Diminished Baroreflex Sensitivity in High Blood Pressure

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SUMMARY

Sudden intravenous injections of small amounts of angiotensin or phenylephrine were given to 30 subjects to produce modest, brief increases in directly measured systemic arterial pressure. A plot of each systolic pressure against the second succeeding cardiac cycle length produced a linear distribution, the slope of which was expressed as the millisecond increase in cycle length per mm Hg rise in systolic pressure. The slope is an index of baroreflex sensitivity and was found to have an average value of 12.8 in 18 subjects without hypertension and 2.8 in 12 others with hypertension. When all results were pooled, there was an inverse relationship between the resting mean arterial pressure and slope of the baroreflex regression lines. The findings demonstrate reduced sensitivity of the baroreflexes in hypertension, with respect to control of heart rate. A distinction is made between this change in sensitivity and simple resetting of the reflex.

Additional Indexing Words:
Hypertension Cardiovascular regulation Baroreceptor
Angiotensin Phenylephrine Heart rate

It seems certain that an alteration of baroreceptor reflex function is associated with systemic arterial hypertension. If this were not so, bradycardia would be characteristic of most hypertensive syndromes, due to a continued high level of reflex activity. The normal heart rate usually found, therefore, reflects either an adaptation of the baroreflex systems to the higher pressure or a primary dysfunction which could have a causative role. There is evidence of abnormal baroreceptor activity induced by experimental hypertension in animals, but little new information has become available in man despite long-standing interest. This paper describes quantitative assessment of one baroreceptor function, that of heart rate control, in subjects with normal and high arterial pressures.

Methods

Observations were made in 30 unsedated subjects who were in the supine or semisupine position. An antecubital vein and a brachial artery were cannulated percutaneously with plastic tubing. Arterial pressure was measured with a strain gauge and respiratory phase was detected by a pneumograph. These signals and lead I of the electrocardiogram were recorded with a direct-writing polygraph. Mean arterial pressure was found by electrical damping or planimetry. The characteristics of the recording system have been described before.

Multiple injections of 0.25 to 2.0 μg of angiotensin II amide were flushed through the venous cannula with 5 ml of isotonic saline, producing modest, transient rises in systemic arterial pressure (BP). Recordings of BP and the other parameters were made at paper speed of 30 or 50
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mm/sec until the peak of the pressure rise had passed. In 16 of the subjects 50 to 100-μg injections of phenylephrine were also administered, again producing increases of BP in order to stimulate the baroreflex. Both drugs caused rises in systolic, diastolic, and mean BP, with little change in pulse pressure.

The records were analyzed by methods which have been described in detail elsewhere, and which are summarized here. All systolic and diastolic pressure pulses and R-R intervals (in milliseconds) were measured from the time of injection of the pressor agent until just after the peak of the pressure rise, usually requiring about 35 beats. Each systolic BP was plotted against the second R-R interval following it, thus allowing time for reflex activity to occur. R-R intervals during inspiration were not included, in order to avoid the influence of sinus arrhythmia. Linear relationships between systolic BP and the R-R interval were found, and from the set of plotted values resulting from each angiotensin or phenylephrine injection the correlation coefficient and the linear regression equation were calculated.

Results are included in this report if the probability value derived from the correlation coefficient and the sample size was less than 0.05; this usually was associated with an r value greater than 0.65.

The brief pressure rise provided a spectrum of cardiac cycle lengths in relation to a range of systolic BPs (fig. 1). The degree of cardiac slowing produced was shown by the slope of the regression line, expressed as milliseconds increase in cycle length (R-R interval) per mm Hg rise in systolic BP. The steeper the slope of the distribution, the more sensitive is overall baroreflex function, with respect to control of heart rate. Previous studies, as well as this one, found the slopes of these lines to be independent of the magnitude of baroreceptor stimulation, that is, the extent of BP rise, or the dose of drug, once a detectable increase in BP was produced. Multiple injections were given to all subjects and a total of 159 regression coefficients was calculated.

Systolic BP was chosen as the pressure measurement for these calculations because of the ease and accuracy of its measurement. We recognize the importance of other components of the pressure wave as determinants of baroreceptor activity (for example, mean BP each pulse), but their measurement beats by beat presents problems not encountered with systolic BP. Since pulse pressure did not change much with the pressor response, the correlations that we observed between systolic BP and cycle length no doubt existed with mean BP as well.

The mean arterial pressure at rest ranged from 72 to 135 mm Hg and presented a continuous se-

Figure 1

Relationship between individual systolic arterial pressures (mm Hg) and subsequent pulse intervals (R-R, in milliseconds) when pressure was transiently increased by the sudden injection of angiotensin. (A) Results of one injection in a subject with a resting mean arterial pressure of 74 mm Hg. (B) Results of one injection in a man with mean pressure of 119 mm Hg. The difference in slopes of the regression lines is evident. Abbreviation: r = correlation coefficient.

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Table 1
Age, Control Blood Pressure, and Baroreflex Slope After Injection of Angiotensin and Phenylephrine

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Control mean arterial pressure (mm Hg)</th>
<th>Angiotensin</th>
<th>Phenylephrine</th>
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<td></td>
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<td>91</td>
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<tr>
<td>Average</td>
<td>37.4</td>
<td>91.4</td>
<td>12.8 ± 2.0†</td>
<td>14.2</td>
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<table>
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<tr>
<th>Subject</th>
<th>Age (yr)</th>
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<th>Angiotensin</th>
<th>Phenylephrine</th>
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<tr>
<td>Average</td>
<td>43.5</td>
<td>123.1</td>
<td>2.8 ± 0.6†</td>
<td>5.1</td>
</tr>
</tbody>
</table>

* = Postural hypotension  † = Mean ± standard error
Subjests are listed in order of increasing control mean blood pressure.

diagnosis of essential hypertension. None had received diuretic, sedative, or antihypertensive therapy for several weeks, and most had not been treated previously at all. The remaining 18 subjects had lower mean BP ranging from 72 to 108 mm Hg (average, 91), and all were healthy save one elderly man with postural hypotension.

Results
The slopes of the systolic BP-RR interval distributions for each subject were averaged and appear in table 1; representative examples are shown in figure 1. With angiotensin injections, individuals with a control mean BP below 110 mm Hg had an average slope of 12.8 (se ± 2.0), compared with 2.8 (se ± 0.6) for those with higher pressures (P < 0.01). Only one hypertensive subject had a slope greater than 5; 15 of the 18 subjects with lower BP had slopes greater than.
5. Three patients with hypertension had virtually no change in heart rate despite the rise in BP produced by drug injection.

As mentioned earlier, the magnitude of rise of BP appears to be independent of the slopes we have described. Nonetheless, in order to be certain that the experimental manipulations were similar in these two groups of subjects the amount of change of pressure produced by the drug was evaluated. Angiotensin injections increased systolic BP an average of 21 mm Hg in those with lower control BP and 32 mm Hg in those with hypertension. When expressed as a percentage of the control level, those with lower BP had an average rise of 17% compared with 20% for the hypertensives. The degree of baroreceptor stimulation thus seemed comparable.

Not all subjects received phenylephrine, but the results were similar to those with angiotensin. The average slope with phenylephrine for 13 subjects with lower pressures was 14.2; the average for the three hypertensives was 5.1.

The angiotensin results from both groups were then pooled and each subject’s mean BP in the control state was plotted against the slope of the systolic BP-RR interval line, as presented in figure 2. A significant negative correlation resulted (r = -0.62, P < 0.001), demonstrating progressively less influence of systolic BP on heart rate at higher control mean pressure.

An attempt was made to determine whether the spontaneous variations in BP during normal breathing were associated with different degrees of variation in heart rate in the two groups. The measurements were made before any drug effects. During the respiratory cycle, the hypertensives demonstrated an average variation of systolic BP of 13 mm Hg, or 8% of the lowest systolic level observed at the time. Those with lower BP varied 9 mm Hg, or 7% of the lowest systolic value. However, the spontaneous variation of the R-R interval during the respiratory cycle was different in the two groups, being 72 msec in the hypertensives and 128 msec in the others (P < 0.05). Although the normal group was weighted by one person with considerable variation in heart rate, it is suggested, nonetheless, that hypertensives have less variation in heart rate than normotensives, yet have slightly more variation in pressure.

**Discussion**

The results contrast the influence of the baroreflexes on heart rate at normal and chronically high levels of BP. The control heart rates were similar in the low and high pressure groups (68 and 71 beats per minute, respectively), but in the hypertensives they changed little with further elevations of BP. We believe that the gross differences in slope.
Two hypotheses for an alteration of baroreflex function in hypertension. (Left) Resetting of the reflex without a change in sensitivity. The slope of the relationship between blood pressure and pulse interval is not changed. (Right) In addition to resetting of the reflex, with the line moved to the right, there is a diminution in sensitivity. Our results support the latter hypothesis.

of the regression lines at low and high control pressures demonstrate a decrease in the sensitivity of the baroreceptor reflexes in essential hypertension, at least with respect to control of heart rate. This is quite different from “resetting” of the reflex at a higher level of BP in hypertensives, but with unchanged sensitivity, as shown in figure 3. Resetting without a change in sensitivity (slope of line) has been produced by alterations in blood gas composition in normal subjects, but this adaptation does not appear to be characteristic of chronic hypertension.

Differences in responsiveness to angiotensin or phenylephrine are not factors to account for the differences in slope, as the magnitude of rise in BP produced by the drugs was similar in proportion to the control level and, if anything, was weighted to provide greater stimulation of the reflex in the high pressure group. Direct effects of the drugs on heart rate have been evaluated previously and do not explain our results.5, 12–15

The relationship of heart rate to blood pressure during ordinary breathing, without drug effects, further supports the idea of abnormal baroreflex function in hypertension. In those with high BP, slightly greater swings in a systolic BP were associated with less variation in heart rate than is seen in normotensives.

It must be emphasized that the baroreflex testing herein employed appraises overall reflex function and allows no firm conclusions about a locus of altered sensitivity. Thus, an influence on heart rate which overrides baroreceptor activity would be interpreted as an influence on the sensitivity of the reflex in our studies.

There was an apparent, inverse relationship between age and the slope of the baroreflex lines ($r = -0.53, P < 0.01$), but the average age of those with high pressures was about 6 years greater than that of those with normal pressures. Thus, our data do not provide unequivocal evidence that there is a strong, specific effect of age on the baroreflexes. Fairly steep slopes were found around age 50 years in the absence of hypertension, and some subjects with lower slope values were in their twenties or thirties. Nonetheless, some decrease in sensitivity of the reflex with advancing years cannot be completely denied.

The relative unresponsiveness of the reflex might be accounted for in several ways. Alexander and DeCuir2 have described results analogous to ours in renal hypertension in rabbits. With development of raised BP the animals lost the ability to produce bradycardia in response to further elevation of pressure produced by injections of angiotensin. The mechanism responsible for this adaptation is not known, but the findings are consistent with the well-known earlier studies of McCubbin and associates, who showed a decrease in baroreceptor afferent nerve impulse frequency associated with renal hypertension in dogs. It is clear, therefore, that adaptation of baroreflex control of heart rate to hypertension can and does occur in animals.

In man, such diminished sensitivity might result from decreased compliance of the arterial walls in baroreceptor regions, allowing less stretch of receptors per unit rise of BP, and thus producing the damped response we found. Medial hypertrophy of arteries or arteriosclerosis would diminish arterial compliance, as might an alteration in the water and electrolyte composition of arterial walls.
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In this regard, the findings of Biglieri and McIlroy are of special interest. Their patients with primary aldosteronism demonstrated qualitative abnormalities of baroreflex function which were associated with deranged potassium, sodium, and water relationships.

Degeneration of receptors in the carotid sinuses of patients who died with hypertension has been described. This is compatible with our results, but it still remains to be shown whether these anatomic findings are a result of high blood pressure or a cause. As Koch showed, the sensitivity of the baroreflex is linear over only a part of its range; at the highest pressures it levels off. Moreover, in acute experiments the baroreflex adapts quickly to a given increase in pressure. Thus less reflex effect might be anticipated at higher pressure. However, when a moderate, acute rise in BP is induced in man by alterations in blood gases, the sensitivity of the baroreflex is not significantly diminished.

Finally, there remains the possibility that baroreflex dysfunction can cause human arterial hypertension. Support for this view is not strong, yet a fault anywhere from receptor cells via central nervous system to end-organ could conceivably establish hypertension. Our demonstration of reduced baroreflex sensitivity in hypertension certainly does not exclude the possibility.

The baroreceptors are concerned with several aspects of circulatory regulation. The reflexes influence venous capacitance, systemic vascular resistance, and myocardial contractility, in addition to the heart rate. Final conclusions about the role of altered baroreflex performance in producing or maintaining hypertension will depend in part upon evaluation of these other functions. Two such studies concluded that the carotid sinuses were functioning in hypertension, because an increase in blood pressure or vascular resistance followed neural blockade of the sinuses by local anesthesia in hypertensive patients. In experimental hypertension, Alexander and DeCuir demonstrated their animals’ ability to buffer the increased BP produced by angiotensin injections, despite the loss of cardiac slowing, mentioned earlier. These studies do not allow one to conclude, however, that baroreflex dysfunction is innocent of any etiological or permissive responsibility in clinical hypertension. Our results suggest a fault in cardiovascular regulation in essential hypertension, and whether eventually shown to be a primary disorder or secondary to the hypertensive process, it may have significance in the maintenance of raised arterial pressure.

References


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