Baroreceptor Reflexes in Human Hypertension

GIUSEPPE MANCIA, JOHN LUDBROOK, ALBERTO FERRARI, LUISA GREGORINI, AND ALBERTO ZANCHETTI

SUMMARY We studied the control of arterial pressure by the carotid sinus baroreceptors in 35 hypertensive humans, using a variable pressure neck chamber to alter carotid sinus transmural pressure in a graded fashion. The results were compared with those obtained from 11 normotensives. As in normotensives, reduction in carotid transmural pressure caused a linearly related pressor response and vice versa. However, whereas in normotensives the pressor response was greater than the depressor, the reverse was the case in hypertensives. Furthermore, the pressor response decreased and the depressor response increased progressively with an increase in severity of the hypertension. Thus while in normotensives the carotid baroreflex is more effective in protecting against hypotension, in hypertensives the antihypertensive function of the reflex is favored. Similar differences between hypertensives and normotensives were found with respect to the carotid baroreceptor control of heart rate. In eight hypertensives, reflex changes in heart rate also were studied by injection of phenylephrine and trinitroglycerine to vary not only carotid baroreceptor activity, but also activity of extracarotid baroreceptors. The results were compared with results of similar studies on eight normotensives. These comparisons suggest that, whereas the carotid baroreceptor reflex remains active in hypertension, reflexes stemming from extracarotid baroreceptor areas are much diminished.

THE TECHNIQUE most widely used to test baroreflexes in human hypertensive and normotensive subjects has been to measure the response of heart rate to injection of pressor and depressor drugs free of direct cardiac effects. Use of this method has provided valuable information on the control of heart rate exerted by the high pressure baroreceptor population, and has demonstrated that the sensitivity of this control is reduced in hypertensives as compared to normotensives. However, the method does not allow one to study that component of the baroreceptor reflex response which is of paramount importance in hypertensives, namely arterial blood pressure. Indeed scant information is available on this point. In hypertensives, supramaximal electrical stimulation of the carotid sinus nerves has been shown to reduce blood pressure markedly and anesthetic blockade of the nerves to increase blood pressure markedly. These findings suggest that in hypertension the carotid baroreceptors retain the capacity to vary blood pressure in both directions. However, procedures such as supramaximal electrical stimulation and nerve blockade act in an all-or-none manner and do not describe the relation between physiological stimuli and reflex effects which characterizes a reflex function.

Another method to test baroreflexes in man is to change pressure within a sealed chamber surrounding the neck and thereby alter carotid sinus transmural pressure. By this method Wagner et al. reported that the magnitude of blood pressure responses in hypertensives was indistinguishable from that of normotensives. However we recently have shown that the transmission of pressure from the neck chamber to the region of the carotid sinus is incomplete and asymmetric. Thus correction factors must be applied to construct stimulus-response curves that relate precise changes in carotid transmural pressures with the reflex changes in mean arterial pressure.

The present study was undertaken in hypertensive subjects to provide a more detailed description of the control of blood pressure that the carotid baroreceptors exert in human hypertension and to compare this control with that exerted in normotensive subjects. Another aspect of the baroreceptor reflex regulation has been investigated in the present study. In our previous study on normotensive subjects we had found that the reflex changes in heart rate due to injection of pressor and depressor drugs are much greater than those due to the neck chamber, presumably because the former stimulus is applied to both carotid and extracarotid baroreceptors, while the latter primarily affects the carotid baroreceptors only. This comparison was made again in the present study to explore whether these differences in heart rate control are maintained or modified in hypertension.

Methods

The study was conducted in 35 hospital inpatients (21 male, 14 female) whose ages ranged from 26 to 67 years (mean 45) and in all of whom diastolic blood pressure was greater than 100 mm Hg. In all patients the arterial
hypertension had been classified as essential. The patients were selected for the study if (1) no cardiac or renal failure was present, (2) no symptoms of coronary or cerebral vascular insufficiency ever had occurred, (3) no major diseases other than the hypertension were diagnosed, and (4) there had been no cardiovascular drug treatment during the 3 weeks preceding the study. All patients gave free consent to the procedure after having had the nature and the purpose of the investigation explained.

The methods employed in the present study are identical to those described in detail in a previous study on normotensive subjects. In brief, in each patient the neck was enclosed in a plastic box extending from the shoulders to a plane just above the chin, the ear lobes, and the occiput. The box had caudal and cranial seals that allowed a commercial vacuum cleaner to produce positive and negative pressure changes in its interior over a range of ± 50 mm Hg. The pressure changes were measured by a strain-gauge transducer connected to the box interior. Pulssatile arterial blood pressure was measured by a femoral artery catheter introduced percutaneously and a strain-gauge transducer; mean arterial pressure was obtained by electronic damping and also by integration of the pulssatile signal over periods of 10 seconds. A cardiograph was triggered by the R wave of an electrocardiogram and from this record heart rate was calculated in beats per minute and heart interval (R-R interval) in milliseconds.

Phenylephrine (25–100 μg) or trinitroglycerin (25–150 μg) was injected via a subclavian or brachiocephalic venous catheter to increase and decrease arterial blood pressure within a range ± 25 mm Hg. The pressure changes were applied to the neck chamber. The stimuli were calculated as changes in transmural pressure. In the control period and during the late response period, hemodynamic values were stable, since in either period mean arterial pressure had a normalized standard error during three successive 10-second periods of no more than 0.2%.

To analyze the effects of drugs, comparison was made between the average mean arterial pressure and heart interval values during the 10-second period immediately before drug injection (control), and during the 5–10 second sustained part of the response. For each subject, linear regressions were calculated to describe the stimulus-response relationships, and the regression coefficients (indicating the slope of the relationships) were taken to indicate the magnitude of the reflex response. When the neck chamber was used, the stimulus was generally taken as the change in neck tissue pressure around the carotid sinus, the responses being the changes in arterial pressure and heart interval. When the changes in heart interval induced by the neck chamber were compared with those induced by drugs, the stimuli were calculated as changes in transmural pressure. With drug injection these were the rise or fall in mean arterial pressure caused by drugs. With the neck chamber these were the changes in neck tissue pressure minus the reflex changes in mean arterial pressure during either the early or the steady state part of the response.

Linear regression coefficients were tested to determine whether they differed significantly from zero. Comparison of slopes or regressions in different circumstances (early vs. steady state responses, increases vs. decreased neck tissue pressure, etc.) was made by covariant analysis within each individual subject, and by paired t-test for the group as a whole. The unpaired t-test or the one-way analysis of variance was used to compare responses among groups of subjects with different values of arterial blood pressure. For this purpose the hypertensive subjects were divided into two groups: a group of 17 "severe" hypertensives with a basal mean arterial pressure above 145 mm Hg (mean age 48 ± 2 years, average mean arterial pressure and heart interval 162 ± 4 mm Hg and 747 ± 28 msec), and a group of 18 "moderate" hypertensives with a basal mean arterial pressure below 145 mm Hg (mean
FIGURE 1  Original traces of hemodynamic changes induced by a decrease (A) and an increase (B) in neck chamber pressure. NCP, neck chamber pressure; HR, tachograph trace; ABP, pulsatile arterial pressure; MAP, mean arterial pressure. fABP, arterial pressure integrated over 10-second periods. Time is at the bottom as 1 and 5 seconds.

age 43 ± 2 years, average mean arterial pressure and heart interval 134 ± 2 mm Hg and 760 ± 28 msec). To provide the necessary comparison with data at normal blood pressure, these two groups were compared with 11 healthy normotensives (mean age 36 ± 4 years, average mean arterial pressure and heart interval 102 ± 3 mm Hg and 780 ± 45 msec) who had been studied previously in an identical manner. Throughout the study, a P value of less than 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

Effects on Arterial Blood Pressure

Hypertensive Subjects. As shown in Figure 1, the hypertensive subjects showed a fall in arterial blood pressure when the neck chamber pressure was decreased and an increase in arterial blood pressure when the neck chamber pressure was increased. Pulse pressure did not change in either circumstance.

A detailed analysis of the effects of the changes in neck chamber pressure was performed by dividing the depressor and pressor responses into an early and late or steady state components as defined under Methods. Within the individual subjects, linear regression analysis showed that reduction in mean arterial pressure was always positively correlated with reduction in neck tissue pressure, both for the early and the steady state responses. Similar calculation showed a positive correlation of the increase in mean arterial pressure with an increase in neck tissue pressure in all except three subjects for the steady state response, and all except five subjects for the early response (Table 1).

Consistent differences were found between the early and the steady state responses (Table 1 and Fig. 2, left).

**TABLE 1  Hemodynamic Responses to Changes in Neck Tissue Pressure***

<table>
<thead>
<tr>
<th></th>
<th>Decreased neck tissue pressure</th>
<th>Increased neck tissue pressure</th>
<th>Increased vs. decreased neck tissue pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Steady state</td>
<td>P</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>147.7</td>
<td>0.78 ± 0.05</td>
<td>0.56 ± 0.05 &lt; 0.001</td>
</tr>
<tr>
<td>Heart interval (msec)</td>
<td>754 ± 20</td>
<td>-4.22 ± 0.53</td>
<td>-2.02 ± 0.29 &lt; 0.01</td>
</tr>
</tbody>
</table>

* Data from 35 subjects with essential hypertension whose mean age was 45.4 ± 1.6 years. Responses shown as means ± SE of individual regression coefficients of changes in mean arterial pressure (mm Hg) and heart interval (msec) on changes in neck tissue pressure (mm Hg). Mean coefficients were statistically significant with the exception only of that referring to the early heart interval response to increased neck tissue pressure. Comparison between coefficients was made by the t-test for paired observations. For blood pressure, mean coefficients are positive because blood pressure decreased when neck tissue pressure decreased, and vice versa. For heart interval, mean coefficients are negative because heart interval increased (i.e., bradycardia) when neck tissue pressure decreased, and vice versa. The first two columns of P values refer to differences between mean regression coefficients of each vs. steady state changes. The last two columns on the right refer to differences between regression coefficients at increased vs. decreased neck tissue pressure, the comparison being made separately for early and steady state responses.
Thus, when neck tissue pressure was increased, the regression coefficient for the steady state response was markedly and significantly greater than that calculated during the early phase, indicating that the blood pressure rise induced by decreasing the stimulus to the carotid baroreceptors has a slow build-up time. On the contrary, when neck tissue pressure was decreased, the mean regression coefficient for the steady state response was significantly less than that for the early phase, indicating that increasing the stimulus to the carotid baroreceptors induces a quick fall in blood pressure, which is later reduced to a sustained smaller hypotensive response.

Consistent differences also were found between regression coefficients at increased and decreased neck tissue pressures (Table 1 and Fig. 2, left). A decrease in neck tissue pressure usually was associated with a significantly greater regression coefficient than was an increase in neck tissue pressure, during both the early and the steady state phase. Thus the carotid baroreceptor reflex of subjects with arterial hypertension is asymmetric, since its immediate and persistent effects on blood pressure are greater when there is an increase in carotid baroreceptor activity than when there is a decrease.

Comparison between Hypertensive and Normotensive Subjects. As shown in Figure 3, left, the changes in arterial blood pressure induced by the changes in neck tissue pressure were significantly different in the 35 hypertensive subjects as compared to the 11 normotensive subjects investigated in a previous study. For an increase in neck tissue pressure, the mean regression coefficient was greater in the normotensives both in the early phase (df = 44, t = 4.142; P < 0.001) and in the steady state (df = 44, t = 2.882; P < 0.01). On the other hand, for a decrease in neck tissue pressure, the mean regression coefficient was greater in the hypertensives in the early phase (df = 44, t = 2.182; P < 0.05), although not in the steady state.

Further differences were revealed when the reflex responses were considered according to the degree of arterial hypertension. When the hypertensive group was divided into the two subgroups of patients with "severe" and "moderate" hypertension (see Methods), the mean regression coefficient for the increase in neck tissue pressure (Fig. 4, left above) was greater in the normotensive subjects than in the moderate hypertensives, and greater...
in the moderate hypertensives than in the severe hypertensives, the one way analysis of variance showing the difference to be significant in early phase (df = 2, 43, F = 11.632; P < 0.01) as well as in the steady state (df = 2, 43, F = 5.232; P < 0.01). Mean regression coefficients for a decrease in neck tissue pressure (Fig. 4, left below) showed an opposite pattern although in this case the difference was significant in the early phase (df = 2, 43; F = 4.870; P < 0.05) but not in the steady state. Similar relationships between the regression coefficients and the level of basal arterial pressure were demonstrated by computing linear regression coefficients on mean arterial pressure including all 11 normotensive and all 35 hypertensive subjects. For increased neck tissue pressure, this regression was highly significant both in the early phase (r = 0.585, P < 0.001) and in the steady state (r = 0.498, P < 0.001). The same was true for reduced neck tissue pressure (r = 0.479, P < 0.001, respectively).

The differences among the normotensives and the two groups of hypertensive subjects also are displayed in Figure 5, left, in which the stimulus to the carotid baroceptors is calculated as the actual value of carotid transmural pressure occurring during the steady state phase of the response, and the effect of the stimulus is plotted as the concomitant value of mean arterial pressure. Furthermore, Figure 5, left, shows that the stimulus-response relationship of the hypertensive subjects is displaced to the right of the stimulus-response relationship of the normotensive subjects, and that the extent of the displacement is greater for the group with the more marked hypertension.

The differences between normotensive and hypertensive subjects were not due to differences in age among the various groups, as correlation of age with the regression coefficient showed no significant association, both when only the hypertensives and when whole population of hypertensives and normotensive subjects were considered.

Effects on Heart Rate

Hypertensive Subjects. Figure 1 shows that a decrease in neck chamber pressure induce a bradycardia, and that a slight increase in heart rate occurred when the neck chamber pressure was raised.

In Table 1 and Figure 2, right, changes in heart rate are expressed as changes in heart interval. Within the individual subjects, linear regression analysis showed that both in the early phase and in the steady state, increase in heart interval was linearly related to the decreases in neck tissue pressure in almost all subjects: the regression coefficient for the early response was significantly greater than that for the steady state, indicating that the bradycardia was maximal at the beginning of the stimulus and then faded partially. When the neck tissue pressure was increased, a linear relation with the decrease in heart interval was present in the majority of the subjects only during the steady state. As shown in Figure 2, right, for the group as a whole the early response to the increase in neck tissue pressure was not significantly different from zero, whereas the overall steady state response consisted in a slight tachycardia.

Comparison between Hypertensive and Normotensive Subjects. Reflex changes in heart interval differed between hypertensives and normotensives in a way similar to the reflex changes in blood pressure. In other words the hypertensives had smaller tachycardic reflex responses, and greater bradycardic reflex responses than normotensives (Table 1 and Figs. 3-5, right).

![Figure 5](http://circres.ahajournals.org/)

**Figure 5** Relation between absolute values of carotid transmural pressure and absolute values of mean arterial pressure in normotensive, "moderate," and "severe" hypertensive subjects (see Methods). In each group of subjects the set-point (open circle, filled circle, or cross) represents the averaged (+ SE) mean arterial pressure during control, the continuous lines the averaged regression coefficients, and the dashed lines the standard errors of the regression coefficients. The absolute values of carotid transmural pressure were obtained by the difference between mean arterial pressure and neck tissue pressure during the steady state part of the neck chamber stimulus.
Injections of Drugs

Hypertensive Subjects. Pressor and depressor drugs were injected in eight of the 35 subjects. The resultant increases and decreases in blood pressure were accompanied by linearly related increases and decreases in heart interval. In all eight subjects there was a significant positive correlation ($P < 0.01$) between changes in heart interval and changes in mean arterial pressure.

Figure 6 compares changes in heart interval induced by drugs with those induced by the neck chamber in the same eight subjects. For comparison, stimuli were calculated as changes in arterial transmural pressure (see Methods). The regression coefficient obtained when transmural pressure was increased by drugs was indistinguishable from that obtained when the neck chamber was used. The regression coefficient obtained when transmural pressure was reduced by drugs was significantly greater ($P < 0.05$) than that calculated for the early response to the neck chamber, but not significantly different from that calculated for the steady state response.

Comparison between Hypertensive and Normotensive Subjects. Regression lines for the eight hypertensive subjects studied with drugs are compared in Figure 7 with those for eight normotensive subjects studied in an identical fashion in a previous investigation. The respective mean ages were 40 ± 2.7 and 38 ± 5 years; average mean arterial pressures were 138 ± 4.5 and 101 ± 5 mm Hg; average heart intervals were 707 ± 28 and 864 ± 61 msec. It will be seen that both the bradycardic and the tachycardic responses were on average some 3 times less in the hypertensives than in the normotensives ($P < 0.01$). It will be remembered that, when the neck chamber was used, only the tachycardic response was found to be decreased in hypertensives, whereas the bradycardic one was increased (see above).

Discussion

The present study shows that the carotid baroreceptor reflex of hypertensive subjects differs in various important ways from that of normotensives.

The most important and previously unreported change brought about by hypertension in the carotid baroreceptor reflex function is a change in shape of the stimulus-response curve. In normotensives the pressor response that follows reduction in carotid baroreceptor activity is greater than the depressor response that follows an increase in carotid baroreceptor activity, whereas in hypertensives the reverse is the case. Moreover, the pressor response becomes progressively smaller, and the depressor response progressively greater, with increasing degrees of hypertension. This means that in normotensives large increases but only slight decreases in pressure can be produced by alterations in baroreceptor activity; on the other hand, with increasing degrees of hypertension, slight increases but large decreases in pressure can be produced by the baroreceptors.

The change in the shape of the stimulus-response curve together with its shift to the right represents the phenomenon defined as "resetting" of the baroreflex regulating blood pressure. There is evidence from investigations on anesthetized animals that experimental hypertension is associated with resetting of the firing threshold and the operating range of baroreceptors to higher levels of pressure. However, in unanesthetized hypertensive animals, and especially in hypertensive human subjects, the evidence is much more limited: indeed, as these studies have been performed by use of vasoactive drugs, the changes in heart rate and blood pressure are of a greater magnitude.
information necessarily has been restricted to a resetting of the heart rate regulating component of the reflex. Our data provide therefore the demonstration that the blood pressure-regulating component of the baroreflex also is reset in hypertensives. Furthermore, it is interesting that the changes in the stimulus-response curves characterizing the carotid baroreceptor reflex are greater in severe than in moderate hypertension; thus the extent of the resetting seems to be directly related to the magnitude of hypertension.

Another difference between reflexes in normotensives and in hypertensives is in the rate of development of the responses to changes in carotid sinus transmural pressure. If the difference between steady state and early responses is taken as an index of the rate of evolution of the reflex response, then the pressor response to reduction in carotid sinus transmural pressure develops more slowly in hypertension, although the rate of development of the depressor response does not differ from that in normotensives.

Since our observations were necessarily made in a closed-loop system, the behavior of baroreceptors located elsewhere than in the carotid sinuses, such as those in the aortic arch and the heart, also must be taken into account. It might be maintained that the different responses to alterations in carotid transmural pressure that are observed in hypertensives as compared to normotensives are in fact due to changes in the characteristics of extracarotid rather than carotid baroreceptor reflexes. This would occur if it were the extracarotid baroreflexes that buffer more effectively the depressor responses to the neck chamber in normotensive subjects and the pressor response in hypertensives. However, our previous study in which the effects of carotid baroreceptor stimulation were compared to those of all arterial baroreceptor stimulation suggests that, in normotensive man, extracarotid baroreflexes, although active in heart rate control, are less involved in control of blood pressure. Moreover, the evidence gained by similar comparison made in the patients of the present study (and discussed below) indicates that the importance of these extracarotid baroreflexes is further and greatly reduced in hypertension. Thus, although it is entirely possible that hypertension is associated with similar changes of all baroreceptor reflexes, the differences in the response to the neck chamber brought about by human hypertension are likely to be due mainly to changes in the carotid baroreflex.

A question which has interested many investigators is whether sensitivity of the baroreceptor reflexes is altered in human hypertension. On the basis of the reflex changes in heart rate caused by injection of vasoactive drugs, several investigators have reported a marked reduction in sensitivity when hypertensives are compared to normotensives. On the other hand, Wagner et al. were unable to observe any effect of hypertension on the blood pressure and heart rate reflex changes when the carotid baroreceptors were tested with the neck chamber technique.

Our data indicate that the question of an alteration in the baroreflex sensitivity by hypertension is a complex one, and that there probably are differences among the various baroreceptor reflexes. In our previous study on normotensive subjects, we found that the slope of the stimulus-response curve characterizing baroreceptor control of heart rate was three times greater when measured by the drug technique (affecting extracarotid and carotid baroreceptors) than that found by the neck chamber (affecting carotid baroreceptors only). We now have found that, in hypertension, the slope of the heart rate reflex as measured by the drug technique is three times less that found in normotensives and is indistinguishable from the slope found by the neck chamber. Thus, as far as the reflex control of heart rate is concerned, there is an overall reduction of the baroreflexes in human hypertension, largely attributable to loss of sensitivity of the extracarotid baroreceptor reflex component.

On the other hand, a marked reduction in sensitivity of the carotid baroreceptor reflex is not as clear. Normally, the sensitivity of a reflex function is defined by the slope of the steepest part of its stimulus-response curve. Because of the differences in the carotid baroreceptor reflex in normotensive and hypertensive subjects, the highest slope for the normotensives is obtained with reduction in carotid baroreceptor activity, and for the hypertensives with an increase in carotid baroreceptor activity. These two slopes appear similar under steady state conditions (see Fig. 5), and this seems to indicate little change in sensitivity of the carotid baroreceptor reflex in human hypertension. It is true, however, that in our hypertensives a reduced buffering function of the extracarotid baroreceptor reflexes (see above) should have caused some increase in the responses to carotid baroreceptor manipulation. Therefore an unchanged carotid baroreceptor slope does not exclude some degree of reduced function of this reflex also.

In summary, baroreceptor reflex control undergoes complex changes in human hypertension. The main change we have found is that the carotid baroreflex is reset in such a way that smaller pressor and greater depressor responses to carotid sinus manipulation are obtained. There is no direct evidence that sensitivity of the carotid baroreflex is affected, whereas the sensitivity of the extracarotid baroreflexes seems to be markedly decreased. Since extracarotid baroreflexes exert a strong control on heart rate, the overall sensitivity of the arterial baroreceptor reflex with respect to heart rate is reduced.

Little can be learned from our study on the mechanisms that might induce the changes in the baroreflexes in human hypertension. Data on renal hypertensive animals indicate a raised threshold of baroreceptor firing, a phenomenon which can suitably explain the resetting of the reflex. If the rise in threshold were such that at hypertensive levels the baroreceptor firing is just above threshold, whereas it is nearly maximum in normotensives, this also would explain why reflex responses are greater for reduction in baroreceptor activity in normotensives and for an increase in baroreceptor activity in hypertensives. Experiments on animals have also shown that the rate of change in baroreceptor firing above threshold is diminished. This finding is compatible with the reduction in sensitivity of the extracarotid bar-
oreflexes that we also have observed, but it also implies that the sensitivity of the carotid baroreflex should be decreased. Caution should be used, however, before applying this information from animal experiments to human hypertension. Studies on animals have been generally performed on a rapidly developing short-term hypertension, while essential hypertension in man certainly develops much more slowly, and in most of our patients it was of unknown duration. These time factors, as well as species differences, may differently influence the baroreceptors in the various receptive areas.

Regardless of the mechanisms involved, the changes in the carotid baroreceptor reflex that occur in human hypertension have important clinical implications. The "resetting" phenomenon prevents saturation of the reflex and abolition of sympathetic vasoconstrictive tone that otherwise would occur with increased blood pressure. Preservation of sympathetic vasoconstrictive control certainly provides a better moment-to-moment adjustment of circulation in hypertension. Moreover, the characteristics of the reflex are so changed that subjects with high blood pressure have a more effective protection against influences that tend to raise blood pressure further. This, and the fact that the speed of the antihypertensive responses is unchanged, are obviously important advantages in subjects in whom blood pressure rises may represent an additional risk. Finally, clinical consequences may also derive from the reduced and sluggish nature of the antihypotensive action of the reflex that characterizes human hypertension. One might expect that this would result in exaggerated postural hypotension, and this has indeed been described recently by Cuche et al. who found that, whereas in normal subjects standing results in a fall of blood pressure, in hypertensives standing results in a fall of blood pressure.

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References

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