

Circulatory Reflexes from Carotid and Extracarotid Baroreceptor Areas in Man

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SUMMARY The carotid sinus baroreceptor reflex was studied in 11 normotensive subjects, using a variable pressure neck chamber and correcting for imperfect pressure transmission to the carotid sinus. Decreased carotid baroreceptor stimulation caused a sustained rise in arterial pressure, and increased carotid baroreceptor stimulation caused a sustained fall. The responses were in linear relation to the stimulus, and, after reaching the steady state, greater for the reduced than for the increased baroreceptor stimulation. Thus the carotid sinus baroreceptor reflex of the normotensive man is an effective antihypotensive and antihypertensive feedback system, though the former function may have more sensitivity. The increased and decreased baroreceptor stimulation by the neck chamber also caused bradycardia and tachycardia which were modest in magnitude and often transient. In eight subjects the reflex changes in heart rate induced by the neck chamber were compared with those induced by altering transmural pressure not merely at the carotid sinus but throughout the arterial tree (injection of phenylephrine and trinitroglycerin). The slopes of these relations were 3 times as great in the latter circumstance. Thus the carotid baroreceptors play a lesser role in heart rate control than do extracarotid baroreceptors.

THE TECHNIQUE most widely used to test baroreflexes in human subjects has been to measure heart rate responses to injection of pressor and depressor drugs free of cardiac action. Some of its characteristics should be considered. First, this technique cannot measure reflex changes in blood pressure and give information on blood pressure control, as there is no available proof that it is correct to extrapolate blood pressure from heart rate responses. Second, this method assesses reflex responses only over a few seconds, i.e., measures transient responses to transient stimuli. Finally, it changes transmural pressure across all the arterial tree, and cannot distinguish between carotid sinus, aortic, and cardiopulmonary reflexes.

Another method to test baroreflexes in man is to change the pneumatic pressure within a sealed chamber surrounding the neck, thus altering carotid sinus transmural pressure. This method primarily influences carotid sinus baroreceptors, assesses both transient and long-lasting reactions, and also allows the study of reflex responses of both the heart and peripheral circulation. This method was first described by Ernsting and Parry.¹ These authors and most of those who repeated and extended their study²⁻⁶ limited themselves to examining the reflex responses to increased carotid sinus transmural pressure. One group,⁷ however, induced bidirectional changes in pneumatic pressure around the neck, and constructed stimulus-response curves for the human carotid baroreflex.

Construction of stimulus-response curves requires also that the stimulus magnitude be known with sufficient accuracy. In all the studies cited above¹⁻⁷ the stimulus to the

carotid baroreceptors was equated with the difference between arterial pressure and neck chamber pressure. However, we have recently shown that pressure changes within a neck chamber are incompletely transmitted to the region of the carotid sinus, and that negative pressures are less well transmitted than positive.⁸ Thus in previous studies the gain of the carotid baroreflex may have been underestimated, and the shape of the stimulus-response curve distorted.

The investigations we here report were performed on normal human subjects by applying both the neck chamber technique and the vasoactive drug method, with two purposes in mind: (1) to reexamine the carotid sinus baroreflex allowing for the imperfect transmission of pressure from the neck chamber to the carotid sinus, in order to describe the stimulus exactly and to calculate the gain more accurately; (2) to compare heart rate responses to changes in transmural pressure limited to the carotid sinus with those produced throughout the arterial tree when vasoactive drugs are injected, in order to explore whether extracarotid baroreceptors contribute to heart rate regulation. This problem has never been investigated in man.

Methods

The study was performed on 11 subjects whose ages ranged from 26 to 68 years (mean, 36) and whose diastolic blood pressures were always less than 95 mm Hg. The subjects were in good health and volunteered their consent to the procedure after having had the nature and the purpose of the investigation explained.

For each subject pneumatic pressure changes at the neck were obtained by means of a chamber the characteristics of which are described elsewhere.⁸ In brief, the neck was enclosed in a plastic box extending caudally to the shoulders and cranially to the plane intersecting the mentolabial sulcus, the ear lobes, and the occiput. Both the

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thoracic and the cranial openings were provided with double valvelike thin rubber seals that could withstand positive and negative pressure changes. One large and one small opening were made in the box; the large one was connected to a commercial vacuum cleaner by means of which pressure changes were effected in the interior. The small opening was connected to a strain gauge transducer to measure pressure changes in the atmosphere of the chamber.

MEASUREMENTS

Pulsatile arterial blood pressure was measured by a catheter [outside diameter (o.d.), 1.0 mm] placed percutaneously in a femoral artery and connected to a strain gauge transducer system with a flat frequency-response curve up to 20 Hz. Mean arterial pressure was obtained by electronic damping of the pulsatile signal and by integration of the pulsatile trace over periods of 10 seconds. A cardiometer was triggered by the R wave of an electrocardiogram. The tachometer display was calibrated as heart rate, and heart interval (as R-R interval) was recalculated in milliseconds from the heart rate reading.

ADMINISTRATION OF DRUGS

A catheter (1.0-mm o.d.) was introduced percutaneously into an antecubital vein and advanced until its tip lay in the subclavian or the brachiocephalic vein. Phenylephrine (25–100 μg) or trinitroglycerin (25–150 μg) was injected via the catheter to increase or decrease arterial blood pressure, permitting thus observation of reflex changes in heart rate.^{9–13} The injection site was excluded from the sight of the subjects, and the drugs (diluted in 2–4 ml of saline) were injected over periods of 5–10 seconds. As described by Korner et al.,¹³ this method of administration causes the arterial blood pressure to increase, or to decrease, progressively over 5–10 seconds, and then to attain a sustained increase or decrease, for an additional 5–10 seconds, during which periods sustained reflex changes in heart rate also occur.

PROTOCOL

At 1–2 days before the study each subject was brought to the laboratory, fitted with the neck chamber, and subjected to a series of positive and negative neck pressure changes in order to make him familiar with the procedure.

The study was performed with the subject in a supine position. In each, a random sequence of four to six different negative and four to six different positive neck pressure changes was applied within the range ± 50 mm Hg. The pressure changes both from and back toward atmospheric pressure occurred very rapidly (90% of the change completed in less than 1 second and less than 2 seconds, respectively). Pressure changes were maintained for 2 minutes. An interval of at least 4 minutes was allowed between pressure changes.

The effects of drug-induced changes in blood pressure on heart rate were tested after completion of the study with the neck pressure chamber. Graded doses of each pressor and depressor drug were injected to obtain arterial pressure variations within a range ± 25 mm Hg. An inter-

val of at least 4 minutes was allowed between each drug-induced pressure change.

DATA ANALYSIS

In our earlier study⁸ we reported that linear regressions calculated separately for positive and negative neck chamber pressures showed that on the average $86 \pm 2\%$ of positive, and $64 \pm 3\%$ of negative pressure was transmitted to the tissues adjacent to the carotid sinus. Because there was little dispersion of these regression coefficients among the subjects studied we used these figures in the present study to correct the values of pressure changes in the neck chamber and thus obtain changes in neck tissue pressure around the carotid sinus. A decrease and increase in neck tissue pressure correspond to an increase and decrease in carotid sinus transmural pressure and therefore to an increase and decrease in baroreceptor stimulation.

To analyze the hemodynamic effects of changes in neck tissue pressure the following measurements of arterial blood pressure and heart interval were taken: (1) control value (the average value during the 30 seconds preceding the change in neck tissue pressure); (2) early response (the average value in the 10-second period from the 5th to the 15th seconds following the change in neck tissue pressure); and (3) late or steady state response (the average value that occurred in the last 30 seconds of the neck tissue pressure change). The control period and the late response period showed stable hemodynamic values because in either condition mean arterial pressure had a normalized standard error during three successive 10-second periods that never was greater than 0.2%.

To analyze the effects of drugs, average mean arterial pressure and heart interval values were taken during the 10-second period immediately before drug injection (control) and during the sustained part of the response.

For each individual subject linear regressions were calculated to describe stimulus-response relationship, and the regression coefficients (indicating the slope of the relationship) were taken to indicate the magnitude of the response. When the neck chamber was used the stimulus was generally taken as the change in neck tissue pressure. In selected instances, as for calculation of open loop gain and

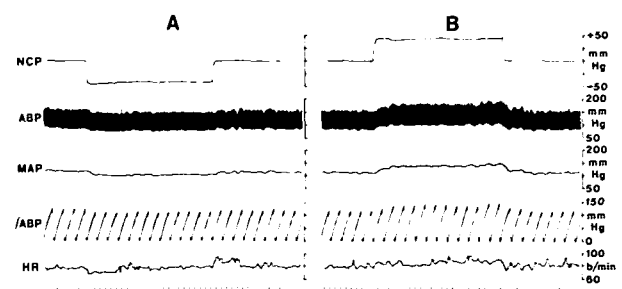


FIGURE 1 Original traces of hemodynamic changes induced by decrease (A) and increase (B) in neck chamber pressure. NCP = neck chamber pressure; ABP = pulsatile arterial pressure; MAP = mean arterial pressure; \int ABP = arterial pressure integrated over 10-second periods; HR = tachograph trace. Time is at the bottom as 1 and 5 seconds.

TABLE 1 Responses of Mean Arterial Pressure (MAP) to Changes in Neck Tissue Pressure

Subject	Age (yr)	Control MAP (mm Hg)	Neck tissue pressure						P (increased vs. decreased)*	
			Increased			Decreased			Early	Steady state
			Early	Steady state	P†	Early	Steady state	P†		
1	26	110±1.0	0.39	0.69	<0.01	0.74	0.58	<0.05	<0.01	<0.02
2	27	109±0.7	0.33	0.46	<0.01	0.44	0.44	NS	NS	NS
3	28	110±1.7	0.53	0.81	<0.01	1.08	0.60	<0.01	<0.05	<0.01
4	29	103±1.3	0.46	0.47	NS	0.51	0.49	NS	NS	NS
5	32	106±2.3	0.44	0.65	<0.01	0.44	0.37	NS	NS	<0.01
6	32	95±1.0	0.56	0.58	NS	0.33	0.33	NS	<0.01	<0.01
7	35	112±3.9	0.52	0.84	<0.01	0.59	0.74	NS	NS	NS
8	36	91±1.2	0.73	0.92	<0.01	0.36	0.27	NS	<0.01	<0.01
9	42	107±0.8	0.29	0.59	NS	0.50	0.36	NS	NS	<0.01
10	42	77±0.5	0.40	0.70	<0.01	0.43	0.16	<0.01	NS	<0.01
11	68	100±1.0	0.18	0.45	<0.01	0.63	0.21	<0.01	<0.01	<0.01
Avg	36±3.6	102±3.2	0.44±0.04	0.65±0.05	<0.01	0.55±0.06	0.41±0.04	<0.01	NS	<0.01

Control values and averages are expressed as mean ± SEM.

Responses are shown as individual regression coefficients (11 subjects) of changes in MAP (mm Hg) on changes in neck tissue pressure (mm Hg). All coefficients are statistically significant. Coefficients are positive because an increased neck tissue pressure is associated with an increased mean arterial pressure and vice versa.

* P values refer to differences between regression coefficients at increased vs. decreased neck tissue pressure, the comparison being made separately for early and steady state responses. NS = not significant.

† P values refer to differences between regression coefficients of early vs. steady state changes.

comparison of cardiac responses to those caused by drugs, the stimulus was taken as the change in calculated carotid sinus transmural pressure (the change in tissue pressure minus the resulting reflex change in mean arterial pressure). When drugs were injected the stimulus was the change in mean arterial pressure. Significance of the regression lines was assessed for individual subjects according to Snedecor and Cochran,¹⁴ and comparison of response slopes in different circumstances (early vs. steady state responses, increased vs. decreased neck tissue pressure) was made by covariant analysis for each individual subject and by paired *t*-test for the group as a whole.¹⁴ In each case a *P* value of at least <0.05 was taken as the level of statistical significance. The symbol ± is used throughout to indicate standard error of the mean.

Results

CHANGES IN NECK CHAMBER PRESSURE

Arterial Blood Pressure

As shown in Figure 1 a rapid decrease in neck chamber pressure induced an immediate fall in arterial blood pressure, and a rapid increase in neck chamber pressure induced a prompt rise in arterial blood pressure. In neither case was there a change in pulse pressure.

A detailed analysis of the time course of both the depressor and the pressor responses was performed by separately considering early and late (or steady state) components of the response as defined in Methods (Table 1 and Fig. 2, left). Both the early and the steady state changes in mean arterial pressure could be linearly related both to the increase and the decrease in neck tissue pressure. The linear regression coefficients were significant for every single subject examined.

Differences were found, however, between the early

and the steady state responses, and between responses to increased and decreased neck tissue pressure. The magnitude of the steady state response to increased neck tissue pressure was significantly greater than that of the early response, indicating that the blood pressure rise induced by decreased carotid sinus baroreceptor stimulation does not immediately reach its maximal value. On the contrary, the steady state response to decreased neck tissue pressure was significantly smaller than the early response. Therefore, an increased carotid sinus baroreceptor stimulation induces a quick fall in arterial blood pressure that is later reduced to a sustained hypotensive response of a slightly smaller magnitude.

Table 1 (last two columns, at right) compares the slopes of responses to increased and decreased neck tissue pressure. No consistent difference was found between the magnitudes of the early responses, indicating that the immediate effects on blood pressure of decreased and

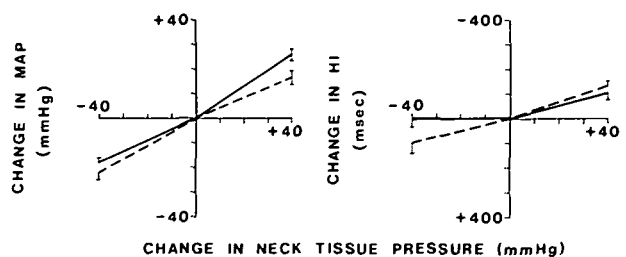


FIGURE 2 Changes in mean arterial pressure (MAP) and heart interval (HI) induced by changes in neck tissue pressure. Data are shown as means ± SE of individual regression coefficients in 11 subjects. The dashed line represents the early response, the continuous line the late or steady state response. Changes in neck tissue pressure were calculated from changes in neck chamber pressure, using correction figures for pressure transmission through neck tissues (see Methods).

TABLE 2 Responses of Heart Interval to Changes in Neck Tissue Pressure

Subject	Control heart interval (msec)	Neck tissue pressure							
		Increased			Decreased			<i>P</i> (increased vs. decreased)	
		Transient	Steady state	<i>P</i>	Transient	Steady state	<i>P</i>	Transient	Steady state
1	705±16	-3.59	-1.26	<0.01	-6.50	2.47	<0.01	<0.01	<0.01
2	789±9	-2.59	-1.37	<0.01	-7.68	-1.64	<0.01	<0.01	NS
3	631±13	-2.85	-3.10	NS	4.72	-0.11*	<0.01	<0.01	<0.05
4	667±4	-3.75	-1.95	NS	-4.69	1.06	<0.01	NS	<0.01
5	749±11	-1.83	-1.73	NS	-3.11	-2.61*	NS	NS	<0.02
6	682±6	-2.23	-2.10	NS	-0.54	0	NS	<0.01	<0.01
7	783±13	-3.62	-3.94	NS	-2.63	1.02*	<0.01	<0.05	<0.05
8	909±19	-7.34	-5.07	<0.01	1.13*	1.13*	NS	<0.01	<0.01
9	682±10	-3.40	-1.36	<0.01	-2.20	-1.85	<0.05	NS	<0.02
10	1160±16	-5.12	-5.08	NS	-3.92	-1.39*	NS	NS	<0.05
11	828±13	-1.35	-2.95	<0.01	-2.22	0.66*	<0.01	NS	<0.01
Avg	780±45	-3.42±0.5	-2.72±0.43	NS	-2.51±1.04	-0.11±0.47	<0.05	NS	<0.01

Control values and averages are expressed as mean ± SEM.

Responses are shown as individual regression coefficients (same 11 subjects of Table 1) of changes in heart interval (msec) on changes in neck tissue pressure (mm Hg). Coefficients are statistically significant except when marked with an asterisk (*). Negative coefficients indicate either a shortening of heart interval (i.e., tachycardia) when neck tissue pressure is increased or lengthening of heart interval (bradycardia) when neck tissue pressure is decreased. Positive coefficients indicate heart interval responses of opposite sign. *P* values as in Table 1.

increased carotid baroreceptor activity are symmetrical. On the other hand, during the steady state the response to increased neck tissue pressure was significantly greater than the response to decreased neck tissue pressure, the average regression coefficients being 0.65 and 0.41, respectively.

Heart rate

Figure 1 also illustrates that the rapid decrease in neck chamber pressure induced a moderate bradycardia, and that a moderate tachycardia was observed when the neck chamber pressure was raised.

As shown in Table 2 and Figure 2 (right), both the early and the steady state changes in heart interval could be linearly related to the increase in neck tissue pressure: the calculated slopes were significant in every single subject examined. On the whole there was no significant difference between the slopes of the early and steady state responses, indicating that the tachycardia was uniform throughout the period of neck tissue pressure increase. On the other hand, when neck tissue pressure was reduced only the early lengthening of the cardiac cycle could be significantly correlated with the stimulus. The steady state response was variable and on the whole was not significantly different from zero. This shows that increased carotid sinus baroreceptor stimulation gives rise to a transient bradycardia that disappears later during the stimulation period, at a time when there is still a considerable reflex hypotension.

Table 2 (last two columns, at right) compares the slopes of the heart interval responses to increased and decreased neck tissue pressure. The differences between the two early responses were not always in the same direction in the various subjects, and for the group as a whole there was no significant difference. During the steady state regression coefficients of responses to increased and to decreased neck tissue pressure were obviously significantly different, as the former stimulus induced a sustained tach-

ycardia whereas the latter stimulus did not induce any sustained change in heart rate.

INJECTION OF DRUGS

Vasoactive drugs were injected in eight of the 11 subjects. Increasing amounts of phenylephrine and trinitroglycerin caused progressive increases and decreases in mean arterial pressure, with little change in pulse pressure. The increases and decreases in blood pressure were accompanied by linearly related increases and decreases in heart interval. These relations were present in every subject, with no consistent significant difference in the slope of the response to the pressor as compared to the depressor drug.

Changes in heart interval induced in these subjects by drugs and by the neck chamber are compared in Table 3 and Figure 3. The heart interval change produced by drugs was compared to the early cardiac response induced by the neck chamber. The early phase was preferred to the late steady state phase because it more closely corresponds to the time when measurements are taken during the short-lived effect of the drug. To permit comparison stimuli were calculated as changes in transmural pressure: when drugs were injected the change in transmural pressure was the rise or fall in mean arterial pressure caused by drugs; when the neck chamber was used the change in transmural pressure was the change in neck tissue pressure minus the resulting reflex change in mean arterial pressure measured at the time of the early cardiac response. In almost every subject, as well as in the group as a whole, lengthening and shortening of the heart cycle were much more marked in response to a change in transmural pressure caused by vasoactive drugs than in response to a change in transmural pressure caused by the neck chamber.

Discussion

This study was aimed at clarifying two aspects of baroreflex physiology in man: (1) to describe the true relation-

TABLE 3 Comparison of Heart Interval Responses to Changes in Transmural Pressure Induced by Vasoactive Drugs and by Neck Chamber

Subject	Decreased transmural pressure			Increased transmural pressure		
	Drugs	Neck chamber	P	Drugs	Neck chamber	P
1	9.7	4.3	<0.01	20.6	8.0	<0.01
2	14.5	3.4	<0.01	13.1	9.0	<0.02
3	5.5	3.5	<0.02	7.1	-2.2	<0.01
4	5.6	5.8	NS	11.6	3.0	<0.01
5	2.9	2.8	NS	14.1	4.8	<0.01
6	22.0	5.4	<0.01	28.8	4.4	<0.01
7	6.5	2.4	<0.01	11.4	3.8	<0.01
8	9.7	1.6	<0.01	8.3	5.0	<0.01
Avg	9.5 ± 2.2	3.6 ± 0.5	<0.01	14.4 ± 2.5	4.5 ± 1.2	<0.01

Averages are expressed as mean ± SEM.

Responses shown as individual regression coefficients (eight subjects) of changes in heart interval (msec) on changes in transmural pressure. The coefficients were all statistically significant, the positive sign indicating that decreased and increased transmural pressures were, respectively, associated with shortening and lengthening of heart interval. For definition of transmural pressure and other details see the text.

ships between blood pressure and heart rate responses and the stimulus to the carotid sinus baroreceptors provided by a neck chamber; (2) to compare the heart rate responses induced by the neck chamber technique and by the more widely used method of injecting vasoactive drugs. These two aspects will be discussed separately.

Our data for the neck chamber show that decreases and increases in neck tissue pressure induce hemodynamic changes that can be linearly related to the stimulus within the range of pressures we explored. Separate analysis of the early and late components of the reflex responses reveal that responses to carotid sinus stimulation and to carotid sinus deactivation have a different time course: baroreceptor stimulation gives rise to phasic hypotension and bradycardia that subsequently decrease to steady state

responses in the same direction but of smaller magnitude; baroreceptor deactivation causes a slowly developing but well maintained hypertension with no evidence of a phasic component. Analysis of the early component only, as when the stimulus is applied for only a few seconds, is likely to provide overestimation of one type of response and underestimation of the other.

The magnitude of reflex responses should be considered separately for blood pressure and heart rate. With respect to arterial pressure Thron et al.,⁷ who previously used the neck chamber technique in man, reported that a decreased neck chamber pressure causes a slight hypotension in contrast with the clear-cut hypertension that follows an increase in the neck chamber pressure. They speculated that in normotensive subjects carotid sinus baroreceptors discharge near their saturation level and thereby provide an effective antihypertensive but no antihypertensive mechanism. Our results, however, show that increased carotid sinus baroreceptor stimulation is accompanied by a pronounced depressor response, and it is likely that the smaller slopes calculated by Thron et al.⁷ resulted from their not taking into account the imperfect transmission of pressure changes from neck chamber to neck tissues. As we have shown, transmission of negative chamber pressure is less effective than transmission of positive pressure;⁸ for this reason overestimation of the stimulus magnitude by previous investigators certainly flattened the slope of the depressor more than that of the pressor response. Indeed, when the data of Thron and co-workers⁷ are calculated on the assumption that with their device pressure transmission through the neck tissues was similar to ours their values approach those found in our study. Likewise, recalculation of the data obtained by Bevegård and Shepherd² with neck suction gives values similar to the present ones.

Although our data indicate that the carotid baroreceptor reflex in normotensive human subjects is not set at the top portion of its stimulus-response curve, and can work both as an antihypertensive and an antihypertensive mechanism, nonetheless we have also found evidence that the sensitivity of the carotid sinus baroreceptors to increased and decreased stimulation is not identical. When steady

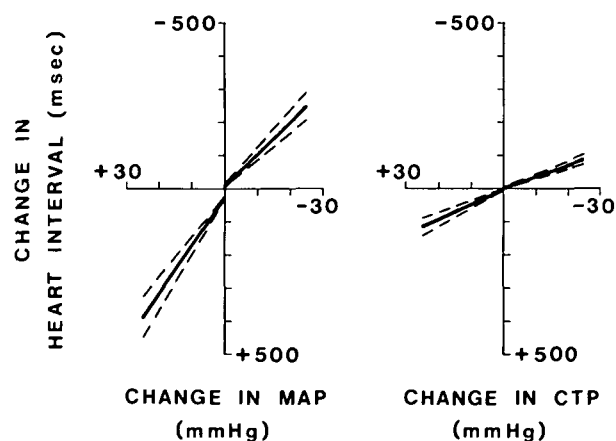


FIGURE 3 Changes in heart interval with drug-induced changes in mean arterial pressure (MAP) (left) and with neck chamber-induced changes in carotid sinus transmural pressure (CTP) (right); means (continuous lines) ± SE (dashed lines) of individual regression coefficients taken from the eight subjects in which both techniques were used. For the neck chamber the early heart interval responses were considered, the changes in carotid sinus transmural pressure being that at the time at which the response was developed. Control mean arterial pressure and heart interval were 101 ± 5 mm Hg and 864 ± 61 msec for the drug studies, and 104 ± 5 mm Hg and 791 ± 59 msec for the neck chamber studies.

state responses are considered, the pressor response to the increased neck tissue pressure is always significantly greater than the depressor response to decreased neck tissue pressure, the correction of the stimulus achieved by the baroreflex being, respectively, 0.65 and 0.41. We have considered elsewhere⁸ the possibility that the pressor response might be increased by a reduction of venous return from the brain and the carotid bodies during the relatively prolonged application of positive neck pressure. Both possibilities, however, can be dismissed because we showed that positive neck pressures of the same magnitude and duration as those used in the present study do not reduce cerebral blood flow or cause chemoreceptor stimulation.⁸ The possibility of an emotional contribution to the pressor rise cannot be completely excluded. However, it seems unlikely for several reasons: the subjects were trained to tolerate the procedure, they did not report it as emotionally disturbing, they displayed similar pressor rises to comparable stimuli both at the beginning and at the end of the recording session, and, most important, the progressive increase in blood pressure during the initial part of the response was not paralleled by a similar progressive increase in heart rate.

It seems likely, therefore, that the asymmetries in the carotid sinus baroreflex depend on the inherent properties of baroreflexes in man. Either (1) the carotid sinus of the normotensive man is more sensitive to a decrease than to an increase in transmural pressure and, though functioning in both ways, works as a better antihypertensive than antihypertensive mechanism, or (2) these properties are shared by the other baroreflexes, aortic and cardiopulmonary, that in the intact subject interfere to buffer the changes caused by carotid sinus manipulation. We have no evidence from our subjects favoring one or the other hypothesis, but data for dogs^{15, 16} indicate that the aortic reflexes function better as an antihypertensive mechanism, and therefore suggest that the asymmetries we observed may properly describe the carotid sinus of man.

A strict quantitative evaluation of the sensitivity of a feedback mechanism consists of measuring input-output relations in an open loop system, in which the output is isolated from the input signal. Working in man we had necessarily to deal with closed loop conditions, and the slopes we measured represent gains of the closed loop reflex. We also tried to evaluate carotid sinus reflex sensitivity by relating the blood pressure response to the corrected signal error, i.e., the difference between change in neck tissue pressure and reflex change in arterial pressure. According to Scher and Young,¹⁷ gain values so calculated approach gains in open loop conditions. In our study these calculations brought the gain of the steady state pressor response to decreased carotid sinus transmural pressure from 0.65 to 1.67, and the gain of the steady state depressor response to increased carotid sinus transmural pressure from 0.41 to 0.64. These are gains in the low range of those found for unanesthetized animals.¹⁸ In our opinion, however, when one studies a closed loop system, as in the naturally functioning carotid sinus reflex, a more direct evaluation of the reflex is obtained by relating the response to the initial stimulus, as we have done. This

measures the percent of the stimulus corrected by the carotid baroreflex, in the presence of the opposing action of extracarotid baroreflexes, and avoids possible errors caused by excessive manipulation of data.

We have discussed blood pressure responses extensively because they represent the most meaningful response in a feedback system originating from baroreceptors; in spite of this, they have been studied only infrequently. Heart rate responses are worth some comments, however, to stress that, as did previous authors,⁷ we also found them to be quite moderate. Tachycardia during increased neck tissue pressure, besides being rather mild, does not progressively increase during the 1st minute of stimulation as does arterial pressure; bradycardia during decreased neck tissue pressure is only transiently evident at the beginning of the stimulation and then almost entirely disappears.

This comment on heart rate responses leads us to discuss the second aspect of our work: the comparison of reflex responses (necessarily limited to heart rate changes) to baroreceptor manipulation either by the neck chamber or by injection of vasoactive drugs. Also in our study alterations in arterial pressure by pressor and depressor drugs caused linearly related reflex changes in heart interval, an observation that confirms previous data of several authors.⁹⁻¹³ However, it is clear from our data that for comparable changes in transmural pressure drugs had much greater effects on heart rate than did the neck chamber, despite the fact that the stimulus caused by drugs had a slower buildup time than that provided by the neck chamber. We see the following possibilities to explain this difference. First, drugs might have had a stronger reflex effect on heart rate if, in addition to changes in mean arterial pressure, they had more strongly influenced pulse pressure. This possibility is excluded by the very small change in pulse pressure induced by both stimuli in our subjects. Second, drugs might have been a more effective stimulus by directly affecting smooth muscle tone in the arterial wall where baroreceptors are located. This action has been found in animals only when relatively large doses of norepinephrine were topically applied to the carotid sinus wall,¹⁹ and there is no available evidence to indicate that the small amounts of phenylephrine we injected systemically could have exerted a similar action. A third possibility is that baroreceptors are more effectively stimulated by a rise in transmural pressure when this is produced by an increase in intravascular pressure rather than by a fall in extravascular pressure. This possibility also can be dismissed because Angell-James²⁰ has shown in the rabbit that changes in arterial transmural pressure caused either from inside or from outside the vessel have an identical effect on baroreceptor discharge.

The most likely reason for the greater reflex influence on heart rate exerted by drugs is that, while transmural pressure changes by the neck chamber are restricted to the carotid sinus area, the systemic action of drugs affects transmural pressure throughout the arterial tree and thus influences additional baroreceptor areas.

The importance of extracarotid baroreceptors in man has been denied.²¹ Our data, however, suggest that reflex control of heart rate in man depends to a large extent on

baroreceptor areas other than the carotid sinuses. Evidence from studies on animals shows that reflex responses to vasoactive drugs are abolished if, in addition to section of the carotid sinus nerves, section of the aortic nerves is performed.²²⁻²⁴ Thus the aortic area is the most likely baroreceptive area contributing to the reflex effects observed with drugs. It must also be remarked that the conspicuous tachycardia observed when transmural pressure was reduced by trinitroglycerin implies a tonic activity of these extracarotid baroreceptors at normal levels of arterial blood pressure.

A final question is whether the carotid sinus and the extracarotid baroreceptors differ in their control of blood pressure and heart rate. Although a precise answer to this question is obviously impossible for man, our data suggest that a difference may exist. Indeed, steady state responses to manipulation of the carotid sinus scarcely involved heart rate and mainly consisted in arterial pressure changes. On the other hand, very large heart rate responses occurred when extracarotid baroreceptors were also involved in the stimulus. This powerful action of extracarotid baroreceptors is likely to have buffered the heart rate responses to changes in carotid sinus transmural pressure; however, the fact that blood pressure responses were not buffered to the same extent suggests that extracarotid baroreceptors may not exert equally powerful control of blood pressure. The conclusion that the carotid sinus is more involved in regulation of arterial pressure and extracarotid baroreceptive areas in regulating heart rate is consistent with findings from experiments on animals.^{25, 26}

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References

- Ernsting J, Parry DJ: Some observations on the effect of stimulating the carotid arterial stretch receptors in the carotid artery of man (abstr). *J Physiol (Lond)* **137**: 45P, 1957
- Bevegård BS, Shepherd JT: Circulatory effects of stimulating the carotid arterial stretch receptors in man at rest and during exercise. *J Clin Invest* **45**: 132-142, 1966
- Beiser GD, Zelis L, Epstein SE, Mason DT, Braunwald E: The role of skin and muscle resistance vessels in reflexes mediated by the baroreceptor system. *J Clin Invest* **49**: 225-231, 1970
- Stegemann J, Busert A, Brock D: Influence of fitness on the blood pressure control system in man. *Aerosp Med* **45**: 45-48, 1974
- Bjursted H, Rosenhamer G, Tyden G: Cardiovascular responses to changes in carotid sinus transmural pressure. *Acta Physiol Scand* **94**: 497-505, 1975
- Eckberg DL, Cavanaugh MS, Marck AL, Abboud FM: A simplified neck suction device for activation of carotid baroreceptors. *J Lab Clin Med* **85**: 167-173, 1975
- Thron HL, Brechmann W, Wagner J, Keller K: Quantitative Untersuchungen über die Bedeutung der Gefäßdehnungsrezeptoren im Rahmen der Kreislaufhomöostase beim wachen Menschen. *Pfluegers Arch* **293**: 68-99, 1967
- Ludbrook J, Mancia G, Ferrari A, Zanchetti A: Factors influencing the carotid baroreceptor response to pressure changes in a neck chamber. *Clin Sci Mol Med* **51** (suppl 3): 347a-349a, 1976
- Glick G, Braunwald E: Relative roles of the sympathetic and parasympathetic nervous system in the reflex control of heart rate. *Circ Res* **16**: 363-375, 1965
- Leon DF, Shaver JA, Leonard JJ: Reflex heart rate control in man. *Am Heart J* **80**: 729-739, 1970
- Gribbin B, Pickering TG, Sleight P, Peto R: Effect of age and high blood pressure on baroreflex sensitivity in man. *Circ Res* **29**: 424-431, 1971
- Pickering TG, Gribbin B, Sleight P: Comparison of reflex heart rate response to rising and falling arterial pressure in man. *Cardiovasc Res* **6**: 277-283, 1972
- Korner PI, West MJ, Shaw J, Uther JB: "Steady-state" properties of the baroreceptor-heart rate reflex in essential hypertension in man. *Clin Exp Pharmacol Physiol* **1**: 65-76, 1974
- Snedecor GW, Cochran WG: *Statistical Methods*, ed 6. Ames, Iowa State University Press, 1967
- Donald DE, Edis AJ: Comparison of aortic and carotid baroreflex in dogs. *J Physiol (Lond)* **215**: 521-538, 1971
- Pelletier CL, Clement DL, Shepherd JT: Comparison of afferent activity of canine aortic and sinus nerves. *Circ Res* **31**: 557-568, 1972
- Scher AM, Young AC: Servoanalysis of carotid sinus reflex effects on peripheral resistance. *Circ Res* **12**: 152-162, 1963
- Scher AM: The gain of the carotid sinus reflex in awake animals; importance of rate of change of pressure at the receptor. *In Baroreceptors and Hypertension*, edited by P Kedzi. Oxford, Pergamon Press, 1967, pp 89-95
- Heymans C, Neil E: *Reflexogenic areas of the cardiovascular system*. London, Churchill, 1958, p 103
- Angell-James JE: The effects of changes of extramural "intrathoracic" pressure on aortic arch baroreceptors. *J Physiol (Lond)* **214**: 89-103, 1971
- Guz A, Nobel MIM, Trenchard D, Cochrane HL, Makey AR: Studies on the vagus nerve in man; their role in respiratory and circulatory control. *Clin Sci* **27**: 293-304, 1964
- Korner PI, Shaw J: Central resetting of the arterial blood pressure control system. *In Cardiovascular Regulation in Health and Disease (International Symposium)*, edited by C Bartorelli, A Zanchetti. Milan, Istituto di Ricerche Cardiovascolari 1970, pp 143-157
- Goetz KL, Bond GC: Reflex diuresis during tachycardia in the dog. *Circ Res* **32**: 434-441, 1972
- Vatner SF, Boettcher DH, Heyndrickx GR, Ritchie RS: Reduced baroreceptor sensitivity with volume loading in conscious dogs. *Circ Res* **37**: 236-242, 1975
- Glick G, Covell JW: Relative importance of the carotid and aortic baroreceptors in the reflex control of heart rate. *Am J Physiol* **214**: 955-961, 1968
- Dampney RAL, Taylor MG, McLachlan EM: Reflex effects of stimulation of carotid sinus and aortic baroreceptors on hindlimb vascular resistance in dogs. *Circ Res* **29**: 119-127, 1971

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