Arterial Baroreflexes and Blood Pressure and Heart Rate Variabilities in Humans

GIUSEPPE MANCIA, GIANFRANCO PARATI, GUIDO POMIDOSI, ROBERTO CASADEI, MARCO DI RIENZO AND ALBERTO ZANCHETTI

SUMMARY The factors responsible for 24-hour blood pressure and heart rate variabilities have never been clarified; however, studies performed in unanesthetized animals have shown an increase in blood pressure variability after sinoaortic denervation, and a negative relation has been reported occasionally between blood pressure variabilities and baroreflex control of heart rate in humans. We have systematically investigated this issue in 82 ambulant hypertensive subjects using 24-hour intra-arterial blood pressure recording (Oxford method) in which blood pressure and heart rate variabilities were measured by calculating the standard deviations of the values obtained throughout the 24 hours or during separate daytime and nighttime periods. Baroreflex sensitivity was assessed by the bradycardic or tachycardic response to intravenous injections of phenylephrine or nitroglycerin and by the blood pressure response to changes in carotid transmural pressure obtained with a neck chamber. The sensitivity of the baroreceptor-heart rate reflex as assessed by the vasoactive drug technique showed a negative relationship with 24-hour blood pressure variability as well as with daytime and nighttime blood pressure variabilities measured separately ($r = -0.28$ to $-0.50$, $p < 0.05$). These variabilities also correlated negatively with the sensitivity of the baroreceptor-blood pressure reflex as assessed by the neck chamber technique. By contrast, baroreflex sensitivity showed a positive correlation with heart rate variabilities ($r = 0.32$ to $0.47$, $p < 0.05$). The relationship between baroreflex sensitivity and blood pressure and heart rate variabilities was confirmed when the data were analyzed by multiple regression to adjust for blood pressure and age differences among the 82 subjects. These results suggest that 1) arterial baroreflexes exert a buffering influence on the magnitude of daytime and nighttime blood pressure variabilities in humans; 2) these reflexes favor heart rate variability, which may represent one of the means by which baroreflex stabilization of blood pressure is accomplished; and 3) because of the low correlation indices between baroreflex sensitivity and blood pressure and heart rate variabilities, other factors (probably central in nature) are important in determining the size of these variabilities. (Hypertension 8: 147-153, 1986)

KEY WORDS • baroreflexes • neck chamber • blood pressure variability • heart rate variability • ambulatory blood pressure monitoring • blood pressure homeostasis • central nervous system

CONTINUOUS intra-arterial blood pressure monitoring in ambulant subjects has shown that the 24-hour blood pressure profile is characterized by a marked variability due to the large difference in daytime and nighttime blood pressure, spontaneous shifts in blood pressure that take place in different half hour or hour periods, and minute-to-minute blood pressure changes. The factors responsible for the magnitude of 24-hour blood pressure variations have not been unequivocally clarified; however, studies performed in unanesthetized animals have shown that the range of blood pressure values undergoes a striking increase following sinoaortic denervation. Furthermore, few human studies have reported a negative relationship between the effectiveness of the arterial baroreceptor control of heart rate and the extent of blood pressure variability. This finding has led to the belief that this phenomenon largely depends on the buffering properties of arterial baroreflexes.

In the present study we attempted to investigate this issue more deeply. To this aim we examined a large number of subjects, using various estimates of baroreflex sensitivity and of blood pressure variability obtained by 24-hour intra-arterial blood pressure record-
Subjects and Methods

The study group comprised 82 hospitalized subjects (44 men; 38 women) ranging in age from 20 to 64 years (mean, 43.6 ± 1.2 [SE] years). All subjects had been diagnosed as having mild to severe essential hypertension. All subjects either had never been treated or had stopped treatment 1 to 2 weeks before admission to the hospital. The subjects had no other major diseases, and all gave informed consent.

Blood pressure was measured intra-arterially using the Oxford method (Oxford Instruments, Oxford, United Kingdom).11 A small catheter (inside diameter, 1.3 mm; length, 11 cm) was inserted in the subject's radial artery after local anesthesia with a 2% procaine solution. The catheter was connected by a rigid polyethylene tube to a small, light Plexiglas box fastened to the subject's thorax at heart level. The box contained a 40-ml saline-reservoir pump unit (operated by a battery), which provided the catheter with a constant slow perfusion to keep it patent for 24 hours, and a blood pressure transducer, which was connected to an amplifier and a battery-operated mini-tape recorder (fasted to the subject's waist) that stored the 24-hour blood pressure signals.

This method provides a reliable blood pressure recording because of the stability of the zero signal, the linearity of the transducer from 50 to 250 mm Hg, and the optimal frequency response of the equipment (tubing, transducer, amplifier) of up to 10 Hz.1,11 These features were checked before and after each recording. The recordings were performed while the subjects were hospitalized, which allowed their environmental and living conditions to be relatively well standardized. For example, all subjects ate a similar diet at similar times, were allowed the same amount of sleep, and could move within the hospital area engaging in inpatient social activities (e.g., watching television, playing cards, visiting with relatives, etc.) at fixed times during the day. In each subject, the recording was begun during the early evening and continued uninterrupted for 24 hours. No subject experienced pain or discomfort.

Analysis of the blood pressure signal and calculation of blood pressure variability were made as described previously.1,12 Briefly, the blood pressure tracing was examined visually at high speed on an oscilloscope to determine the quality of the signal throughout the 24-hour recording. The signal was then sent to a Digital computer (PDP 11/34; Maynard, MA, USA) that had been programmed to sample it every 60 msec and to provide average mean arterial pressure values every 3 seconds. These values were further processed to obtain the means, the standard deviations, and the variation coefficients (i.e., standard deviation divided by the mean multiplied by 100) of each of the 48 half-hour subperiods. Several measures of blood pressure variability were then derived. The 48 standard deviations and variation coefficients were averaged to evaluate the tendency of blood pressure to vary within these subperiods (i.e., to display a short-term variability). The 48 means were averaged, and the resulting standard deviation was used as a measure of the tendency of blood pressure to vary among subperiods (i.e., to display a longer term variability). Average standard deviations were also calculated for a 2-hour period during the day and during the night to obtain separate evaluations of the tendency of blood pressure to vary during wakefulness and sleep. Similar evaluations of variability were obtained for heart rate based on beat-to-beat computer analysis of the blood pressure tracings.

Arterial baroreflexes were studied by means of the vasoactive drug and the neck chamber techniques described previously.14-17 The vasoactive drug technique consisted of injecting intravenous boluses of phenylephrine (100 μg in 4 ml of 150 mM NaCl) and nitroglycerin (100 μg in 4 ml of 150 mM NaCl) and calculating the baroreflex sensitivity from the slopes of the linear regressions between the progressive rise and fall in systolic blood pressure induced by these drugs and the resulting progressive lengthening and shortening in RR interval. The neck chamber technique consisted of applications of 2-minute negative (−25 mm Hg) and 2-minute positive (+25 mm Hg) pneumatic pressures within a neck collar and calculating the baroreflex sensitivity from the ratio between the increase and reduction in neck tissue pressure outside the carotid sinuses (calculated by adjusting for the loss of pressure transmission through neck tissues16) and the resulting maximal fall and rise in mean arterial pressure. The baroreflex studies were done with the subjects supine at the end of the 24-hour blood pressure recording. For each technique, measurements were repeated twice and the results averaged.

The relationship between baroreflexes and blood pressure or heart rate variations was evaluated by means of linear regression analysis between each measure of baroreflex sensitivity (the independent variable) and the standard deviation or variation coefficient for mean arterial pressure or heart rate (the dependent variable). Multiple regressions were also calculated with baroreflex sensitivities, age, and 24-hour mean arterial pressure as the independent variables and the standard deviations for mean arterial pressure or heart rate as the dependent ones. A p value less than 0.05 was taken as the minimal level of significance of the regressions.

Results

Table 1 shows the overall characteristics of the study group. Age and mean blood pressure varied greatly among subjects, as did baroreflex sensitivity and blood pressure and heart rate variabilities. Baroreflex sensitivities were greater when assessed by the phenylephrine than by the nitroglycerin method (p < 0.01), a finding that agreed with results from several stud-
Baroreflex Reflexes and Blood Pressure Variabilities

As shown in Figure 1, baroreflex sensitivities measured by the phenylephrine and nitroglycerin methods, although unrelated to percent blood pressure variations, showed a significant relationship to short-term and long-term, as well as daytime and nighttime, absolute blood pressure variabilities. Nighttime blood pressure variations, however, were significantly correlated with baroreflex sensitivity only when the sensitivity was assessed by the phenylephrine method. The relationships obtained by employing the baroreflex sensitivity evaluated by the phenylephrine method were closer than those obtained with the nitroglycerin method. Negative correlations were obtained with both methods (as indicated by the regression lines displayed in the left panel of Figure 3).

Table 2 illustrates the results obtained by correlating blood pressure variabilities with the baroreflex sensitivities as measured by the deactivation and stimulation of the carotid baroreceptors induced by increasing and decreasing, respectively, neck tissue pressure (see Methods). The baroreflex sensitivity calculated by means of carotid baroreceptor deactivation did not result in any significant correlation with blood pressure variations. The baroreflex sensitivity calculated by means of carotid baroreceptor stimulation showed a significant inverse relationship with all absolute and percent measures of blood pressure variabilities, except those obtained during night sleep.

Baroreceptor Reflexes and Heart Rate Variabilities

As shown in Figure 2, baroreflex sensitivity was significantly related to the absolute and percent short-term, long-term, daytime, and nighttime heart rate variations. The relationship between blood pressure variability and heart rate variations was weakest for the variations occurring during the nighttime. In contrast to the blood pressure data, however, the nitroglycerin and phenylephrine methods gave similar results. More importantly, blood pressure and heart rate data differed strikingly with regard to the sign of the relationship: it was invariably positive for heart rate variability and baroreflex sensitivity (Figure 3, right panel).

Multiple Regression Analysis

Absolute blood pressure variability increases with aging and arterial pressure level.12,17 Both of which affect baroreflex sensitivity.14,18,20 The interrelationship between these variables was examined by multiple regression analysis, which considered age, 24-hour mean blood pressure, and baroreflex sensitivity (measured by any of the 4 methods already described) as the independent variables and absolute blood variability as the dependent variable. The overall value was improved by the multiple regression as compared to the value obtained by the single regressions. The most important determinant of the regression coefficient (i.e., the slope) of the multiple regression was the baroreflex sensitivity, followed by blood pressure and age. An example of these results (i.e., that in which the slope of the multiple regression was the baroreflex sensitivity) is shown in Table 3.

Discussion

In our subjects the 24-hour blood pressure variation coefficients showed little or no relationship to the sensitivity of the arterial baroreflexes. However, the 24-hour blood pressure standard deviations showed an inverse correlation with the arterial baroreflex sensiv-
Figure 1. Correlation indices between mean arterial pressure (MAP) standard deviations (upper panels) and variation coefficients (lower panels) and arterial baroreflex sensitivities obtained by the phenylephrine (PHE) and nitroglycerin (TNG) techniques. Data from 62 subjects.

Table 2. Correlations Between Mean Arterial Pressure and Heart Rate Standard Deviations and Variation Coefficients and Baroreflex Sensitivities Measured by the Neck Chamber Technique in 58 Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>During baroreceptor stimulation (−MAP/−NTP)</th>
<th>During baroreceptor deactivation (+MAP/+NTP)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r</td>
<td>b</td>
</tr>
<tr>
<td>MAP standard deviations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among half hours</td>
<td>0.31</td>
<td>−0.02</td>
</tr>
<tr>
<td>Within half hours</td>
<td>0.36</td>
<td>−0.04</td>
</tr>
<tr>
<td>2 hr, day</td>
<td>0.35</td>
<td>−0.02</td>
</tr>
<tr>
<td>2 hr, night</td>
<td>0.15</td>
<td>−0.02</td>
</tr>
<tr>
<td>MAP variation coefficients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among half hours</td>
<td>0.28</td>
<td>−0.02</td>
</tr>
<tr>
<td>Within half hours</td>
<td>0.38</td>
<td>−0.04</td>
</tr>
<tr>
<td>2 hr, day</td>
<td>0.31</td>
<td>−0.03</td>
</tr>
<tr>
<td>2 hr, night</td>
<td>0.24</td>
<td>−0.03</td>
</tr>
<tr>
<td>HR standard deviations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Among half hours</td>
<td>0.15</td>
<td>−0.008</td>
</tr>
<tr>
<td>Within half hours</td>
<td>0.25</td>
<td>1.73</td>
</tr>
<tr>
<td>2 hr, day</td>
<td>0.03</td>
<td>0.001</td>
</tr>
<tr>
<td>2 hr, night</td>
<td>0.03</td>
<td>0.001</td>
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<tr>
<td>HR variation coefficients</td>
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<tr>
<td>Among half hours</td>
<td>0.17</td>
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<tr>
<td>Within half hours</td>
<td>0.03</td>
<td>0.002</td>
</tr>
<tr>
<td>2 hr, day</td>
<td>0.07</td>
<td>0.002</td>
</tr>
<tr>
<td>2 hr, night</td>
<td>0.06</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Baroreceptor sensitivities were obtained by calculating the fall and rise in MAP induced by a fall and a rise, respectively, in neck tissue pressure (NTP). r refers to correlation indices and b to regression coefficients. See Table 1 for key to abbreviations.
BAROREFLEXES AND BLOOD PRESSURE AND HEART RATE VARIATIONS/Mancia et al.

Figure 2. Correlation indices between heart rate (HR) standard deviations (upper panels) and variation coefficients (lower panels) and arterial baroreflex sensitivities obtained as indicated in Figure 1. Data from the same subjects as in Figure 1. Explanations as in Figure 1.

Figure 3. Regression lines of mean arterial pressure (MAP) and heart rate (HR) standard deviations and baroreflex sensitivities measured by the changes in RR interval induced by increasing and reducing systolic blood pressure through phenylephrine and nitroglycerin injections. Only the regression lines that achieved statistical significance have been drawn. SBP = systolic blood pressure.

ity that was at least in part independent of the subject’s age and mean blood pressure level. This finding supports previous suggestions that human arterial baroreflexes buffer the magnitude of absolute spontaneous blood pressure variations and that their greater or lesser effectiveness represents a factor responsible for its different size in different persons. This role appears to be similar to that observed in several animal species.

Several other findings merit discussion. First, arteri-
al baroreflex sensitivity was inversely related to all measures of absolute blood pressure variability used to single out short-term from more sustained blood pressure variations and to examine separately daytime and nighttime components. Thus, this reflex mechanism exerts its buffering action on blood pressure changes regardless of their duration and occurrence during the 24 hours, including the hours when the subjects are asleep. This finding is interesting because sleep markedly alters the pattern of neural cardiovascular regulation and also affects baroreflex control of blood pressure in a complex fashion.

Second, although statistically significant, the correlation coefficients between baroreflex sensitivity and blood pressure variability never exceeded 0.5, regardless of the different estimates of baroreflex sensitivity and the percent or absolute measures of the variability phenomena. This finding suggests that baroreflex mechanisms may account for a fraction of the overall difference in blood pressure variability in different persons and that this fraction is unlikely to be greater than 25%. In this context it is important to emphasize that blood pressure variability shows a marked increase during emotional behaviors and a marked reduction during physical inactivity and sleep and that its variations are accompanied by parallel changes in heart rate variations. These points suggest that central factors jointly modulating the heart and the peripheral circulation are responsible for the production of blood pressure variations and for much of their interindividual differences.

Third, baroreflex sensitivities also were correlated with the various measures of heart rate variabilities, including those obtained during sleep. However, in contrast to the observations made for blood pressure variations and baroreflex sensitivities, the correlations between heart rate variations and baroreflex sensitivities were always positive. This result agrees with the observation in animal experiments that the increase in blood pressure variability accompanying sinoaortic denervation is associated with a reduction in heart rate variability. Thus, baroreflexes reduce blood pressure variations but enhance heart rate variations. It is likely that this enhancement represents a means through which baroreflexes alter cardiac output to achieve blood pressure stabilization.

As was mentioned previously, blood pressure and heart rate changes show an overall parallelism over the 24 hours, which supports the theory that central factors are important in daily cardiovascular modulation. This parallelism is not incompatible with our present findings that arterial baroreflexes exert opposite effects on blood pressure and heart rate variations. Our results suggest that central factors cause parallel blood pressure and heart rate changes on which baroreflexes are likely to act by 1) reducing the size of the centrally induced blood pressure oscillations and 2) inducing a series of short-lived changes in heart rate opposite in direction to the blood pressure changes, increasing heart rate variability without modifying the centrally dependent tendency of heart rate to parallel blood pressure changes throughout the 24 hours. Thus, this parallelism would be characterized by smaller blood pressure and larger heart rate oscillations when baroreflexes are effective and by larger blood pressure and smaller heart rate oscillations when they are ineffective.

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