Evaluation of the Baroreceptor–Heart Rate Reflex by 24-Hour Intra-arterial Blood Pressure Monitoring in Humans

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SUMMARY The baroreceptor control of the sinus node was evaluated in 10 normotensive and 10 age-matched essential hypertensive subjects in whom ambulatory blood pressure was recorded intra-arterially for 24 hours and scanned by a computer to identify the sequences of three or more consecutive beats in which systolic blood pressure (SBP) and pulse interval (PI) progressively rose (+ PI/+ SBP) or fell (- PI/- SBP) in a linear fashion, according to a method validated in cats. In normotensive subjects, several hundred +PI/+SBP and -PI/-SBP sequences of 3 beats were found whereas the number of sequences of 4, 5, and more than 5 beats showed a progressive drastic reduction. The mean slopes of + PI/+ SBP (7.6 ± 2.0 msec/mm Hg) and - PI/- SBP (6.4 ± 1.5 msec/mm Hg) sequences were similar, but in both instances there was a large scattering of the values around the mean (variation coefficients: 64.2 ± 4.7 and 62.6 ± 2.4%). The slopes decreased as a function of the sequence length and baseline heart rate and increased to a marked extent during the night as compared with daytime values. All sequences were more rare (-33.2% for +PI/+ SBP and -31.7% for -PI/-SBP) and less steep in hypertensive subjects (-40.3 and -36.2%, respectively), who failed to show the marked nighttime increase in slope observed in normotensive subjects. To our knowledge, these observations provide the first description in humans of the baroreceptor–heart rate reflex in daily life. This reflex is characterized by marked within-subject variations in sensitivity due in part to hemodynamic, temporal, and behavioral factors. All features of the baroreceptor–heart rate reflex are impaired in essential hypertension. (Hypertension 12: 214–222, 1988)

KEY WORDS • baroreceptor reflexes • ambulatory blood pressure monitoring • hypertension • sleep • humans • heart rate

We have previously reported1–2 that blood pressure in unanesthetized cats exhibits spontaneous rises or falls that are accompanied by linearly related increases or reductions in pulse interval (PI). We have also reported1–2 that sinoaortic denervation abolishes these events, which therefore reflect baroreceptor modulation of the sinus node. We have concluded that evaluation of these events by computer analysis of intra-arterial blood pressure tracings represents a powerful tool for studying the baroreceptor–heart rate reflex in daily life.

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Intra-arterial blood pressure recordings performed for a limited amount of time under laboratory conditions have shown that spontaneous and progressive rises in blood pressure and PI also occur in humans.3 In the present study we systematically analyzed the spontaneous and progressive rises or falls in both blood pressure and PI of ambulant subjects in whom blood pressure was monitored intra-arterially for 24 hours. The study (which employed a method validated in cats) was performed in normotensive and essential hypertensive subjects to describe baroreceptor modulation of the sinus node, not only under normal daily life conditions but also under disease conditions in which laboratory methods have documented an impairment of baroreceptor influences on the heart.4–6

Subjects and Methods

The study was conducted on 18 normotensive subjects hospitalized for noncardiovascular dis-
cases and 16 subjects hospitalized for essential hypertension. In all subjects a 24-hour intra-arterial blood pressure recording was performed 1 week after admission to the hospital ward, using the Oxford method (Oxford Instruments, Oxford, UK). Because the recording was unsatisfactory in eight normotensive and six hypertensive subjects (frequent arrhythmias, shift in the 0 signal, deviation of calibration from linearity), the analysis of the blood pressure tracing was performed in only 10 normotensive (age, 41.7 ± 3.7 years) and 10 hypertensive subjects (age, 50.0 ± 3.4 years). No subjects were given cardiovascular drugs during the 24-hour blood pressure recording; the hypertensive subjects had discontinued their therapy at least 15 days earlier. The protocol of the study was approved by the ethical committee for our institution. Each subject gave his or her consent to the procedure after being informed about its nature and purpose.

Blood Pressure Recording
A detailed description of the Oxford method as employed in our laboratory has been published. Briefly, a catheter (length, 11 cm; internal diameter, 1.3 mm) was introduced percutaneously into a radial artery with the subject under local anesthesia with 2% lidocaine. The catheter was connected through a rigid cannula (length, 91.5 cm; internal diameter, 1.3 mm) to a transducer and a miniperfusion unit fastened to the thorax at the level of the heart. The unit was plugged to a minicassette tape recorder worn at the subject’s waist, in which the blood pressure signal was stored over 24 hours. The frequency response of the catheter, the cannula, the transducer, and the recording system together ranged from 0 to 8 Hz within ± 3 dB.

Calibrations were performed before and immediately after the 24-hour recording to check the reliability of the blood pressure values obtained throughout it. Only the recordings in which the 0 signal showed no shift and the response to a rise in pressure from 50 to 250 mm Hg was linear were accepted. During the recording the subjects were allowed to freely move within the hospital area and to engage in the social activity of hospital inpatients not confined to bed (e.g., television watching, playing cards, visits from relatives, physical exercise). They were only asked to comply with the hospital round and meal times and to stay in bed from 2200 to 0600.

Data Analysis
Each blood pressure recording was sampled at 165 Hz (intersample interval, 6 msec), digitized into 12 bits, and stored on a magnetic disk by a Digital PDP 11/34 computer (Maynard, MA, USA). The digitized signal was edited by an interactive program to eliminate morphological aberrances of the blood pressure tracing. The edited signal was analyzed by a VAX 750 computer (Digital), which calculated the systolic (SBP), diastolic, and mean blood pressures of each available pulse wave. Calculation was extended to beat-to-beat PIs, which were obtained from the intervals between consecutive systolic peaks.

Further analysis allowed calculation of 24-hour mean SBP, diastolic blood pressure, mean arterial pressure (MAP), and heart rate, together with the corresponding coefficients of variation (σ/μ · 100; i.e., the corresponding 24-hour variabilities). In addition, a specifically designed program identified when during the recording SBP and PI had both progressively increased over 3, 4, 5, 6 or more consecutive beats (+ PI/+SBP sequences) or progressively decreased over 3, 4, 5, 6 or more consecutive beats (− PI/−SBP sequences). The threshold change was set at 1 mm Hg for SBP and at 6 msec for PI. For each sequence the relationship between SBP values and subsequent PIs was found to be linear (correlation coefficient ≥ 0.85). The regression coefficient or slope was thus taken as a measure of the sensitivity of the baroreceptor–heart rate reflex, as done when changes in SBP and PI are induced by intravenously administered boluses of vasopressor and vasodepressor drugs.

Calculations were made of the number of + PI/+SBP or − PI/−SBP sequences during each hour, 2 hours in the morning, the afternoon, and the nighttime (selected when the subject’s diary demonstrated occurrence of uninterrupted sleep), and all 24 hours of the recording. Slope values were averaged over the same time intervals, the resulting coefficients of variation being used as measures of the variability of baroreceptor reflex sensitivity. Data from sequences of different lengths were separately analyzed and pooled to obtain overall estimates of the baroreceptor reflex in each subject. The slopes were related to the SBP or PI measured at the beginning of the sequence, to see whether baroreceptor reflex sensitivity depended on the different blood pressure or heart rate levels observed over the 24 hours.

Individual data were averaged separately to obtain mean values for the normotensive and the hypertensive subjects. In each group the statistical significance of the differences among the number or the slopes of the sequences identified over 2-hour subperiods was assessed by two-way analysis of variance followed by the Bonferroni test. Comparisons between the two groups were performed by the t test for unpaired observations and by mixed factorial analysis of variance with repeated measurements. Multiple regression analysis was used to assess the independent influence of age, 24-hour mean blood pressure, and 24-hour mean PI on the slope of the baroreceptor reflex sequences. A p value less than 0.05 was taken as the minimal level of statistical significance. Values are presented as means ± SE.

Results

Normotensive Subjects
In normotensive subjects mean 24-hour SBP was 124.6 ± 5.0 mm Hg, mean 24-hour diastolic blood
pressure was 63.9 ± 2.5 mm Hg, and mean 24-hour PI was 828.7 ± 48.4 msec. The corresponding variation coefficients were 12.3 ± 2.1, 18.9 ± 1.6, and 19.4 ± 1.7%.

The +PI/+SBP and −PI/−SBP sequences of normotensive subjects are shown in Figure 1 as averages from individual data. During the 24 hours several hundred sequences of either type were identified. The sequences lasting 3 beats were the most frequent, while the sequences lasting 4, 5, 6 or more beats were progressively and significantly (p < 0.01) more rare (see Figure 1, upper panels). For either type of sequences, the mean 24-hour slope showed a tendency to lessen as the duration of the sequence increased, although the differences were not statistically significant (see Figure 1, middle panels). For any given duration the slope showed a large scattering around the mean value (i.e., it showed a high variation coefficient; see Figure 1, lower panels). The 24-hour frequency and mean slope of the + PI/ + SBP sequences did not differ significantly from those of the − PI/−SBP sequences.

**Hypertensive Subjects**

In hypertensive subjects mean 24-hour SBP was 173.4 ± 4.0 mm Hg, mean 24-hour diastolic blood pressure was 88.6 ± 2.2 mm Hg, and mean 24-hour PI was 837.2 ± 31.8 msec. The corresponding variation coefficients were 11.5 ± 0.5, 14.6 ± 1.0, and 15.8 ± 0.9%. The blood pressure values of the hypertensive subjects differed significantly (p < 0.01) from those of the normotensive subjects.

As shown in Figure 2, in hypertensive subjects the 24-hour frequency of the + PI/ + SBP and − PI/ − SBP sequences also decreased progressively and significantly as the duration of the sequences increased. The number of both types of sequences was less in hypertensive as compared with normotensive subjects, although the reduction fell just short of statistical significance (−33.2% for + PI/ + SBP and −31.7% for − PI/−SBP; NS for both; Figure 3). Furthermore, the slope of all sequences was clearly less in the former than in the latter group, the overall reduction amounting to 40.3 and 36.3% for the + PI/ + SBP and − PI/−SBP sequences, respectively (p < 0.05; see Figure 3). Finally, the slope of the + PI/ + SBP and − PI/−SBP sequences showed an inverse relationship with mean 24-hour blood pressure and age when multivariate analysis was made on normotensive and hypertensive subjects together. In contrast, the slope of the + PI/ + SBP and − PI/−SBP sequences was directly related to mean 24-hour PI (Table 1).

**Relationship of + PI/ + SBP and − PI/−SBP Sequences to the Hemodynamic and Behavioral Changes Within the 24 Hours**

In most normotensive and hypertensive subjects the slopes of the individual + PI/ + SBP and − PI/−SBP sequences observed during the 24 hours were directly related to the PIs existing at the beginning of the sequences (Figure 4 and Table 2). The same slopes were inversely related to the SBPs existing at the beginning of the sequences, but these relationships...
were significant in only a few subjects and their correlation coefficients were usually low (see Table 2).

As shown in Figures 5 and 6, in both normotensive and hypertensive subjects the hourly frequency of +PI/ + SBP and −PI/ − SBP sequences displayed a fall during the nighttime as compared with the daytime. In contrast, the mean hourly slope of both sequences increased during the nighttime. This was the case, however, only in normotensive subjects; the daytime and nighttime slopes were not obviously different in hypertensive subjects.

This finding is further illustrated in Figure 7, which refers to average values of 2 hours of the morning, 2 hours of the afternoon, and 2 hours of the night. Compared with morning and afternoon values, +PI/ + SBP and −PI/ − SBP sequences showed a marked nighttime increase in slope in normotensive but not in hypertensive subjects. On the other hand, the nighttime reduction in blood pressure and heart rate was similar in the two groups (Table 3).

Finally, in normotensive but not in hypertensive subjects, the number of +PI/ + SBP sequences decreased and the slope increased during the afternoon siesta (−20.8 ± 28.5 and +17.7 ± 23.0%; see Figure 5), thereby showing changes qualitatively similar to those of the night period. The number of −PI/ − SBP (but not their slope) showed an analogous though less evident trend.

**Discussion**

In the present study we examined the baroreceptor–heart rate reflex of ambulant humans by analyzing on 24-hour intra-arterial blood pressure tracings the sequences of 3 or more beats during which spontaneous and progressive changes in blood pressure were accompanied by opposite changes in heart rate. The
TABLE 1. Multiple Regression Analysis Between 24-Hour Mean Slopes of +PI/+SBP and -PI/-SBP Sequences and Subjects' Age, 24-Hour MAP, and 24-Hour Mean PI

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Slope of +PI/+SBP (msec/mm Hg)</th>
<th>Slope of -PI/-SBP (msec/mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regression coefficient</td>
<td>Regression coefficient</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>p</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>-0.15</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>24-hr MAP (mm Hg)</td>
<td>-0.06</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>24-hr PI (msec)</td>
<td>+0.02</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data from all normotensive and hypertensive subjects (n = 20). Regression coefficient refers to the slope of the regression between the independent variables (age, MAP, and PI) and the +PI/+SBP or -PI/-SBP slopes. The $R^2$ values of the multiple regressions were 0.77 and 0.84 for the +PI/+SBP and -PI/-SBP sequences, respectively. PI = pulse interval.

results 1) provide information on the baroreceptor modulation of the sinus node during the daytime and nighttime, 2) identify a number of factors that are responsible for the large variations in the sensitivity of this baroreceptor reflex function occurring in daily life, and 3) describe the daily life differences in the baroreceptor–heart rate reflex between normotensive subjects and subjects with essential hypertension.

Baroreceptor Modulation of the Sinus Node over 24 Hours

In our 24-hour blood pressure recordings spontaneous increases and reductions in blood pressure were accompanied in several hundred instances by opposite changes in heart rate. This finding provides direct evidence that baroreceptors in humans are often engaged in a cardiac modulation that limits the extent of spontaneous blood pressure oscillations, a conclusion so far reached only indirectly by the relationship between 24-hour blood pressure variability and the sensitivity of the baroreceptor–heart rate reflex as defined by laboratory methods.10-14-16 However, the most interesting finding of our study is that in any given subject the sensitivity of the baroreceptor–heart rate reflex is by no means a constant feature but undergoes pronounced 24-hour variations. Thus, the way this function operates in each person may be more properly described by a range of values than by the single or few values obtained through available laboratory methods such as vasoactive drug injection and the neck chamber device.5, 6, 12, 14, 17, 18 This can be achieved by the continuous evaluation allowed by our approach, although the difficulties posed by the need to record 24-hour intra-arterial blood pressure in ambulant subjects and to analyze the results by complex computer programs may represent an obstacle to its widespread use in cardiovascular research.

Two further points need to be mentioned. First, the sequences characterized by progressive opposite changes in SBP and heart rate had several features (decreasing frequency with increasing duration, decreasing sensitivity with increasing duration, variability of the sensitivity) in common with those observed in unrestrained cats.1-2 Second, in humans these sequences were more rare, and on the whole they encompassed only about 15% of the cardiac beats occurring over the 24 hours. However, this finding cannot be interpreted to mean that in 85% of cardiac beats baroreceptors did not exert any modulation of the sinus node (i.e., that over most of the 24-hour period this function is inactive). For technical reasons we analyzed only blood pressure and PI changes greater than 1 mm Hg and 6 msec, respectively; thus, sequences characterized by subthreshold changes in these variables were excluded. Furthermore, baroreceptors probably modulate the sinus node not only in a sequence-like fashion but also by causing a single beat change in PI in response to a single beat disturbance in blood pressure.1, 2, 14, 19 Finally, this modulation also may take place when a blood pressure increase is accompanied by tachycardia or a blood pressure reduction is accompanied by bradycardia, its role being that of restraining the magnitude of the heart rate change that would otherwise take place. Thus, although providing a large amount of data, the sequence method we employed presumably accounts for only...
TABLE 2. Correlation Coefficients Between the Slopes of the +PI/+SBP or −PI−SBP Sequences and the SBP or PI Values Existing at the Beginning of the Sequences

<table>
<thead>
<tr>
<th>Dependent variable</th>
<th>Initial PI (msec)</th>
<th>Initial SBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean correlation coefficient (r)</td>
<td>% with significant correlation*</td>
</tr>
<tr>
<td>Slope, +PI/+SBP</td>
<td>0.36 ± 0.03</td>
<td>62.1</td>
</tr>
<tr>
<td>Slope, −PI−SBP</td>
<td>0.55 ± 0.02</td>
<td>79.4</td>
</tr>
</tbody>
</table>

Data are shown as means ± SE (n = 20). Percent data were calculated separately on sequences of 3, 4, 5, and more than 5 beats for each subject. The percentages of correlations with positive or negative signs (right-hand columns) refer only to statistically significant correlations. PI = pulse interval.

* p < 0.05.

Factors Involved in the Determination of Baroreceptor Reflex Sensitivity

In our subjects the different baroreceptor reflex sensitivities occurring during the 24 hours had either no or only a weak inverse relationship with the widely different baseline blood pressures encountered over the same interval. In other words, there was little or no tendency for the baroreceptor reflex sensitivity to lessen as the blood pressure values around which the reflex modified PI increased. This finding suggests that 24-hour changes in blood pressure do not consistently bring the baroreceptor reflex toward the flattened portion of the stimulus-response curve corresponding to saturation. This may depend on the fact that, although modifiable by a number of influences (as will be explained), the baroreceptor reflex operates in daily life largely along the linear portion of this curve. It may also be favored by the occurrence of a downward resetting, which rapidly neutralizes the effect of a blood pressure increase, always allowing the baroreceptor reflex to return to or near to its original operating position. That in daily life the baroreceptor–heart rate reflex operates in the linear portion of its input-output relationship is also suggested by the observation that the sensitivity of the response to baroreceptor stimulation was similar to that of the response to baroreceptor deactivation.

Three other factors were associated with the widely different values of baroreceptor reflex sensitivity observed during the 24 hours, however. First, baroreceptor reflex sensitivity decreased progressively as the time over which baroreceptors modulated the sinus node lengthened. Thus, this reflex seems to be most effective when engaged briefly; some unknown factors (central influences? loss of responsiveness of the sinus node?) interfere with its influence on the heart as the engagement is prolonged. Second, baroreceptor reflex sensitivity

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

**FIGURE 5.** Frequency and mean regression coefficients (or slopes) of +PI/+SBP sequences during each hour of the 24-hour recording. Data are shown separately as means ± SE for normotensive and hypertensive subjects. Sequences of different duration are pooled.
was greater when baseline heart rate values were less and vice versa, a finding that confirms and extends data obtained by laboratory evaluation of the baroreceptor–heart rate reflex.\textsuperscript{12, 14, 22} Whether it is the increased baroreceptor reflex sensitivity that causes a bradycardia or vice versa\textsuperscript{22} cannot be clarified by our data.

Third, the bradycardic response to baroreceptor stimulation, though largely similar during the daytime, increased during the night much more than might be accounted for by the concomitant reduction in baseline heart rate. This was the case also for the tachycardic response to baroreceptor deactivation. These observations confirm previous data in which nighttime and daytime differences in baroreceptor-induced bradycardia were studied by bolus injection of a vasopressor drug.\textsuperscript{12, 16} They extend these observations in a number of ways, however. For example, the nighttime potentiation of the baroreceptor–heart rate reflex\textsuperscript{1} involves both the upper and lower portion of its stimulus-response curve (i.e., it involves this reflex function...
as a whole), 2) is not episodic but can be seen over the entire night, and 3) is only partly explained by the reduction in heart rate occurring during the night; it is largely independent of the concomitant blood pressure fall, and it also occurs during the afternoon siesta. Thus, this phenomenon cannot be ascribed to the hemodynamic changes of sleep or to a circadian influence that has its peak effect during the night, as was suggested in a previous study.\(^{23}\) The most likely explanation is that it depends on the modification induced by sleep on the central integration of the baroreceptor influences on the vagal and sympathetic neurons modulating the sinus node.\(^{16,24}\)

Finally, it should be emphasized that many other factors not addressed by our study are likely to be involved in the sensitivity of the baroreceptor–heart rate reflex occurring in daily life. To mention a few examples, baroreceptor reflex sensitivity may be altered by 1) 24-hour changes in angiotensin II, because this substance can affect the baroreceptor reflex arc,\(^{25}\) 2) variations in the activity of cardio-pulmonary receptors, chemoreceptors, skeletal muscle receptors, and other reflexogenic areas,\(^{25–27}\) and 3) central factors causing behavioral changes in blood pressure,\(^{9,11}\) and simultaneously modulating the central integrating mechanisms of the baroreceptor reflex.\(^{27}\) Some of these factors can be investigated by the new method we have employed in this study.

### Differences Between Normotensive and Hypertensive Subjects

The mean 24-hour sensitivity of the baroreceptor–heart rate reflex was independently reduced by aging and essential hypertension, with a progressive impairment from the subjects with normal blood pressure to those with the most pronounced degree of blood pressure elevation. This finding confirms on a large data base the observations obtained by stimulating and deactivating baroreceptors through vasoactive drug injection and the neck chamber method.\(^{5,6,28–30}\) However, in our essential hypertensive subjects 1) the sensitivity of the baroreceptor–heart rate reflex was reduced throughout the 24 hours, 2) the baroreceptor reflex type sequences (i.e., the sequences characterized by progressive and opposite changes in blood pressure and heart rate) were persistently less frequent than in normotensive subjects, and 3) the nighttime increase in sensitivity of the reflex observed in normotensive subjects was small or absent. Thus, hypertension impairs the cardiac modulation that baroreceptors exert in daily life. This impairment, however, becomes manifest not only as a reduced sensitivity but also as a more rare engagement of the baroreceptor reflex in response to progressive alterations in blood pressure. Furthermore, the impairment prevents baroreceptor reflex sensitivity from increasing in behavioral conditions in which a rise normally occurs.

Finally, an intriguing aspect of our study is that while hypertension caused an impairment of the baroreceptor–heart rate reflex, the acute blood pressure rises occurring during the 24 hours had a limited effect on this function. This suggests that the reduced baroreceptor reflex sensitivity observed in hypertensive patients may not depend on the high blood pressure per se but on the abnormalities of the cardiovascular system that are associated with the chronic hypertensive state. These may consist of functional alterations in neural and humoral cardiovascular control as well as in structural changes in the heart and the blood vessels leading to abnormal responses to stimuli.

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