurred during the first three to four cardiac cycles after NP application, during which time there was no change in either SAP or MAP from levels during PE infusion alone (Fig. 4). As can be calculated from Table I, NP at a level assuming 86% transmission resulted in a partial reversal of the HI response to PE from ΔHI = 230±24 ms over control values to ΔHI = 65±22 ms. The percent reversal of the heart rate response when the carotid component was neutralized averaged 72% and ranged from 41 to 70% in five subjects and was >93% in five subjects (Table I).

If we assumed 100% transmission of NP to the carotid sinus region, the quantitative results were slightly different but qualitatively the same. Although not shown in Table I, application of NP at a level equivalent to the steady-state, PE-induced increase in arterial pressure (assuming 100% transmission) resulted in a ΔHI = 104±28 ms above control, compared to ΔHI = 230±24 ms above control during PE alone. This represents an average carotid baroreflex contribution of 55%.

Studies to determine if PE sensitized the carotid baroreflex. In six of the first 10 subjects, we measured responses to graded

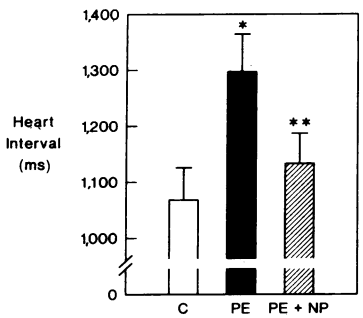

Figure 3. Responses to NP during steady-state PE infusion (subjects 1–10) (carotid and aortic baroreceptor stimulation) and during PE plus NP (aortic baroreceptor stimulation). HI was significantly prolonged during PE infusion PE over control (C) values. This prolongation was significantly attenuated during application of brief-timed NP. Entries are mean±SE for $n = 10$. *$P < 0.05$ PE vs. control; **$P < 0.05$ PE vs. PE + NP.

Table I. Mean Arterial Pressure and HI Responses to Steady-state PE Infusion Alone and during NP: Subjects 1–10

	Control		Steady-state PE alone					PE + NP				
Subject	MAP	HI	MAP	Δ MAP*	HI	Δ HI*	GAIN	HI	Δ HI*	GAIN	NP level	Gain ratio
	mmHg	*ms*	*mmHg*	*mmHg*	*ms*	*ms*	*ms/mmHg*	*ms*	*ms*	*ms/mmHg*		
1	74	956	95	+21	1,285	+329	15.7	1,150	+194	9.2	25	0.59
2	90	1,203	109	+19	1,386	+183	9.6	1,205	+2	0.1	25	0.01
3	92	1,115	99	+7	1,408	+293	41.9	1,250	+135	19.3	10	0.46
4	82	1,442	101	+19	1,671	+229	12.1	1,440	−2	0.0	20	0.00
5	89	1,218	96	+7	1,562	+344	49.1	1,235	+17	2.4	10	0.05
6	87	894	102	+15	998	+104	6.9	900	+6	0.4	15	0.06
7	97	909	106	+9	1,066	+157	17.4	920	+11	1.2	10	0.07
8	79	974	90	+11	1,160	+186	16.9	1,055	+81	7.4	15	0.44
9	83	868	96	+13	1,106	+238	18.3	940	+72	5.5	20	0.30
10	92	1,096	96	+4	1,332	+236	59.0	1,230	+134	33.5	5	0.57
Mean±SEM	86.5±2.2	1,067.5±57.8	99.0±1.8	+12.5±1.9	1,297.4±69.1	+229.9±24.1	24.7±5.8	1,132.5±55.4	+65.0±22.1	7.9±3.4	15.5±2.2	0.26±0.08

Gain ratio = ratio of gain (ms/mmHg) for PE plus NP to gain for neck pressure alone. * Change from control value.

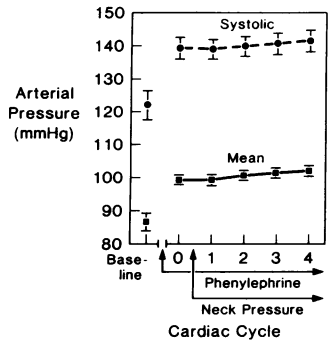

Figure 4. Response of arterial pressure to steady-state PE infusion and NP. PE infusion results in significant increase in both mean and systolic arterial pressure. There is no significant change in mean or systolic arterial pressure during the four cardiac cycles following onset of brief-timed NP. Entries are mean±SE for n = 8. C, control.

levels of NP in the control state and during sustained PE infusion to examine the possibility of sensitization of the baroreflex by PE. Fig. 5 summarizes these results. Baseline HI and MAP in the control state and during sustained infusions of PE were control HI = 1,104±6 ms and MAP = 88.3±0.6 mmHg and PE HI = 1,139±6 ms and MAP = 103.9±0.8 mmHg. During the application of graded levels of brief-timed NP there were similar degrees of attenutation of the HI in the control state and during PE. As can be seen from Fig. 5, the changes in HI under both control and PE conditions were linear in nature.

Responses to bolus PE alone and with superimposed dynamic NP pressure (dynamic study). Figs. 6 and 7 and Table II summarize the responses of subjects 11–20 to dynamic (ramp) elevation of arterial blood pressure after bolus intravenous injections of PE, both alone and during superimposed application of dynamic NP. After bolus injection of PE, SAP increased form 135.4±3.6 mmHg to 152.6±3.1 mmHg ($P < 0.001$) and HI prolonged from 1,067.3±49.9 to 1,370±69.7 ms ($P < 0.001$). The slope of arterial baroreflex control of HI after PE bolus alone was 20.2 ms/mmHg. In the second part of these studies, PE bolus was combined with dynamic NP applied during the increase in SAP. The increase in SAP with PE bolus injection plus NP was similar to that with PE alone, with SAP increasing from 136.7±3.8 mmHg to 153.2±3.2 mmHg ($P < 0.001$). HI increased from 1,108.7±53.2 to 1,317.0±77.9 ms ($P < 0.001$). The slope of the arterial baroreflex control of HI during PE bolus plus superimposed dynamic NP application was significantly attenuated to 14.1±2.8 ms/mmHg ($P < 0.02$ vs. slope after PE bolus alone). This overall represented a 30% reduction in baroreflex sensitivity.

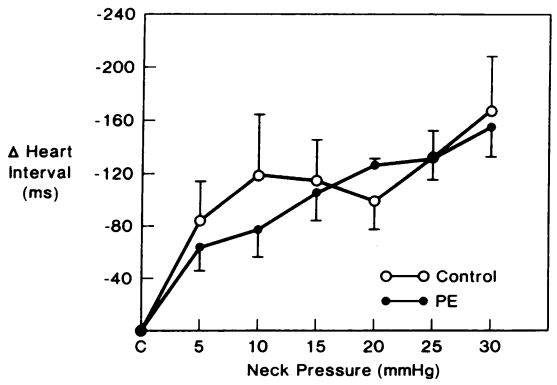

Figure 5. Effects of PE on HI responses to graded levels of NP. NP at graded levels produced HI attenuation that was not different before and during steady-state PE infusion. Entries are mean±SE for n = 6.

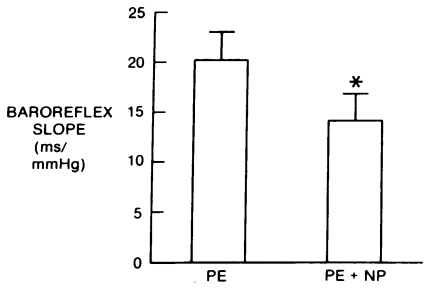

Figure 6. Baroreflex slope during bolus PE alone and during bolus PE with superimposed dynamic NP (subjects 11–20). The slope of the arterial baroreflex control of HI during PE bolus plus superimposed dynamic NP application (aortic baroreflex activation alone) was reduced by 30% over that during bolus PE alone (aortic and carotid baroreflex activation). Entries are mean±SE for n = 10. *$P < 0.02$.

Fig. 7 shows the recordings of one trial of the dynamic protocol in subject 11. Bolus administration of PE alone (Fig. 7, left panel) resulted in an increase in SAP from 145 to 164 mmHg with an increase in HI from 860 to 1,220 ms with a calculated baroreflex slope = 21.0 ms/mmHg (r = 0.99). During bolus PE plus superimposed dynamic NP (Fig. 7, right panel), SAP similarly increased from 143 to 165 mmHg, with an increase in HI from 920 to 1,140 ms. However, this activation of aortic baroreflexes alone was associated with a reduced baroreflex slope = 11.7 ms/mmHg (r = 0.97) in this subject.

Discussion

Using new experimental strategies, we were able to selectively perturb carotid and extracarotid (presumably aortic) baroreflexes in normal man. This study demonstrates that each of these afferent baroreflex pathways are involved in the control of heart rate during both steady-state and dynamic increases in arterial pressure. In particular, the findings provide strong evidence for an important role of the aortic baroreflex in the control of heart rate in man. Indeed, the results suggest that aortic baroreflexes may have a greater role than carotid baroreflexes in heart rate control during dynamic increases in arterial pressure in supine normal man.

The strategies and conclusions of the study involve several assumptions and considerations. The discussion will focus on seven points: first, transmission of the NP stimulus to the carotid sinus region; second, the possibility of sensitization of baroreceptors by PE; third, the possibility of altered stimulus to the aortic baroreceptors during NP; fourth, a comparison between steady-state vs. dynamic perturbation of baroreceptors; fifth, a discussion of the mechanisms of the heart rate responses to elevated arterial pressure; sixth, discussion of the mechanism of dissociation between effects of NP on HI and arterial pressure; and finally, potential limitations of the study.

NP transmission (carotid baroreceptor inhibition). The experimental strategy employed in this study relies on the use of NP to inhibit increased carotid baroreceptor activity during sustained and bolus PE administration, thus allowing selective perturbation of the aortic baroreceptors. We used a modified neck chamber apparatus as previously described (13). This chamber permits rapid initiation of NP at levels leading to a stimulus-related cardiac acceleration with the peak heart rate response occurring within two to three cardiac cycles following the onset of this brief-timed stimulus (Fig. 2).

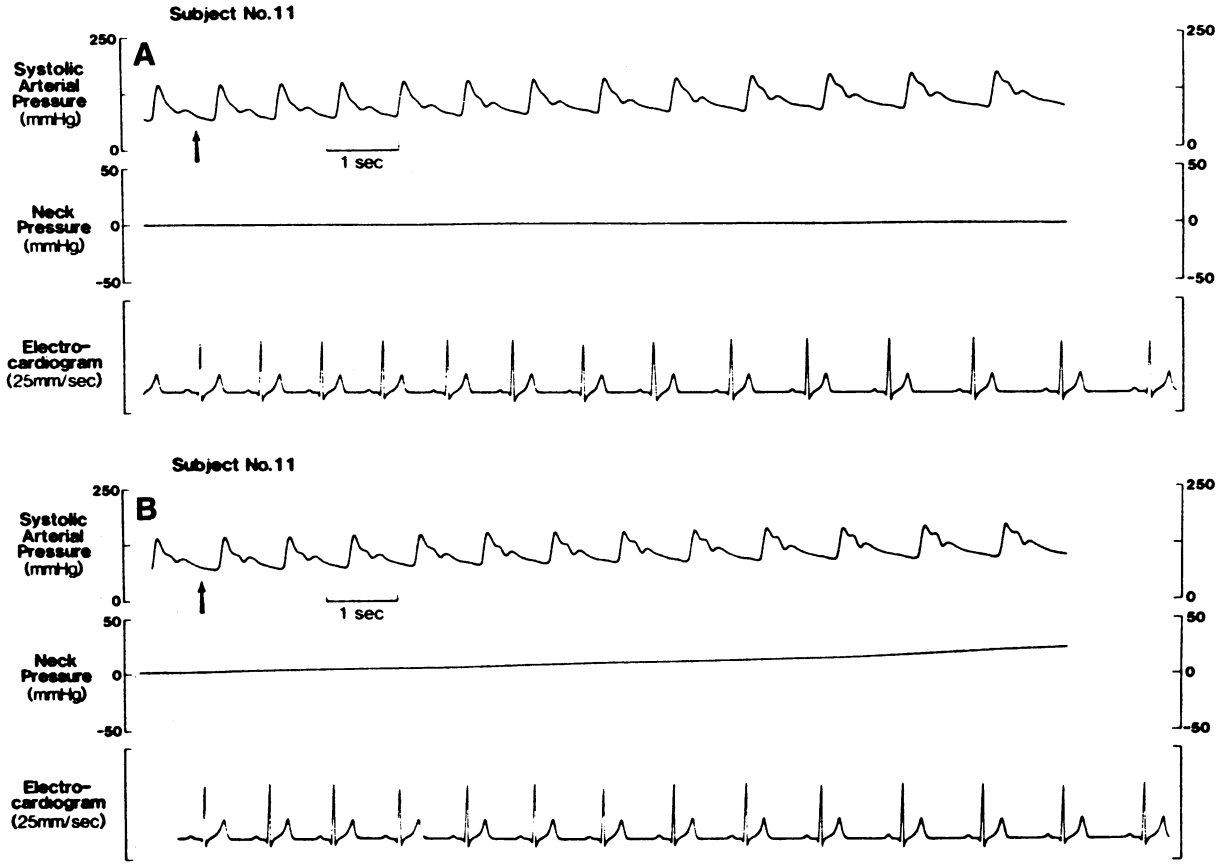

Figure 7. Hemodynamic recording of one trial of dynamic protocol for subject 11. (*A*) The changes in arterial pressure and HI (R-R interval) resulting from bolus administration of PE (onset of rise of arterial pressure indicated by arrow). Administration of 150 μg of PE resulted in an increase in systolic arterial pressure from 145 to 164 mmHg that produced an increase in HI from 860 to 1,220 ms with a baroreflex slope = 21.0 ms/mmHg (r = 0.99). (*B*) Responses during PE with superimposed dynamic NP. PE (150 μg bolus) increased systolic arterial pressure from 143 to 165 mmHg with a resultant increase in HI from 920 to 1,140 ms. This was a reduced baroreflex slope = 11.7 ms/mmHg (r = 0.97).

The neck chamber technique has been systematically evaluated in recent years with regard to the quality and quantity of pressure transmissions to the carotid sinus region. Kober and Arndt (16) have shown that positive NP results in reduction of diameter of the common carotid arteries, thus validating the premise on which the technique is based. Ludbrook et al. (12) and Eckberg et al. (13) have shown that NP changes were transmitted with negligible delay to the internal jugular vein (a vessel adjacent to the carotid artery). While the transmission of pressure to the carotid region was prompt and sustained throughout the stimulus, Ludbrook et al. (12) have shown that it is not perfect. Using catheter inserted percutaneously under local anesthesia into the tissue immediately outside the carotid sinus in human volunteers, these investigators showed that the tissue pressure varied in a reliable and linear fashion with the externally applied NP. They found that 86±2% of applied NP was transmitted to the pericarotid tissues. This transmission was found to be constant and similar amoung subjects regardless of the shape or thickness of their neck. Therefore, these investigators suggested that a sufficiently precise estimation of the stimulus applied to the carotid sinus areas could be obtained by estimating 86±2% pressure transmission.

The experimental design of this study was to elevate arterial pressure by two different mechanisms (steady-state infusion and bolus administration of PE) to achieve either steady-state or ramp elevation of arterial pressure. The influence of this increased arterial pressure on the carotid sinus baroreceptors would then be briefly negated by the application of brief-timed NP at a level equal to the steady-state elevation in MAP produced in subjects 1–10 or through a dynamic ramp application of NP equal to the change in SAP on a beat-by-beat basis in the dynamic portion of the protocol involving subjects 11–20. The design of our neck collar device is different from that used by Ludbrook et al. (12) and is similar to that designed by Eckberg (13), who assumes 100% transmission of neck suction to the carotid sinus region (14). In the steady-state model, we were able to apply NP at 1.2 times (assuming 86% transmission) and at 1.0 time (assuming 100% transmission) the MAP. Assuming 86% transmission, NP application during sustained elevation of MAP produced on average a 72% reversal in HI response (range 41–99%, Table I). Assuming 100% NP transmission, the carotid contribution was estimated at 55%. Thus, in the studies employing steady-state increases in arterial pressure, NP eliminated 55–72% of the HI prolongation produced by PE infusion.

Because of study design, in the experiments with ramp increase in arterial pressure (subjects 11–20) we attempted to match with dynamic application of NP the beat-by-beat change in SAP following PE bolus administration. Fortunately, we achieved

Table II. Systolic Arterial Pressure and HI Responses to Bolus PE Alone and during Dynamic NP: Subjects 11–20

		PE bolus alone					PE bolus plus NP				
		SAP		HI			SAP		HI		
Subject	PE bolus	Min	Max	Min	Max	Baroreflex slope	Min	Max	Min	Max	Baroreflex slope
	μg	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*ms/mmHg*	*mmHg*	*mmHg*	*mmHg*	*mmHg*	*ms/mmHg*
11	150	143.7	163.0	900.0	1,200.0	16.7	142.7	164.7	920.0	1,120.0	9.8
12	150	139.7	161.7	853.3	1,006.7	9.0	143.7	161.7	973.3	1,053.3	6.2
13	150	133.7	152.3	873.3	1,113.3	16.8	134.0	151.7	926.7	1,133.3	15.4
14	300	154.0	163.7	1,086.7	1,313.3	27.5	154.3	164.0	1,000.0	1,200.0	19.8
15	200	127.3	140.7	1,153.3	1,593.3	30.0	129.0	141.3	1,366.7	1,726.7	31.0
16	150	135.0	151.0	1,013.3	1,553.3	37.0	138.0	152.7	1,120.0	1,480.0	24.6
17	150	116.3	143.3	1,306.7	1,640.0	8.8	118.0	142.0	1,360.0	1,570.0	10.1
18	300	130.0	149.7	1,253.3	1,586.7	17.0	128.0	150.0	1,246.7	1,580.0	13.7
19	300	149.0	162.3	1,066.7	1,306.7	22.1	153.7	164.3	1,033.3	1,086.7	4.6
20	200	125.3	138.3	1,166.7	1,386.7	17.1	125.3	139.3	1,140.0	1,220.0	6.0
Mean±SEM	205.0±21.7	135.4±3.6	152.6±3.1*	1,067.3±49.9	1,370.0±69.7*	20.2±2.9	136.7±3.8	153.2±3.2*	1,108.7±53.2	1,317.0±77.9*	14.1±2.8‡

Min, minimum value; Max, maximum value. * $P < 0.001$ Min vs. Max. ‡ $P < 0.02$ PE alone vs. PE plus NP. Individual values are means of three trials each.

nearly perfect correlation of NP to ΔSAP ($r = 0.996$, $P < 0.001$), and the increase in NP averaged 1.12 times the increase in SAP (assumes 92% transmission). In this portion of the experiment, which employs dynamic increases in arterial pressure, we found the carotid contribution to heart rate control to average 30%, based on change in baroreflex slope after application of NP (Table II).

PE sensitization. We considered the possibility that PE might sensitize the baroreceptors (17) and that we might therefore overestimate the contribution of the aortic baroreflex on heart rate control during combined PE and NP interventions. We compared the response of HI to graded levels of brief timed NP before and during sustained PE infusion. As shown in Fig. 5, PE did not augment HI responses to NP in these subjects. Thus, in the doses employed, PE does not appear to sensitize arterial baroreceptors to graded levels of NP. In addition, Faris et al. (18) showed comparable baroreceptor–heart rate reflex responses in rabbits when assessed by either injecting PE intravenously or by inflating descending aortic cuffs to induce elevation of arterial pressure.

Aortic baroreceptor stimulation. The strategies employed in the steady-state portion of this study are dependent on the assumption that the stimulation of aortic baroreceptors remained at a constant level while NP was applied to inhibit the effect of increased pressure on carotid baroreceptors. As shown in Fig. 2, the peak HI response to NP occurred in the second to third cardiac cycle following the onset of the stimulus. Fig. 4 demonstrates that during this time of peak HI response, there was no significant change in either MAP or SAP during combined NP and PE administration. Thus, the stimulation of the aortic baroreceptors by PE-induced elevation of arterial pressure remained constant during the period of measurement.

One might suggest that NP and carotid baroreceptor inhibition could produce an abrupt sympathetic discharge, even in the absence of an increase in arterial pressure, and that this sympathetic discharge would sensitize the aortic baroreceptors. We cannot exclude this possibility, but we doubt that it was an important influence. Felder et al. (19) have recently demonstrated that reflex changes in sympathetic nerve discharge can alter the firing of carotid baroreceptors, but the magnitude of the changes in arterial pressure and sympathetic nerve activity required to produce significant sensitization of carotid baroreceptors was large. Our study involved the first few seconds of the response to a small change in carotid transmural pressure at a time when aortic pressure was constant. We therefore assume that the stimulus to the aortic baroreceptors was constant during the first few seconds of NP.

Steady-state vs. dynamic baroreceptor stimulation. Two principal methods have been employed in the quantitation of reflex heart rate responses during drug-induced blood pressure alteration. Ramp activation of arterial baroreceptors by bolus injection of angiotensin or PE has been described by Smyth et al. (20) and Bristow et al. (21) in which immediate reflex changes in heart rate are analyzed. Korner et al. (22) have used a steady-state method of blood pressure alteration by drug infusion and then studied reflex alterations in R-R interval after the progressive increase or reduction in blood pressure when the pressure alterations stabilized for 10–15 s.

In this study, we have attempted to examine heart rate control in man using both the steady-state and dynamic (ramp) methods of arterial pressure elevation. During the steady-state protocol (subjects 1–10), we superimposed brief-timed NP during sustained PE infusion and examined peak responses in HI during the first few seconds after application of NP. We could not use a steady-state method of carotid baroreceptor inhibition by prolonged application of NP, as this would have resulted in a rise in arterial pressure (due to withdrawal of carotid baroreflex inhibition) and therefore would have increased the stimulus to the aortic baroreceptors. Thus, in the steady-state protocol (subjects 1–10), we counteracted a steady-state increase in carotid transmural pressure with a dynamic decrease in transmural pressure. This combination of techniques may have potential limitations. If there is baroreceptor adaptation during a steady-state increase in blood pressure, then one could suggest that the dynamic NP would more than neutralize the effect of the steady-state increase in arterial pressure. Consequently, our results from the studies using steady-state increases in arterial pressure may have overestimated the carotid baroreflex contribution and underestimated the aortic baroreflex influence on prolongation of HI during the increase in arterial pressure.

Previous studies suggest that carotid baroreceptor adaptation occurs rapidly in man (23). We would note, however, that using the steady-state method in this study we found a mean 24.7 ms/mmHg (Table I) increase in HI during PE-induced rise in MAP that is greater than the value achieved by the ramp method of Bristow et al. (21), which showed a 13 ms/mmHg response. It is also slightly greater than the pulse interval prolongation per mmHg increase in arterial pressure observed in our studies with dynamic increases in SAP (Table II). Thus, the data suggest that adaptation did not have a significant effect on the gain of the baroreflex control of HI during the steady-state increases in pressure. This suggests that the use of a dynamic stimulus to counteract a steady-state stimulus may not have significantly affected our findings.

However, to overcome any potential limitations in the design of the steady-state protocol, we performed an additional series of experiments (subjects 11–20) using a different strategy. We produced a dynamic or ramp increase in arterial pressure using bolus injections of PE (20, 21) and counteracted the influence of this dynamic stimulus to carotid baroreceptors with a dynamic or ramp increase in NP that matched the increase in arterial pressure. Using this technique, we found a significant (30%) reduction in baroreflex slope when the carotid contribution to HI control during elevation in SAP was neutralized by NP. This is a lesser carotid contribution than we observed in the studies employing steady-state increases in arterial pressure. This difference may reflect (*a*) fewer limitations in the design of the studies employing ramp increases in arterial pressure, or (*b*) a greater aortic contribution during dynamic increases in pressure.

Mechanism of heart rate responses. Previous studies in animals and man have evaluated the autonomic mechanisms involved in heart rate responses to changes in arterial pressure. There is general agreement that the bradycardia in response to elevation of arterial blood pressure is primarily mediated through vagal cholinergic mechanisms. Pickering et al. (24), as well as others (25–27), have shown that atropine, but not propranolol (28), blocks the early increase in HI following PE-induced increases in arterial pressure. The use of the neck collar to produce neck suction and activate the carotid baroreceptors has produced similar findings relating to the early lengthening of HI (29). The reflex cardiac sympathetic responses to baroreceptor activation are slower than the parasympathetic responses (30–32). Thus,

while sympathetic mechanisms may play some role in the sustained bradycardic response to baroreceptor stimulation (33), it appears to be minimal.

Dissociation between effects of NP on HI and arterial pressure. During dynamic increases in arterial pressure produced by PE, application of NP reduced the prolongation in HI but did not alter the increase in arterial pressure. This indicates a dissociation between the effects of NP, i.e., decreasing the stimulus to carotid baroreceptors, on heart rate and arterial pressure. The rise in arterial pressure following PE bolus represents the net effect of direct vasoconstriction and the opposing baroreflex buffering. One would, therefore, expect a decrease in the carotid baroreflex buffering to augment the increase in arterial pressure during PE. There are two possible explanations for the finding that NP attenuated the heart rate response but failed to alter the arterial pressure response. The first is that the carotid baroreflex regulates heart rate but not vascular resistance. This seems improbable. The second explanation relates to the concept of redundancy in baroreceptor control of vascular resistance. Guo et al. (4) have demonstrated in animals that when one set of baroreceptors, e.g., carotids, are eliminated, there is impairment in reflex parasympathetic control of heart rate but preservation of reflex sympathetic control of vascular resistance. This dissociation suggests that there is sufficient reserve or redundancy so that the remaining set of baroreceptors can maintain reflex sympathetic control of vascular resistance. We speculate that a similar phenomenon may explain the differential effect of NP on HI and arterial pressure in our studies in humans.

Potential limitations. Several potential limitations in the design and interpretation of this study are recognized. First, the increases in arterial pressure produced in this study ranged from +4 to +27 mmHg. We were constrained from producing larger increases in pressure by concern with pronounced bradycardia. It is possible that the relative contribution of aortic and carotid baroreflexes may be different at high levels of pressure. Studies in animals suggest that the aortic contribution might be relatively greater at higher pressures (34, 35). We would note that over the range of increases in pressure produced in the first part of this study (Table I), there was no correlation ($r = 0.20$, $P = 0.65$) between the magnitude of increase in pressure and the aortic baroreflex contribution as assess by the gain ratio.

A second caution that must be applied in the interpretation of this data is that all studies were performed in the supine position. We cannot exclude the possibility that differences in arterial hydrostatic forces may produce a different balance between carotid and aortic baroreflex influences in the upright position.

Finally, while we have concentrated on the relative influence of carotid and aortic baroreflexes on heart rate control during elevation of arterial pressure, one must recognize that other neurogenic pathways might also be involved. These could include the cardiopulmonary baroreflexes and the possible role of sympathetic excitatory afferents from the aortic arch as described by Pagani et al. (36).

Several studies in animals have suggested that cardiopulmonary afferents modulate arterial baroreflex responses (37, 38). However, recent studies by Guo et al. (4) in rabbits have suggested that the cardiopulmonary baroreflexes play a minimal role in reflex heart rate responses to PE-induced increases in arterial pressure, whereas the predominant control is exerted by aortic and carotid sinus baroreceptors. In addition, studies by Takeshita et al. (27) in normal humans have shown that physiological variations of cardiac filling pressure do not influence sinus node responses to arterial baroreceptor stimulation in man.

Pagani et al. (36) have described a positive feedback sympathetic pressor reflex in the dog that is elicited by aortic distention within physiologic ranges and produces tachycardia and a reduction in arterial baroreflex control of heart rate. Whether this afferent pathway plays a role in humans is unclear. However, even if operative, this reflex should have been engaged similarly under both experimental conditions in our studies (increases in arterial pressure vs. NP during increases in arterial pressure). Thus, we believe that the possible role of a sympathetic pressor reflex does not detract from the use of our experimental strategy to obtain a comparative analysis of aortic vs. carotid baroreflexes.

Summary

Using new experimental strategies to selectively perturb arterial baroreflexes in normal man, we have acquired strong evidence that aortic as well as carotid baroreflexes contribute to the control of heart rate during both steady-state and dynamic (ramp) elevation of arterial pressure. Indeed, the findings suggest that aortic baroreceptors may exert a greater influence than carotid baroreceptors to increases in HI during modest dynamic increases in arterial pressure in supine normal man.

Acknowledgments

We wish to gratefully acknowledge the research assistance to Ms. Jinx Tracy and Ms. Joan Kempf, the statistical assistance of Mr. Tom O'Gorman, and the secretarial assistance of Ms. Jan Ellsworth, Ms. Jill Christy, and Ms. Nancy Perrine in the preparation of the manuscript.

This research project was supported by Program Project grant HL14388 and HL24962 from the National Institutes of Health as well as research funds from the Veterans Administration. Dr. Ferguson was a recipient of the American College of Cardiology/Merck Fellowship Award 1982–83 and was a Clinician Scientist of the American Heart Association, 1983–84.

References

1. Vatner, S. F., D. Franklin, R. L. Van Citters, and E. Braunwald. 1970. Effects of carotid sinus nerve stimulation on blood flow distribution in conscious dogs at rest and during exercise. *Circ. Res.* 27:495–503.

2. Ito, C. S., and A. M. Scher. 1978. Regulation of arterial blood pressure by aortic baroreceptors in the unanesthetized dog. *Circ. Res.* 42:230–236.

3. Ito, D. S., and A. M. Scher. 1979. Hypertension following denervation of aortic baroreceptors in unanesthetized dogs. *Circ. Res.* 45:26–43.

4. Guo, G. B., M. D. Thames, and F. M. Abboud. 1982. Differential baroreflex control of heart rate and vascular resistance in rabbits. Relative role of carotid, aortic and cardiopulmonary baroreceptors. *Circ. Res.* 50:554–565.

5. Kendrick, J. E., G. L. Matson, and P. N. Lolley. 1979. Central interaction between the baroreceptor reflexes from the carotid sinus and aortic arch. *Am. J. Physiol.* 236:H127–H133.

6. Ernsting, J., and B. J. Parry. 1957. Some observations on the effects of stimulating the stretch receptors in the carotid artery of man. *J. Physiol. (Lond.).* 137:45. (Abstr.)

7. Bevegard, S. B., and J. T. Shepherd. 1966. Circulatory effects of stimulating the carotid arterial stretch receptors in man at rest and during exercise. *J. Clin. Invest.* 45:132–142.

8. Pickering, T. G., B. Gribbin, and P. Sleight. 1972. Comparison of the reflex heart rate response to rising and falling arterial pressure in man. *Cardiovasc. Res.* 6:277–283.

9. Eckberg, D. L., G. F. Fletcher, and E. Braunwald. 1972. Mechanisms of prolongation of the R-R interval with electrical stimulation of the carotid sinus nerves in man. *Circ. Res.* 30:131–138.

10. Abboud, F. M., D. L. Eckberg, U. F. Johannsen, and A. L. Mark. 1979. Carotid and cardiopulmonary baroreceptor control of splanchnic and forearm vascular resistance during venous pooling in man. *J. Physiol. (Lond.).* 286:173–184.

11. Mancia, G., A. Ferrari, L. Gregorini, R. Valentini, J. Ludbrook, and A. Zanchetti. 1977. Circulatory reflexes from carotid and extracarotid baroreceptor areas in man. *Circ. Res.* 41:309–315.

12. Ludbrook, J., G. Mancia, A. Ferrari, and A. Zanchetti. 1977. The variable-pressure neck-chamber method for studying the carotid baroreflex in man. *Clin. Sci. Mol. Med.* 53:165–171.

13. Eckberg, D. L., M. S. Cavanaugh, A. L. Mark, and F. M. Abboud. 1975. A simplified neck suction device for activation of carotid baroreceptors. *J. Clin. Lab. Med.* 85:167–173.

14. Eckberg, D. L. 1976. Temporal response patterns of the human sinus node to brief carotid baroreceptor stimuli. *J. Physiol. (Lond.).* 258: 769–782.

15. Eckberg, D. L. 1977. Baroreflex inhibition of the human sinus node: importance of stimulus intensity, duration and rate of pressure change. *J. Physiol. (Lond.).* 269:561–577.

16. Kober, G., and J. O. Arndt. 1970. Druck-Durchsnesser-Beziehung der A. Carotis communis des machen Menschen. *Pflügers Arch. Gesamte Physiol. Menschen Tiere.* 314:27–39.

17. Goldman, W. F., and W. R. Saum. 1980. Alpha-adrenergic modulation of multi- and single unit baroreceptor discharge. *Fed. Proc.* 39: 839. (Abstr.)

18. Faris, I. B., J. Iannos, G. G. Jamieson, and J. Ludbrook. 1980. Comparison of method for eliciting the baroreceptor-heart rate reflex in conscious rabbits. *Clin. Exp. Pharmacol. Physiol.* 7:281–291.

19. Felder, R. B., C. M. Heesch, and M. D. Thames. 1983. Reflex modulation of carotid sinus baroreceptor activity in the dog. *Am. J. Physiol.* 244:H437–H443.

20. Smyth, H. S., P. Sleight, and G. W. Pickering. 1969. Reflex regulation of arterial pressure during sleep in man: a quantitative method assessing baroreflex sensitivity. *Circ. Res.* 24:109–121.

21. Bristow, J. D., A. J. Honour, G. W. Pickering, P. Sleight, and H. S. Smyth. 1969. Diminished baroreflex sensitivity in high blood pressure. *Circulation.* 39:48–54.

22. Korner, P. I., M. J. West, J. Shaw, and M. B. Uther. 1974. Steady state properties of the baroreceptor-heart rate reflex in essential hypertension in man. *Clin. Exp. Pharmacol. Physiol.* 1:65–76.

23. Eckberg, D. L. 1977. Adaptation of the human carotid baroreceptor-cardiac reflex. *J. Physiol. (Lond.).* 269:579–589.

24. Pickering, T. G., B. Gribbin, E. Strage-Peterson, D. J. C. Cunningham, and P. Sleight. 1972. Effects of autonomic blockage on the baroreflex in man at rest and during exercise. *Circ. Res.* 30:177–185.

25. Eckberg, D. L., M. Drabinski, and E. Braunwald. 1971. Defective cardiac parasympathetic control in patients with heart disease. *N. Engl. J. Med.* 285:877–883.

26. Simon, A. C. H., M. E. Safar, Y. A. Weiss, J. M. London, and P. L. Milliez. 1977. Baroreflex sensitivity and cardiopulmonary blood volume in normotensive and hypertensive patients. *Br. Heart J.* 39:799–805.

27. Takeshita, A., A. L. Mark, D. L. Eckberg, and F. N. Abboud. 1979. Effect of central venous pressure on arterial baroreflex control of heart rate. *Am. J. Physiol.* 236:H42–H47.

28. Jose, A. D., and R. R. Taylor. 1969. Autonomic blockade by propranolol and atropine to study intrinsic myocardial function in man. *J. Clin. Invest.* 48:2029–2031.

29. Eckberg, D. L., F. M. Abboud, and A. L. Mark. 1976. Modulation of carotid baroreflex responsiveness in man: effects of posture and propranolol. *J. Appl. Physiol.* 41:383–387.

30. Coleman, T. G. 1980. Arterial baroreflex control of heart rate in the conscious rat. *Am. J. Physiol.* 238:H515–H520.

31. Thames, M. D., and H. A. Kontos. 1970. Mechanisms of baroreceptor-induced changes in heart rate. *Am. J. Physiol.* 218:251–256.

32. Wang, S. C., and H. L. Borison. 1974. An analysis of the carotid sinus cardiovascular reflex mechanism. *Am. J. Physiol.* 150:712–721.

33. Ripley, R. C., J. W. Hollifield, and A. S. Nies. 1977. Sustained hypertension after section of the glossopharyngeal nerve. *Am. J. Cardiol.* 623:297–302.

34. Donald, D. E., and A. J. Edis. 1971. Comparison of aortic and carotid baroreflexes in the dog. *J. Physiol. (Lond.).* 215:521–538.

35. Pelletier, C. L., D. L. Clement, and J. T. Shepherd. 1972. Comparison of afferent activity of canine aortic and sinus nerves. *Circ. Res.* 31:557–568.

36. Pagani, M., P. Pizzinelli, M. Bergamasch, and A. Malliani. 1982. A positive feedback sympathetic pressor reflex during stretch of the thoracic aorta in conscious dogs. *Circ. Res.* 50:125–132.

37. Koike, H., A. L. Mark, D. D. Heistad, and P. G. Schmid. 1975. Influence of cardiopulmonary vagal afferent activity on carotid chemoreceptor and baroreceptor reflexes in the dog. *Circ. Res.* 37:422–429.

38. Vatner, S. F., D. H. Boettcher, G. R. Heyndrickx, and R. J. McRitchie. 1975. Reduced baroreflex sensitivity with volume loading in conscious dogs. *Circ. Res.* 37:236–242.