Factors Influencing Blood Pressure and Heart Rate Variability in Hypertensive Humans

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SUMMARY We examined the influence of baroreceptor reflex sensitivity (the increase in pulse interval in response to a phenylephrine-induced increase in blood pressure), age, blood pressure, and β-adrenergic receptor blockade on the variability of blood pressure and heart rate in essential hypertension. Fifty-six subjects were studied before treatment; intra-arterial blood pressure was recorded outside the hospital for 24 hours. Variability was defined (from all beats occurring while subjects were awake) as the standard deviation about the average waking value for mean arterial pressure (MAP) or pulse interval. The correlation (r) between baroreceptor reflex sensitivity and blood pressure variability was -0.47 (p<0.0002). Baroreceptor reflex sensitivity was the only independent determinant of blood pressure variability on multiple regression analysis. Thirty subjects were restudied after 5 months of β-adrenergic receptor blockade. Ambulatory blood pressure was lower during treatment, whereas pulse interval, its variability, and baroreceptor reflex sensitivity were higher. Blood pressure variability was unchanged. The variability of MAP was inversely correlated with baroreceptor reflex sensitivity before (r = -0.42, p<0.02) and during (r = -0.45, p<0.02) treatment, but it was unrelated to the average ambulatory MAP or to the variability of pulse interval either before or during β-blockade. Sixteen subjects whose average waking ambulatory blood pressure was 140/90 mm Hg or less were not treated. This group of borderline hypertensive subjects had less variable MAP than did the remaining 40 subjects (12.4 ± 2.3 [SD] vs 14.5 ± 2.5 mm Hg; p<0.01). We conclude that 1) the decline in baroreceptor reflex sensitivity is the principal determinant of increased blood pressure variability in hypertension, 2) MAP and its variability are regulated independently, 3) heart rate variability is not influenced by baroreceptor reflex sensitivity and is unrelated to blood pressure variability, and 4) the blood pressure of subjects with borderline hypertension is not excessively labile. (Hypertension 11: 273-281, 1988)

KEY WORDS • ambulatory blood pressure • baroreceptor reflex sensitivity • β-adrenergic receptor blockade • borderline hypertension • labile hypertension • age

INTRA-ARTERIAL ambulatory blood pressure recordings demonstrate graphically the great beat-to-beat variability of blood pressure present in normal and hypertensive humans, but factors that might influence and regulate this variability remain imperfectly understood. Considerable experimental evidence supports the concept that the arterial baroreceptor reflex is intimately involved in the short-term regulation of arterial blood pressure. Denervation of the sinoaortic baroreceptors in rats and dogs consistently increases the beat-to-beat variation of blood pressure but has less dramatic and disputed effects on its level. Central interruption of the baroreceptor reflex by lesioning nucleus tractus solitarii produces hypertension, tachycardia, and increased blood pressure variability in awake animals. Selective removal of the noradrenergic innervation of this nucleus does not induce hypertension, but it does cause an increase in blood pressure variability that is inversely related to a decrease in the baroreceptor reflex control of heart rate.

In hypertension, the threshold for baroreceptor firing is reset and the receptors themselves are less sensi-
tive to further increases in arterial pressure. One might predict, as a consequence, that the reflex parasympathetic and sympathetic responses to a similar pressor stimulus would be attenuated. Indeed, the ability of the arterial baroreceptor reflex to inhibit efferent sympathetic activity is impaired in several experimental models of hypertension, and the lability of blood pressure is increased in rabbits whose baroreceptor afferent discharge is reduced, whether due to renal hypertension, experimental atherosclerosis, or medial sclerosis.

In humans, the arterial baroreceptor reflex control of cardiac cycle length has been well studied using techniques that quantify the reflex changes in heart rate in response to stimuli that alter blood pressure. If phenylephrine is administered, a linear relationship between the systolic blood pressure of each beat and the subsequent pulse interval can be established over the course of the pressure rise. The slope of this line has been used as an index of baroreceptor reflex sensitivity (BRS). This technique examines primarily the parasympathetic efferent limb of this reflex. Persons with more sensitive baroreceptor reflexes exhibit a greater reflex bradycardia for a similar absolute increase in blood pressure. Increasing age and mean arterial pressure (MAP) act independently to lower the slope of this response.

The aim of the present investigations was to determine the influence of factors such as age, blood pressure, heart rate variability, and β-adrenergic receptor blockade on intra-arterial blood pressure variability in awake, ambulatory subjects. Our hypotheses were that 1) the reduction in BRS in hypertension would be associated with increased variability of ambulatory blood pressure, 2) the variability of blood pressure would be inversely related to the variability of heart rate, 3) subjects with greater plasma norepinephrine concentrations would also display increased blood pressure variability, and 4) β-adrenergic receptor blocking drugs would increase BRS and reduce the lability of blood pressure.

### Subjects and Methods

Fifty-six subjects (41 men, 15 women) were referred for assessment of newly diagnosed, untreated hypertension. They ranged in age from 16 to 69 years (mean age, 46 ± 11 [SD] years; Table 1). Hypertension was diagnosed if supine cuff pressures, obtained on three or more separate occasions over 1 week apart were 140/90 mm Hg (Phase V diastolic) or greater in subjects under 40 years of age and 160/95 mm Hg or greater in subjects over 40 years of age. Readings below these values were recorded at other times in some subjects. Their average clinic pressure ranged from 137 to 216 mm Hg systolic (mean, 172 ± 19 [SD] mm Hg) and from 80 to 137 mm Hg diastolic (mean, 107 ± 10 mm Hg).

No subject had fundal changes greater than Grade 2. In 18, the chest radiograph or electrocardiogram showed changes of left ventricular enlargement. None were in heart failure. Secondary hypertension was excluded by routine investigations in all patients but one, who had renal artery stenosis. Two were taking medications concurrently: One was taking digoxin, 0.125 mg/day, for control of atrial fibrillation, and another, sulfasalazine, 2 g/day, for Crohn’s disease.

The purpose and nature of the protocol were explained during recruitment and again on the morning of the first study, when informed written consent was obtained. Consent was also obtained before the second study day, when the protocol was repeated during long-term β-adrenergic receptor blockade. Permission for these investigations was granted by the hospital ethics committee.

### Protocol

Subjects arrived at 0930 after a light breakfast at home, avoiding tea, coffee, or cigarettes. There were no other dietary restrictions.

Arterial pressure was recorded from a left brachial catheter connected to a strain gauge transducer calibrated at all times at midchest level. An adjacent antecubital vein was cannulated for blood sampling or phenylephrine injection. The electrocardiogram (Lead II) and blood pressure were displayed on an oscilloscope and recorded continuously onto ultraviolet light-sensitive paper, magnetic tape, and minicomputer disk.

### Plasma Norepinephrine

Venous blood was withdrawn from the antecubital catheter in 44 of these subjects as they sat quietly for 15 minutes on a bicycle ergometer and again in the 10th minute of upright bicycle exercise (5 minutes at 50 W, then 5 minutes at 75 W). A 10-ml sample was obtained and immediately centrifuged for 10 minutes at room temperature (1000 g) and frozen and stored at −40°C. Norepinephrine concentration was measured by radioenzymatic assay. Interassay and intra-assay coefficients of variation were 9.6% and 8.7%, respectively.

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### Table 1. Subject Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All subjects (n = 56)</th>
<th>Subjects in whom PNE was measured (n = 44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>46 ± 11</td>
<td>45 ± 11</td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>118.3 ± 17.9</td>
<td>119.0 ± 18.5</td>
</tr>
<tr>
<td>VMAP (mm Hg)</td>
<td>13.8 ± 2.4</td>
<td>13.5 ± 2.3</td>
</tr>
<tr>
<td>PI (msec)</td>
<td>678 ± 87</td>
<td>691 ± 82</td>
</tr>
<tr>
<td>VPI (msec)</td>
<td>132 ± 34</td>
<td>130 ± 30</td>
</tr>
<tr>
<td>LBRS</td>
<td>0.78 ± 0.30*</td>
<td>0.80 ± 0.30</td>
</tr>
</tbody>
</table>

Values are means ± SD. PNE = plasma norepinephrine; V = variability; PI = pulse interval; LBRS = log baroreceptor reflex sensitivity.

* n = 55.
Measurement of Baroreceptor Reflex Sensitivity

From 30 to 140 µg of phenylephrine hydrochloride (Boots, Nottingham, UK), 100 µg/ml, was administered by bolus intravenous injection with 6 ml of dextrose over 5 seconds. Doses were adjusted to increase systolic blood pressure by 20 to 30 mm Hg. Blood pressure and heart rate usually returned to baseline levels within a minute of the injection; 5 minutes was allowed between injections, and between five and eight injections were given to each subject.

Ambulatory Blood Pressure Monitoring

A portable blood pressure transducer unit22, 23 was calibrated, then connected to the arterial cannula. Output from this unit was recorded by analog cassette tape recorder.22, 23 Lead II of the electrocardiogram and time were recorded on additional channels. The transducer unit and recorder were placed in a comfortable pouch worn across the chest. Subjects were supplied a digital watch and voice recorder to keep an accurate record of their activities, paying particular attention to times of sleeping and waking. Subjects then left the hospital to resume their routine daily activity and returned in the evening for about 15 minutes, at which time the transducer was recalibrated, the line flushed, and the subject's pulses and arm checked. The following afternoon, the cannula was removed from the artery and a pressure bandage applied. All of the procedures were well tolerated and without incident.

Since the frequency response of the entire ambulatory recording and replay system falls off rapidly above 10 Hz,23 we used mean arterial blood pressure in these calculations.

Calculation of Baroreceptor Reflex Sensitivity

Cardiac cycles from the beginning of the rise in arterial pressure until the peak of the pressure rise were used to calculate a regression line of pulse interval on systolic pressure with its regression coefficient (or slope), variance, and correlation coefficient for each injection. All cardiac cycles during the pressure rise were included in these calculations since respiration does not alter this determination of BRS in subjects with slopes less than 15 msec/mm Hg.17

For each phenylephrine injection, regression equations were calculated with shifts, or delays, of from 0 to +3 cardiac cycles interposed between the systolic pressure and pulse interval regressed against it.24 At heart rates below 75 beats/min the correlation between these two variables was usually best with a delay of 0 to +3 cardiac cycles was used. Slopes could not be obtained in one subject.

The delay that consistently gave slopes with the highest correlation coefficients was determined for each subject; regression coefficients and variances corresponding to this delay were used to compute weighted mean BRS. A weighting factor, the inverse of the variance, was applied to each slope. From the several slopes obtained, all estimates of the "true" slope or BRS of the subject, a weighted mean slope that took these relative weightings into account was calculated for each subject.25 This method gives estimates of BRS with less variance greater weight when determining the mean slope.

Blood Pressure Variability

Analysis of the Ambulatory Blood Pressure Record

The 24-hour record was replayed at 25 times real time. Raw blood pressure was sampled at a frequency of 16 kHz and analyzed using a Fortran IV program with display and interaction facilities to allow validation of the signal.26 If more than a third of an hour's pulses were edited because of damped waveforms or artifacts, that hour was excluded from further analysis. Each 24-hour record was divided into waking and sleeping periods according to subjects' diaries. Frequency histograms of waking MAP were computed using all valid beats during this period. Hourly frequency histograms were also calculated, and histograms from selected hours were combined to cover larger periods of the record. Data in these histograms were normally distributed. The standard deviation of these blood pressure measurements (i.e., the square root of the variance), was used to describe blood pressure variability.

Short-term and Medium-term Variability of Blood Pressure in Individual Subjects

In eight subjects, ten 2-minute intervals from a 20-minute segment of the tape, recorded at the time of waking, were selected to study short-term variability of blood pressure in individual subjects. This interval was chosen because blood pressure and heart rate increase markedly on waking.27 We correlated the blood pressure and pulse interval with their respective standard deviations within each 2-minute segment in each subject. If blood pressure variability is dependent on the absolute level of arterial pressure, one should find a parallel increase in blood pressure and its variability at this time.

All waking hours from eight subjects' records were used to examine medium-term blood pressure variability in individual subjects. The waking record was divided into (14-17) hourly histograms. We correlated MAP and pulse interval, with their standard deviations, for each hour in each subject.

β-Adrenergic Receptor Blockade

Although hypertension had been diagnosed clinically in all subjects, the ambulatory blood pressure of many subjects was often well below 140/90 mm Hg. Sixteen with mean waking ambulatory blood pressures less than 140/90 mm Hg (12 men, 4 women; mean age, 43 ± 9 years) were considered to have borderline hypertension and were not treated.

Thirty of the hypertensive subjects (22 men, 8 women; mean age, 46 ± 12 years) participated in the second half of this study. They were randomized to a regimen of one of four β-adrenergic receptor blocking drugs, each to be taken once daily in the morning. The initial dose of each drug was atenolol, 100 mg (n = 7);
metoprolol, 200 mg (n = 9); pindolol, 15 mg (n = 8); propranolol, 160 mg (n = 1); and slow-release propranolol, 160 mg (n = 6). The manufacturers provided white, unmarked formulations. The randomization schedule was held in the hospital pharmacy until after the second study.

Subjects were evaluated subsequently at monthly intervals at the same time of day, and doses were titrated as required. After 3 to 8 months (mean time, 5 months), the protocol was repeated at the same time of day as in the first (control) study with the assigned drug taken as usual at 0800. Average doses were atenolol, 121 ± 57 mg (mean ± SD); metoprolol, 300 ± 107 mg; pindolol, 32 ± 10 mg; and propranolol, 457 ± 194 mg. The average clinic blood pressure of these subjects was 175 ± 25/107 ± 11 mm Hg before the first (control) study and 146 ± 24/93 ± 15 mm Hg at the last clinic visit before the second (treatment) study.

Rest and exercise samples of venous blood for plasma norepinephrine concentrations were obtained on both study days in 21 of these subjects.

Statistics

The Statistical Package for the Social Sciences Program (SPSS) was used for paired comparisons (Student's t test), stepwise multiple regression analysis, and calculation of partial correlation coefficients. The Bonferroni method was used to calculate a modified t statistic when multiple comparisons were performed. Partial correlation coefficients were also calculated to determine the relationship between two variables while excluding the confounding effect of other variables. Results are reported as means ± SD throughout.

Results

All Subjects

Baroreceptor Reflex Sensitivity

Mean weighted baroreceptor reflex slopes (expressed as BRS) ranged from 1.6 to 38.1 msec/mm Hg (mean, 8.0 ± 7.8 msec/mm Hg; n = 55), and as described by Gribbin et al., they were inversely related to age and MAP and displayed a skewed distribution. A normal distribution and linear relationships between BRS, age (r = -0.62, p < 0.0001), and systolic blood pressure (r = -0.61, p < 0.0001), but not heart rate, were established when these slopes were transformed logarithmically (log_{10} BRS; LBRS). Therefore, LBRS was used to represent BRS in subsequent calculations.

Correlation Between Short-term and Medium-term Variability of Blood Pressure and Level of Pressure

Within Subjects

In no subject was the short-term variability of blood pressure (2-minute intervals about the time of waking) related to the absolute level of arterial pressure (Table 2). In three of the eight subjects studied, pulse interval and its variability were positively correlated. Over the medium term (1-hour segments), variab-

<table>
<thead>
<tr>
<th>Table 2. Correlation Between MAP and Systolic Blood Pressure and Pulse Interval and Their Short-term (2 min) Variability in Eight Subjects</th>
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</thead>
<tbody>
<tr>
<td>VMAP vs MAP</td>
</tr>
<tr>
<td>0.10</td>
</tr>
<tr>
<td>0.07</td>
</tr>
<tr>
<td>0.50</td>
</tr>
<tr>
<td>-0.02</td>
</tr>
<tr>
<td>0.24</td>
</tr>
<tr>
<td>-0.31</td>
</tr>
<tr>
<td>-0.27</td>
</tr>
<tr>
<td>0.21</td>
</tr>
</tbody>
</table>

Values are correlation coefficients. PI = pulse interval (msec); SBP = systolic blood pressure; V = variability.

*p < 0.05.

Correlation Between MAP and Systolic Blood Pressure and Pulse Interval and Their Medium-term (1 hr) Variability in Eight Subjects

| VMAP vs MAP | VSBP vs SBP | VPI vs PI |
|---------------------------------------------------------------|
| -0.14 | 0.20 | -0.29 |
| 0.22 | -0.12 | -0.15 |
| 0.28 | 0.21 | 0.23 |
| -0.26 | -0.06 | 0.23 |
| -0.38 | -0.47 | 0.11 |
| 0.36 | 0.52* | -0.07 |
| 0.46 | 0.26 | -0.34 |
| 0.28 | 0.70* | 0.05 |

Values are correlation coefficients. PI = pulse interval (msec); SBP = systolic blood pressure; V = variability.

*p < 0.05.
Variability of Ambulatory Heart Rate Between Subjects

There was no relationship between BRS and the variability of pulse interval (r = 0.22). For example, the variability of pulse interval (or coefficient of variation) in the 20 subjects with the most sensitive baroreceptor reflex responses was 144 ± 32 msec (0.20 ± 0.03%) and in the 10 subjects with the least sensitive baroreceptor reflex responses was 143 ± 40 msec (0.21 ± 0.05%). The variability of pulse interval was unrelated to subjects’ age or ambulatory blood pressure.

Influence of \( \beta \)-Adrenergic Receptor Blockade

Patient Randomization

Subjects’ ages and clinic blood pressures before randomization (control study) were similar within each of the four groups.

Exercise Heart Rate

In 26 subjects, \( \beta \)-blockade reduced resting heart rate from 81 ± 14 to 61 ± 9 beats/min. Maximum exercise heart rate during cycling was reduced from 128 ± 24 to 93 ± 15 beats/min. The increase in heart rate with exercise was significantly attenuated by \( \beta \)-blockade (p < 0.001).

Plasma Norepinephrine Concentration

Cycling increased plasma norepinephrine concentrations from 648 ± 223 to 1098 ± 433 pg/ml (p < 0.001) before and from 730 ± 275 to 1330 ± 444 pg/ml (p < 0.001) during treatment. \( \beta \)-Blockade had no significant effect on baseline plasma norepinephrine or on the increase in plasma norepinephrine with exercise.

Baroreceptor Reflex Sensitivity

BRS increased from 6.6 ± 5.2 to 9.2 ± 2.6 msec/mm Hg (p < 0.01). LBRS increased from 0.7 ± 0.3 to 0.8 ± 0.3 (p = 0.02).

Ambulatory Blood Pressure and Its Variability

\( \beta \)-Blockade reduced awake ambulatory MAP (from 126.4 ± 14.7 to 105.8 ± 16.1 mm Hg; p < 0.001) but did not reduce its variability (14.6 ± 2.5 before vs 14.9 ± 3.3 mm Hg during \( \beta \)-blockade). Mean pulse interval increased from 667 ± 80 to 846 ± 103 msec (p < 0.00001), and the variability of pulse interval increased from 120 ± 22 to 186 ± 97 msec (p < 0.002), leaving the coefficient of variation of pulse interval unchanged (0.18 ± 0.04% before and 0.21 ± 0.09% during \( \beta \)-blockade).

The variability of MAP was inversely correlated with BRS both before (r = -0.42, p < 0.02) and during (r = -0.45, p < 0.02) \( \beta \)-blockade (Figure 3), according to the following regression equations:

- control VMAP = 17.32 - (3.68 × LBRS)
- \( \beta \)-blockade VMAP = 18.53 - (4.40 × LBRS)

Variability of MAP was unrelated to average waking MAP in this smaller group either before (r = 0.28)
or during \((r = 0.18)\) \(\beta\)-adrenergic receptor blockade. Similarly, there was no relationship between blood pressure variability and the variability of pulse interval before or during treatment.

In contrast to the control state, the variability of MAP was not related to the relative increase in plasma norepinephrine with bicycle exercise during \(\beta\)-blockade \((r = -0.08, n = 21)\).

**Discussion**

The principal findings in this study were 1) decreased BRS in hypertension is associated with increased variability of blood pressure; 2) the variability of blood pressure is not always dependent on its absolute level; 3) subjects with borderline hypertension do not have more labile blood pressure than subjects with mild or moderate hypertension; and 4) subjects with evidence of greater sympathetic responsiveness to exercise also display greater blood pressure variability. We were unable to demonstrate 1) a relationship between either the variability of blood pressure or BRS and the variability of heart rate, either before or after \(\beta\)-adrenergic receptor blockade, or 2) an effect of \(\beta\)-adrenergic receptor blockade on blood pressure variability.

These results suggest that persons with impaired baroreceptor reflex regulation of heart rate are less able to buffer short-term fluctuations in blood pressure. Such intermittent elevations in blood pressure might lead to adaptive changes in the heart and resistance vessels.\textsuperscript{30}

These data relate to the waking period of the 24-hour record. The sleep portion of the record was specifically excluded from the current analysis. Sleep, which lowers both blood pressure and heart rate by about 25%, becomes the greatest source of blood pressure variability and heart rate variability when 24-hour ambulatory records are analyzed uncritically. This sleep effect would obscure any attempt to determine mechanisms by which waking blood pressure is regulated using ambulatory blood pressure recordings.

Other groups have used direct ambulatory blood pressure monitoring to document relationships between BRS and arterial blood pressure variability.\textsuperscript{31-33} However, Mancia et al.\textsuperscript{33} analyzed fluctuations in blood pressure over brief periods, rather than its beat-to-beat variability, whereas Watson et al.\textsuperscript{31} confined their patients to hospital and restricted them to a standard protocol of rest and exercise. Our study of ambulant, unrestricted subjects confirms the presence of an inverse relationship between BRS and the beat-to-beat variability of blood pressure during conditions that simulate, as near as possible, subjects' daily activities. Despite the free-ranging activity permitted in this study, which might be expected to limit our ability to detect such an association, the variability of waking MAP before treatment was more closely related to BRS than to the average ambulatory MAP, or age, and was unrelated to the level of MAP during \(\beta\)-blockade. Multiple regression analysis revealed BRS to be the only independent predictor of blood pressure variability.

Blood pressure variability appeared to provide a useful index of sympathetic nervous activity, correlating well with the increase in plasma norepinephrine during bicycle exercise in untreated subjects.

The independence of pressure and its variability in individual subjects when measured over the short and medium term indicates that it is not necessary to convert this index of variability into a coefficient of variation (SD/mean). The similarity of blood pressure variability despite the markedly different pressures before and after \(\beta\)-blockade also suggests that MAP and its variability are regulated independently. This conclusion is supported by data from experimental studies that have demonstrated that selective interruption of baroreceptor reflex pathways either centrally or peripherally can increase the variability of arterial pressure independently of the blood pressure level.\textsuperscript{3,33}

Our measure of BRS reflects largely the vagal response to an increase in arterial blood pressure.\textsuperscript{17,34,35} Blood pressure variability can be attenuated in conscious dogs by atropine.\textsuperscript{35} Therefore, one interpretation of our findings is that regulation of cardiac output by the parasympathetic nervous system is the principal determinant of blood pressure variability in normal and uncomplicated hypertensive subjects. Our observations during \(\beta\)-adrenergic receptor blockade support...
such an interpretation: The significant inverse correlation between BRS and blood pressure variability was preserved. Indeed, although β-blockade may reduce blood pressure variability during selected periods of activity, 35 neither α-adrenergic nor β-adrenergic receptor blockade appears to alter ambulatory blood pressure variability overall. 36

Although arterial compliance is a major determinant of BRS, the baroreceptor reflex can be altered independently of changes in arterial compliance at the level of the central nervous system, autonomic ganglia, or the neuroeffector junction. Angiotensin, for example, decreases BRS in humans 37 through a central mechanism, likely at the level of the area postrema, and facilitates noradrenergic transmission through a prejunctional action. In addition, there is considerable evidence that modulation of these reflexes by ionic mechanisms, endogenous peptides, and drugs can occur at the level of sensory afferents; these changes can occur independently of alterations in arterial compliance. 38 Our data permit us to conclude that the baroreceptor reflex control of pulse interval, as assessed by the phenylephrine technique, bears an inverse correlation with blood pressure variability. Without an accurate measure of arterial compliance, we are not able to determine whether this is the major determinant of blood pressure variability in hypertensive subjects or whether the effect of arterial compliance on the BRS of each of these subjects may have been modulated by one or more of these mechanisms.

We did not observe a significant relationship between blood pressure variability and heart rate variability, in contrast to others, or between blood pressure and heart rate variability either before or after β-blockade. 39, 40 Differing patient populations or methods may be responsible. We included all cardiac cycles in our analysis of these data, whereas Mancia et al. 33 processed their records to provide mean values for each 3-second interval. The latter approach may have contributed to their finding by eliminating extremes of blood pressure and heart rate (regression to the mean). Further, we assessed the variability of pulse interval, rather than heart rate itself. The use of pulse interval has several advantages: The unit interval of time is used in the calculation of BRS; the use of pulse interval permits analysis of beat-to-beat variability of the cardiac cycle length; and frequency histograms of pulse interval over the waking period are normally distributed, whereas those of heart rate, its inverse, are skewed. 39 Nonetheless, the standard deviation may be too crude an expression of heart rate or blood pressure variability. More sophisticated techniques, such as spectral analysis, 40, 41 may provide additional insight into the relationship between these two variables.

Recent studies have suggested an important contribution of heart rate to the buffering of acute changes in blood pressure in humans, such that subjects with more sensitive baroreceptor reflexes buffer these changes (and hence reduce arterial pressure variability) by greater variations in pulse interval. 42 However, our results did not permit us to conclude that the variability of cardiac cycle length is influenced by either BRS or blood pressure variability. The variability of heart rate may reflect emotional and physical factors that cannot be controlled in studies of unrestricted subjects. This possibility may explain our inability to identify a relationship between BRS and cardiac cycle variability.

The effect of such factors on the baroreceptor reflex control of heart rate is well documented. Mental arithmetic, 43 handgrip, 44, 45 and dynamic exercise 46 attenuate (probably centrally) the baroreceptor reflex regulation of heart rate. The extent of this attenuation cannot be predicted from heart rate responses to pressor doses of phenylephrine given when subjects are resting quietly.

In contrast to the regulation of heart rate, the carotid arterial baroreceptor reflex regulation of blood pressure, as tested by the neck collar technique, is not suppressed by mental stress 47 or isometric exercise. 48 It may be attenuated during supine (not upright) bicycle exercise in humans. 49 This latter point remains controversial; arterial baroreceptor reflexes of conscious dogs appear to continue to operate effectively during treadmill exercise. 50-52 The strong association we observed between BRS and blood pressure variability could be explained if the reflex regulation of blood pressure was preserved during physical activity but was less potent in hypertensive than in normal subjects.

Intermittent, noninvasive ambulatory monitoring 53 and clinic blood pressure measurements 54 have been used to investigate the variability of blood pressure in borderline hypertension. Although such techniques cannot evaluate beat-to-beat blood pressure variability, our observations support the overall conclusion of these studies, namely, that blood pressure is not excessively labile in borderline hypertension. Blood pressure variability in untreated subjects was directly related to the level of arterial pressure and age; young borderline hypertensive subjects had less variable blood pressure than older, more hypertensive subjects did, even though the latter may have been less active.

We conclude that 1) of the factors studied, the decline in BRS that occurs in both borderline and established hypertension diminishes the ability to buffer changes in arterial pressure and becomes the principal determinant of increased blood pressure variability in essential hypertension; 2) MAP and its variability are regulated independently; 3) blood pressure variability is not affected by β-adrenergic receptor blockade; 4) heart rate variability is not influenced by BRS and is unrelated to blood pressure variability; and 5) patients with borderline hypertension do not have more labile pressure than those with established hypertension. It is not known how variability over the 24-hour period relates to blood pressure variability in the same subject over weeks, months, or years. Nor is it clear whether an increase in variability of blood pressure leads, with time, to more cardiovascular complications 50, 55 or whether the impairment of BRS may itself contribute to the development and maintenance of essential hypertension.
Acknowledgment

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