Abstract We dynamically evaluated the effects of \(\beta\)-blockade on the sensitivity of arterial baroreflex control of heart rate in 10 mild or moderate essential hypertensive patients in whom blood pressure was recorded intra-arterially for 24 hours in ambulatory conditions. Twenty-four-hour baroreflex sensitivity was assessed by both (1) a time-domain approach based on the calculation of the slope of the regression line between linearly related progressive increases in systolic blood pressure and pulse interval (\(+PI/+SBP\) sequences) and decreases in systolic blood pressure and pulse interval (\(-PI/-SBP\) sequences) and (2) a frequency-domain approach, ie, the ratio between the spectral powers of pulse interval and systolic blood pressure around 0.1 Hz (\(\alpha\) coefficient). Data were obtained before and after 1 month of administration of either acebutolol (n=5) or labetalol (n=5). Before treatment, the 24-hour average slopes of the \(+PI/+SBP\) and \(-PI/-SBP\) sequences were 4.36±0.32 and 4.05±0.27 ms/mm Hg, respectively, while the \(\alpha\) coefficient was 7.78±0.7 ms/mm Hg. After \(\beta\)-blockade, these values were increased by 25.3±6.8%, 25.0±8.0%, and 32.1±9.3%, respectively (\(P<.01\) for all values). Thus, \(\beta\)-blockers potentiate baroreflex sensitivity in daily life. Time-domain and frequency-domain methods yielded superimposable results in dynamically evaluating 24-hour baroreflex sensitivity and its changes after \(\beta\)-blockade. (Hypertension. 1994;23[part 2]:992-996.)

Key Words receptors, adrenergic, \(\beta\) pressoreceptors • sequence analysis • blood pressure monitors • blood pressure • hypertension, essential • heart rate • spectral analysis

Methods

Subjects

Our study included 10 patients (5 men, 5 women) with mild or moderate uncomplicated essential hypertension, whose age averaged (±SD) 42.9±4.4 years. No subject received cardiovascular drugs during a 4-week period of diagnostic evaluation before the study. Each subject consented to the procedure after its methods and purposes were explained.

Blood Pressure Measurements

Systolic and diastolic blood pressures were measured by a mercury sphygmomanometer at the initial clinic visit. The means of three sitting values were 174.0±16.4/110.5±8.3 mm Hg. Blood pressure was then directly recorded for 24 hours (see below) by the method described by Bevan et al and used in the past 20 years in our as well as others’ laboratories. The details of the method as used in our laboratory have been described elsewhere. Briefly, a catheter (length, 11 cm; internal diameter, 1.1 mm) was inserted percutaneously into the radial artery of the nondominant arm and connected by a rigid polyethylene tube to an Oxford transducing/perfusing unit contained in a Plexiglas box at the level of the heart. The transduced blood pressure signal was amplified and stored in a magnetic tape cassette by an Oxford Medilog recorder. The whole system had a frequency response of −3 dB at 8 to 10 Hz and showed no drift of the 0 signal and a linear response between 50 and 250 mm Hg before and after the 24-hour recording time.

Protocol

After the initial visit to the clinic, each subject underwent the 24-hour intra-arterial blood pressure recording twice, before and after 1 month of antihypertensive treatment with two drugs commonly used in our clinics, ie, acebutolol (n=5, 200 mg BID) or labetalol (n=5, 300 mg BID). Patients were admitted to the hospital 1 week before each 24-hour blood pressure recording, which was started around 6 PM. Mealtimes,
bedtimes, and recreational times (watching TV, playing cards, visiting with relatives) followed the hospital schedule and thus were standardized. During the recording, the subjects were allowed to move within the hospital building and gardens but not to walk outside the hospital area. This was done both for safety and for preventing differences in blood pressure and heart rate variability as a result of uncontrolled physical activities and behaviors. The study protocol was approved by the Ethical Committee of our institution.

Data Analysis

The 24-hour blood pressure recording was sampled at 168 Hz, digitized on 12 bits, and subjected to further analysis by a computer. This consisted of (1) editing the signal from artifacts and pulse pressure dampening by an interactive procedure described in previous studies by our group; (2) calculating systolic, diastolic, and mean blood pressures for each pulse wave; and (3) calculating pulse interval and its reciprocal value, ie, heart rate, from the interval between consecutive systolic peaks. For each parameter, mean values and the corresponding standard deviations (ie, measure of variability) were computed for each hour of the recording period and for the whole 24 hours.

Baroreflex Sensitivity

The sensitivity of the baroreceptor heart rate reflex was assessed throughout the 24 hours by computer analysis of systolic blood pressure (SBP) and pulse interval (PI) variations with both a time-domain and a frequency-domain approach. Pulse interval was used instead of heart rate because its changes in relation to SBP changes display a linear behavior and no asymptote over the range of values explored. The time-domain approach was based on automatic identification of the sequences of three or more consecutive beats in which SBP and PI increased progressively (+PI/+SBP sequence) or decreased progressively (−PI−SBP sequence) by at least 1 mm Hg and 6 milliseconds, respectively. If the relation between SBP and PI changes was linear (correlation coefficients >0.85), the regression coefficient or slope was taken as a measure of the sensitivity of baroreflex control of the heart, as done when changes in SBP and PI are induced in the laboratory by intravenous injections of vasoactive drugs. The number and the slope of the +PI/+SBP and −PI−SBP sequences were averaged separately for each hour of the recording and for the whole 24 hours. The frequency-domain approach was based on spectral analysis of SBP and PI fluctuations. According to a procedure described in detail previously, the SBP and PI fluctuations with a period greater than 40 seconds (frequency=0.025 Hz) were removed by high-pass filtering (Chebyshev filter, cutoff frequency set at ωc=0.025 rad/s). The filtered time series were split into contiguous segments of 256 values. Segments containing non-stationarities were detected and excluded by the reverse arrangement test. Power spectral densities of each stationary segment were estimated after a 10% cosine tapering of the raw data using the fast Fourier transform. For each segment, the powers of the SBP and PI oscillations between 0.07 and 0.14 Hz were computed, and the square root of the ratio between SBP and PI powers (called α coefficient) was taken as an index of the sensitivity of baroreflex control of the heart. This was done because in the frequency region around 0.1 Hz, (1) the SBP and PI powers are related to each other, ie, their coherence (the equivalent in the frequency domain of the correlation coefficient in the time domain) is usually higher than 0.51,18 and (2) PI effects are produced by sympathetic and vagal influences, ie, by both autonomic branches modulated by baroreceptors.

Previous studies11,12,18 have shown that, over the 24 hours, either approach provides a strikingly large number of observations on the baroreceptor heart rate reflex. They have also shown that the number of sequences for the time-domain approach and the degree of coherence between PI and SBP powers for the frequency-domain approach are strikingly reduced by sinoaortic denervation in conscious cats, docu-
menting their baroreceptor origin.\textsuperscript{11,18} It should be emphasized that SBP and PI powers show a coherence higher than 0.5 also between 0.14 and 0.35 Hz.\textsuperscript{13,18} However, data from this higher-frequency region were excluded from the calculation of the $\alpha$ coefficient because the PI/SBP coherence in the 0.14- to 0.35-Hz region does not disappear after sinoaortic denervation, indicating its origin also from factors (eg, respiratory-driven fluctuations of blood pressure and heart rate) other than the baroreflex.\textsuperscript{18} Furthermore, PI modulation in this frequency region does not include sympathetic influences.\textsuperscript{19}

Statistical Analysis

For each measure, individual data were averaged to obtain group mean values. Comparisons between the no-drug and the treatment condition were made by Student’s $t$ test for paired observations. The relation between hourly baroreflex sensitivity and hourly blood pressure or PI variability was assessed by linear regression analysis. A value of $P<.05$ was taken as the level of statistical significance.

Results

As shown in Fig 1, compared with the hourly values obtained in the no-drug condition, SBP, diastolic blood pressure, and mean arterial pressure fell during $\beta$-blocking treatment, the differences in the 24-hour averages being more evident for SBP. Hourly PI values increased during $\beta$-blocking treatment.

In the pretreatment conditions, 24-hour systolic, diastolic, and mean blood pressure standard deviations were $20.44\pm0.85$, $11.59\pm0.56$, and $14.4\pm0.6$ mm Hg (mean$\pm$SEM), respectively. $\beta$-Blockade reduced these values by $-10.8\pm6.6\%$, $-3.7\pm7.0\%$, and $-9.2\pm4.3\%$. Twenty-four-hour PI standard deviation was $135.7\pm9.2$ milliseconds in the pretreatment condition and showed a marked reduction during $\beta$-blockade ($-27.7\pm7.8\%$, $P<.05$).

Baroreflex Sensitivity: Time-Domain Approach

The number of the $+\text{PI}+\text{SBP}$ and the $-\text{PI}−\text{SBP}$ sequences identified over the 24 hours before treatment was reduced to less than half during $\beta$-blocking therapy ($653.1\pm83.6$ versus $299.1\pm85.1$ for $+\text{PI}+\text{SBP}$; $714.2\pm162.0$ versus $320.7\pm129.9$ for $-\text{PI}−\text{SBP}$; $P<.01$ for both). In contrast, the average 24-hour slope (regression coefficient) of either type of sequence was significantly higher under than before $\beta$-blockade ($5.34\pm0.5$ versus $4.36\pm0.3$ ms/mm Hg for $+\text{PI}+\text{SBP}$; $5.1\pm0.6$ versus $4.05\pm0.3$ ms/mm Hg for $-\text{PI}−\text{SBP}$; $P<.05$ for both). For either type of sequence, the increase in slope was not related to the drug-dependent increase in 24-hour average PI ($r=−.18$ and $−.29$, respectively; $P=\text{NS}$).

Fig 2 illustrates that the reduction in the number and the increase in the slope of the $+\text{PI}+\text{SBP}$ and $-\text{PI}−\text{SBP}$ sequences observed under $\beta$-blockade were evident for most of the 24 hours. In the pretreatment condition, the number of either type of sequence fell during the night compared with the day, whereas the corresponding slope increased. A similar pattern was observed during $\beta$-blockade, although the day and night modulation in the sequence number became less evident.

Baroreflex Sensitivity: Frequency-Domain Approach

As shown in Fig 3 (top), in the pretreatment condition, the segments in which SBP and PI powers displayed a coherence $>0.5$ comprised more than 80% of the available ones for virtually each hour of the 24-hour
MEAN VALUES

Fig 3. Graphs show percentage of segments with pulse interval/systolic blood pressure (PI/SBP) power coherence >0.5 and average values (±SEM) of the α coefficient for each hour of the recording and for the whole 24-hour period (triangles). Data are shown separately for the baseline and the treatment conditions. *Statistical significance of 24-hour values.

period. The "coherent" segments were slightly although significantly less during β-blockade. Fig 3 (bottom) shows that the α coefficient was greater than before β-blockade throughout most of the 24-hour time and that the increase in nighttime baroreflex sensitivity seen also with this method was preserved under β-blockade. The increase in the 24-hour average α coefficient induced by β-blockade was +32.2±9.3% and was comparable to the increase in the 24-hour average slope of the +PI/+SBP and -PI/-SBP sequences (+25.3±6.8% and +25.0±8.0%, respectively) with no relation with the drug-dependent increase in PI (r = −.20; P = NS). Before treatment, the hourly average α coefficients showed a very close relation with the hourly average slope of either the +PI/+SBP (n = 24, a = −0.82, b = 1.4, r = .94, P < .01) or the −PI/−SBP sequences (n = 24, a = −0.13, b = 1.4, r = .93, P < .01). This was the case also during β-blockade, the r values of these relations being .89 and .83, P < .01, respectively.

Baroreflex Sensitivity and Blood Pressure and PI Variability

As shown in the Table, in the pretreatment condition, hourly average α coefficients correlated inversely with hourly standard deviation of SBP and directly with hourly standard deviation of PI. The inverse relation between α coefficient and blood pressure variability was preserved under β-blockade, whereas the direct relation between α coefficient and PI variability was no longer evident. Similar results were obtained when baroreflex sensitivity was assessed by the sequence method.

Labetalol and Acebutolol

Twenty-four-hour mean blood pressure was reduced similarly in the five subjects taking labetalol (−10.3±11.8 mm Hg) and in the five subjects taking acebutolol (−10.4±5.2 mm Hg). The 24-hour change in PI was greater with labetalol than with acebutolol (+79.9±35.5 versus +61.8±17.9 milliseconds), whereas the effects of the two drugs on the slopes of the +PI/+SBP and −PI/−SBP sequences and on the α coefficient were similar (+0.8 versus +2.1, P = NS; +0.5 versus +0.8, P = NS, and +1.8 versus +1.2 ms/mm Hg, P = NS for labetalol and acebutolol, respectively).

Discussion

In our hypertensive patients, chronic administration of β-blockers was associated with a significant increase in the 24-hour average sensitivity of the baroreceptor heart rate reflex both when the baroreflex function was estimated by the sequence approach and by the spectral approach. Furthermore, the increase in baroreflex sensitivity was evident throughout the 24 hours and similar (α coefficient) or greater (sequence approach) for daytime than for nighttime. Finally, an increased sensitivity was observed both for the reflex effects of baroreceptor stimulation and deactivation (+PI/+SBP and −PI/−SBP sequences). This provides the first evidence that in hypertensive subjects, administration of β-blockers does potentiate daily life baroreceptor control of heart rate and that this occurs uniformly throughout the different behavioral conditions of the 24 hours, involving the entire stimulus-response curve. By comparing the present results with those obtained in a previous study using the sequence method to examine the 24-hour baroreflex sensitivity of normotensive and essential hypertensive subjects, it is clear that even after β-blockade, the 24-hour baroreflex sensitivity remained far below normal and that this was the case during either the day or the night.

Three other results of our study deserve to be discussed. (1) In line with data obtained by laboratory baroreflex assessment,5-7 in our patients, no relation was found between the fall in mean 24-hour arterial pressure induced by β-blockers and the degree of concomitant baroreflex potentiation as quantified by the 24-hour +PI/+SBP and −PI/−SBP slopes and by the α coefficient (r = −.1, −.4, and +.1, P = NS, respectively). Thus, this potentiation may not be primarily involved in the antihypertensive effect of this class of drugs. (2) In our untreated hypertensive patients, hourly baroreflex sensitivity correlated inversely with hourly blood pressure variability and directly with hourly PI variability. This provides critical evidence that the arterial baroreflex buffers daily life blood pressure variations and that this is exerted at least in part by modulating heart rate and cardiac output changes, in line with classic animal data20 and with preliminary suggestions obtained by laboratory baroreflex assessment in humans.15,29 It should be emphasized that during treatment, the inverse correlation between baroreflex sensitivity and blood pressure variability
ability was unchanged, whereas the direct correlation between baroreflex sensitivity and PI variability was no longer evident. This implies that the buffering action of the baroreflex is preserved under β-blockade, although blood pressure stabilization is probably achieved less via reflex cardiac mechanisms (and more via reflex modulation of peripheral vascular resistance) than in control states. (3) In our patients, the sequence and the α coefficient methods provided similar absolute values of 24-hour baroreflex sensitivity and similar estimates of its changes under treatment. This represents the first available evidence that time-domain and frequency-domain approaches to dynamically assess the baroreflex yield comparable results and can therefore be used interchangeably, according to the protocol requirement and needs.

Finally, although a dynamic assessment of the baroreflex represents a technical improvement over traditional baroreflex assessment, our study has some limitations. (1) Intra-arterial blood pressure monitoring did not allow us to have a parallel placebo group with which to compare the data obtained by active drug treatment. (2) Although data obtained in the two subgroups with different treatment did not differ, one of the two β-blockers used (acebutolol) had a small intrinsic sympathomimetic activity, whereas the other (labetalol) did not but rather characterized by additional α-adrenergic blocking properties, albeit attenuated in the chronic condition of our study. (3) Our methods allow us to dynamically assess only the baroreceptor heart rate reflex, and evidence in both animals and humans indicates that this reflex function may not always reflect baroreceptor control of peripheral circulation and blood pressure. No methods are yet available, however, to examine the latter in a dynamic fashion.

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