Cardiovascular Autonomic Modulation in Essential Hypertension

Effect of Tilting

Alberto Radaelli, Luciano Bernardi, Felice Valle, Stefano Leuzzi, Fabrizio Salvucci, Luisa Pedrotti, Eugenia Marchesi, Giorgio Finardi, Peter Sleight

To better understand the role played by the autonomic nervous system in essential hypertension, we used autoregressive power spectrum analysis to study the noncausal oscillations in RR interval, blood pressure, and skin blood flow in 40 subjects with mild to moderate hypertension and in 25 age-matched control subjects at low frequency (index of sympathetic activity to the heart and the peripheral circulation) and high frequency, respiratory related (index of vagal tone to the heart). RR interval, respiration, noninvasive systolic blood pressure, and skin arteriolar blood flow were simultaneously and continuously recorded with subjects in the supine position and immediately after tilting. The low-frequency component was not significantly different in the two groups either at the cardiac level (control versus hypertensive subjects: 39.1 ± 4.3 versus 39.9 ± 3.7 normalized units [NU]) or at the vascular level (1.52 ± 0.17 versus 1.69 ± 0.13 in mm Hg²). After head-up tilting, the RR interval fluctuations were less in hypertensive subjects (low-frequency components from 39.9 ± 3.7 to 48.4 ± 4.1 NU, P < .05; high-frequency components from 53.9 ± 3.7 to 44.2 ± 4.4 NU, P < .05) than in control subjects (low-frequency components from 39.1 ± 4.3 to 64.2 ± 4.9 NU, P < .001; high-frequency components from 56.0 ± 4.5 to 31.2 ± 4.6 NU, P < .001); the low-frequency components in systolic blood pressure increased similarly in hypertensive subjects (to 2.43 ± 0.17 in mm Hg², P < .001) and in control subjects (to 2.44 ± 0.21 in mm Hg², P < .01), but the low-frequency components in skin blood flow increased only in control subjects (from 5.34 ± 0.45 to 6.65 ± 0.53 mm Hg², P < .01), not in hypertensive subjects (from 5.55 ± 0.34 to 5.60 ± 0.35 in mm Hg²). In hypertensive subjects with left ventricular hypertrophy, the low-frequency components in systolic blood pressure did not increase after tilting (from 1.75 ± 0.33 to 2.05 ± 0.41 in mm Hg²). Baroreflex sensitivity, as assessed by spectrum analysis, was significantly lower in hypertensive than in control subjects (5.17 ± 0.49 versus 13.18 ± 2.44 ms/mm Hg, P < .001). Power spectrum analysis did not reveal an increased sympathetic activity or reactivity either at the cardiac or at the vascular level. The decreased baroreceptor sensitivity in hypertensive subjects could explain the reduced change in sympathovagal balance in the tilt position at the cardiac level. In hypertensive subjects without left ventricular hypertrophy, cardiopulmonary reflex deactivation induced by tilting and/or amplification of sympathetic nervous tone by arteriolar structural change could have preserved the sympathetic activation at the vascular level. (Hypertension. 1994;24:556-563.)

Key Words • hypertension, essential • heart rate • spectrum analysis • autonomic nervous system

The arterial baroreceptors are known to maintain blood pressure in a normal range by actions on cardiac output and peripheral resistance.1-2 In essential hypertension, cardiovascular homeostasis is partially lost or at least is maintained at a level of blood pressure different from that of normotensive subjects.3-4 The cause of this abnormality is currently not known, but the early alteration of baroreceptor control suggests that the autonomic nervous system is deeply involved in the process.5-6 An alteration of sympathovagal balance, caused by increased sympathetic tone or decreased parasympathetic activity, has also been postulated.7-8 RR interval, blood pressure, and arteriolar blood flow show noncasual oscillations closely related to the activity of the cardiovascular control systems. Spectral analysis of these oscillations shows low-frequency (0.03 to 0.14 Hz) and high-frequency, respiratory-related, oscillatory components.9 The low-frequency component influences cardiac (RR interval) and, particularly, vascular control (blood pressure and arteriolar blood flow) mostly through sympathetic activity. However, our recent work10 confirms the hypothesis of de Boer et al11 that arterial baroreflexes play a major role in the origin of the low-frequency component. The high-frequency oscillatory component, synchronous with respiration, acts through parasympathetic activity at the cardiac level.12-14 Different studies15-21 with different methodologies have investigated cardiovascular control in hypertensive patients. While it is clear that early alteration of the parasympathetic activity is present in hypertension, the role played by the sympathetic activity is still being debated. Therefore, we used a new technique to study simultaneously the parasympathetic activity to the heart and the sympathetic activity to the peripheral blood vessels both in baseline conditions and during physiological maneuvers, such as passive tilting, that can increase sympathetic activity.

Methods

Subjects

We studied 40 subjects with mild to moderate hypertension and 25 age-matched healthy control subjects. Thirty-five
of the hypertensive subjects were newly diagnosed and untreated. The remaining 5 hypertensive subjects, who were on angiotensin-converting enzyme inhibitors (3) and diuretics (2), discontinued the treatment 4 weeks before the study. The characteristics of the subjects are shown in Table 1. Arterial blood pressure was measured with a random-zero sphygmomanometer (Hawksley). Subjects with a diastolic blood pressure consistently greater than 95 mm Hg as assessed by repeated measurements (at least three) on separate days (at least 3) were classified as established hypertensive patients. Only 1 hypertensive patient was obese; none had insulin resistance. No other cardiovascular or kidney disease was found by electrocardiogram, chest radiograph, or routine blood examination (blood urea nitrogen, creatinine, electrolytes, hematocrit, fasting plasma glucose, cholesterol, and triglycerides). The hypertensive subjects underwent two-dimensional echocardiograph examination (Hewlett-Packard 1000).

Protocol and Data Acquisition

The subjects were asked not to smoke or drink coffee, tea, chocolate drinks, or alcohol on the day of the study, and they had a light meal at noon. Studies were always carried out at the same hour (3:30 PM) in a quiet room at a stable temperature (22°C). The study was approved by the Hospital Review Committee, and informed consent was obtained from all volunteers and patients. Insulin resistance was tested with the oral glucose tolerance test. All patients had blood drawn for fasting insulin and fasting glucose determination. All patients received 100 g oral glucose. Blood was drawn for glucose and insulin determination at 30, 60, 120, and 180 minutes. Hyperinsulinemia was defined as fasting or sum of insulin levels (60- and 120-minute postload) above the 75th percentile of the sum insulin distribution in the reference group. Left ventricular diameters were measured by monodimensional echocardiography by using bidimensional Doppler echocardiography to perform the measurements from the septal leading edge to the posterior wall leading edge. The measurements were made at the peak of the R wave of the electrocardiogram and were accompanied by measurements of septal wall thickness and left posterior wall thickness. Left ventricular mass index was calculated according to the Penn convention formula. The following signals were directly and continuously recorded on a computer (Macintosh II Apple) by means of a 12-bit analog-to-digital converter (NB-Mio-16 board, National Instruments; sampling rate of 500 samples per second per channel): RR interval (with an electrocardiograph), respiration (with an impedance method), blood pressure (with Finapres [Ohmeda 2300], which has been shown to follow blood pressure oscillations accurately during tests), and skin arteriolar blood flow by infrared photoplethysmography (measured on the volar surface of the finger, on the same hand as the Finapres). This sample device, which measures the fluctuations of a 1-mW, 950-nm infrared light backscattered from the red blood cells moving in the skin vessels, particularly the arterioles, can detect spontaneous fluctuations in skin arteriolar flow related to autonomic control of the microcirculation. The theory and applications of this device have been reviewed elsewhere. After at least 20 minutes for stabilization, the signals were simultaneously and continuously recorded for 10 minutes with subjects both in the supine position and immediately after 90° passive tilting on an electrically driven tilt table (Akron) during free (first 5 minutes) and controlled breathing (15 breaths per minute, second 5 minutes).

Univariate Analysis

The power spectrum analysis program was written in our laboratory as previously described. A C program identified all the QRS complexes in each sequence and then located the peak of each R wave. The RR intervals were obtained from these data. For each step of the protocol, 250 consecutive RR intervals were analyzed. The nonoscillatory (DC) component was removed from each sequence. The respiratory signal obtained by the impedance pneumograph and the skin arteriolar blood flow obtained by the infrared plethysmograph were expressed in absolute arbitrary values (millivolt output from the device). Total variability of each signal has been expressed as the SD because variance does not have a normal distribution. Power spectral analysis was carried out by using an autoregressive model. Model coefficients were evaluated according to the Burg algorithm; model order was assessed by Akaike criteria. In most cases, a model order of 1 was found to be adequate. Spectral components were obtained by a decomposition method to measure the area below each spectral peak. The respiration-related oscillations on the RR interval, blood pressure, and skin arteriolar blood flow spectra were identified by comparison with the oscillations of the respiratory spectrum. Spectral analysis of all signals except respiration shows two separate peaks: the low-frequency peak (between 0.03 and 0.14 Hz) is usually thought to reflect mainly the sympathetic nervous activity at both the cardiac and vascular levels. However, more recent analyses suggest that this is an oversimplification, so the low-frequency peak may be reduced considerably if the baroreflex control of vagal efferent activity is reduced (see “Discussion”). The low-frequency peak should be better considered as the result of the slower response of the sympathetic system and/or of the vascular reactivity to any mechanical change in blood pressure sensed by the baroreceptors. The high-frequency peak, identified on the different signals by correspondence with the peak on the respiratory spectrum, reflects at the cardiac level the efferent parasympathetic activity, and at the vascular level it largely reflects the mechanical effects of respiration on cardiac output. Thus, the ratio of low-frequency to high-frequency (LF/HF) ratio reflects at the cardiac level (RR) a complex interaction of the sympathovagal balance but modulated by the gain of the baroreflex arc and particularly the vagal arm of the baroreflex. To further highlight the relative aspects of the sympathovagal balance to the heart, the low- and high-frequency oscillations in the RR interval were also expressed as a percentage of total oscillatory power (ie, normalized units [NU]). Normalized units also allow comparison between different subjects or different situations characterized by different variabilities. Conversely, low- and high-frequency components, derived from the analysis of blood pressure and blood flow, have been expressed as absolute values because they reflect not only a balance between the two interacting branches of the autonomic nervous system but also the sympathetic versus the mechanical effects of respiration at the vascular level.

Bivariate Analysis

Baroreceptor Sensitivity

Pagani et al described a method to obtain an index for the analysis of the relation between the best-to-best variability of RR and systolic blood pressure (SBP) during steady-state
controlled breathing or in hypertensive subjects (RR interval: from 809±18 to 923±31, P=NS; SD: from 40.8±3.4 to 41.4±3.6, P=NS) did not induce important dynamic changes. Nevertheless, controlled breathing induced a significant decrease in low-frequency normalized units and in the LF/HF ratio on the RR spectrum both in control subjects (low frequency: from 59.9±4.0 to 39.1±4.3 NU, P<.0001; LF/HF ratio: from 4.18±1.40 to 1.12±0.25, P<.05) and in hypertensive subjects (low frequency: from 57.8±3.7 to 39.9±3.7 NU; P<.0001; LF/HF ratio: from 4.60±1.68 to 1.30±0.26, P<.05), with a significant increase in high-frequency normalized units in both groups (control subjects: from 37.4±4.1 to 56.0±4.5, P<.0001; hypertensive subjects: from 36.4±3.6 to 53.9±3.7, P<.001). To verify whether in the two groups the decrease in the LF/HF ratio during controlled breathing was due to an increase in parasympathetic tone, and thus of RSA, or to the mechanical effect of changing the rate of breathing (see Fig 1), we independently estimated the RSA by the cross-correlation method and calculated the baroreceptor sensitivity (BRS_{psa}) during free and controlled breathing. Cross-correlation function did not show a significant change from free to controlled breathing in control subjects (from 6.22±0.13 to 6.51±0.13, P=NS). There was a just significant increase in hypertensive subjects (from 5.66±0.10 to 5.92±0.10, P<.05). The BRS_{psa} did not change significantly from free to controlled breathing either in control subjects (low-frequency BRS_{psa}: from 15.27±2.44 to 13.18±2.44 ms/mm Hg, P=NS; high-frequency BRS_{psa}: from 15.83±1.76 to 14.11±1.61 ms/mm Hg, P=NS) or in hypertensive subjects (low-frequency BRS_{psa}: from 6.08±0.81 to 5.17±0.49 ms/mm Hg, P=NS; high-frequency BRS_{psa}: from 8.60±0.99 to 7.58±0.69 ms/mm Hg, P=NS). Thus, there was a nonsignificant trend toward a reduction in BRS_{psa} with the central effect of controlled breathing; this might have been counteracted by the greater depth of breathing. The small increase in cross-correlation observed in hypertensive subjects could be due to an increase in the depth of respiration that is usually observed during controlled breathing. The increase in parasympathetic tone during controlled breathing might have involved an increase in baroreceptor sensitivity, but this was not the case. Therefore, because uncontrolled respiration could have interfered with the calculation of sympathetic activity while controlled respiration allowed better discrimination of the two autonomic components without inducing important changes of autonomic activity, we preferred to compare the two groups while the
TABLE 2. RR Interval: Effect of Tilting in Control and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Subjects</th>
<th>Hypertensive Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
</tr>
<tr>
<td>Mean</td>
<td>923±31</td>
<td>789±30*</td>
</tr>
<tr>
<td>SD</td>
<td>41.4±3.6</td>
<td>34.6±2.2</td>
</tr>
<tr>
<td>LF, In-ms²</td>
<td>5.62±0.20</td>
<td>5.55±0.23</td>
</tr>
<tr>
<td>LF, NU</td>
<td>39.1±4.3</td>
<td>64.4±4.9∥</td>
</tr>
<tr>
<td>HF, In-ms²</td>
<td>6.07±0.24</td>
<td>4.67±0.20*</td>
</tr>
<tr>
<td>HF, NU</td>
<td>56.0±4.5</td>
<td>31.2±4.6∥</td>
</tr>
<tr>
<td>LF/HF ratio</td>
<td>1.12±0.25</td>
<td>4.45±0.92∥</td>
</tr>
<tr>
<td>BRS&lt;sub&gt;psa&lt;/sub&gt; LF</td>
<td>13.1±2.4</td>
<td>5.3±0.6∥</td>
</tr>
<tr>
<td>BRS&lt;sub&gt;psa&lt;/sub&gt; HF</td>
<td>14.1±1.6</td>
<td>4.8±0.7</td>
</tr>
</tbody>
</table>

LF indicates low frequency; NU, normalized units; HF, high frequency; BRS<sub>psa</sub>, baroreceptor sensitivity by power spectrum analysis. Values are mean±SEM.

*P<.0001, supine vs upright (paired t test).
†P<.001, §P<.01, hypertensive vs control (unpaired t test).
∥P<.05, ¶P<.01, U<.001, supine vs upright (paired t test).
#P<.05, **P<.001, hypertensive vs control (unpaired t test).

TABLE 3. Systolic Blood Pressure: Effect of Tilting in Control and Hypertensive Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Subjects</th>
<th>Hypertensive Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Supine</td>
<td>Upright</td>
</tr>
<tr>
<td>Mean</td>
<td>127±3</td>
<td>121±7</td>
</tr>
<tr>
<td>SD</td>
<td>4.6±0.2</td>
<td>6.4±0.4∥</td>
</tr>
<tr>
<td>LF, In-ms²</td>
<td>1.52±0.17</td>
<td>2.44±0.21∥</td>
</tr>
<tr>
<td>HF, In-ms²</td>
<td>1.44±0.11</td>
<td>1.93±0.17∥</td>
</tr>
</tbody>
</table>

LF indicates low frequency; HF, high frequency. Symbols indicating significance are as in Table 2.

The BRS was significantly lower in hypertensive than in control subjects (Table 2).

Effect of Tilting

In the tilt position, the RR interval decreased significantly both in control and in hypertensive subjects, but this decrease was significantly greater in the hypertensive subjects. The low-frequency component increased and the high-frequency component decreased more in control than in hypertensive subjects, so in the tilt position these were significantly different in the two groups. Consequently, the LF/HF ratio increased more in control than in hypertensive subjects (Table 2, Figs 2 and 3). SBP did not change significantly in the tilt position in either control or hypertensive subjects. SBP variability (SD) and the low-frequency oscillatory component increased significantly in both groups. In the tilt position, the high-frequency oscillatory component increased more significantly in hypertensive than in control subjects (Table 3). DBP, DBP variability (SD), and the low-frequency oscillatory component increased significantly in both groups, while the high-frequency oscillatory component increased significantly only in the hypertensive subjects (Table 4). Skin arteriolar blood flow variability (SD) did not change significantly in either control or hypertensive subjects. The low-frequency oscillatory component of the skin blood flow...
increased significantly only in control subjects, and the high-frequency oscillatory component increased significantly only in hypertensive subjects (Table 5). Baroreceptor sensitivity decreased significantly with tilt in both control and hypertensive subjects; it remained significantly lower in hypertensive than in control subjects (Table 2).

Effect of Left Ventricular Hypertrophy

Seven hypertensive subjects with echocardiographic evidence of left ventricular hypertrophy (LVH) and the remaining hypertensive subjects without any echocardiographic or electrocardiographic evidence of LVH were compared (Table 6). The BRS was not significantly different in the two subgroups either supine or in the tilt position. Nevertheless, at the vascular level the low-frequency oscillatory component of SBP and DBP increased significantly on tilting only in the subgroup without LVH, on both the SBP and the DBP signals.

Discussion

Effect of Breathing Pattern on RR Interval Variability

To study the two oscillatory components of the RR power spectrum, it is necessary that the frequencies of breathing and of RSA are higher than the 0.1 Hz characteristic of sympathetic activity. On the other hand, we realized that during free breathing the presence of a slow breaths could generate a low-frequency component superimposed on that related to the sympathetic activity, thus interfering with its calculation. To avoid this artifact, we asked our subjects to breathe in a regular way at 15 breaths per minute. Because controlled breathing did not induce important changes in autonomic modulation, we focused on the results obtained during controlled respiration.

Baseline Observations

With subjects in the supine position, heart rate and blood pressure were higher in hypertensive than in control subjects. Previous studies suggested a parasympathetic inhibition and/or a sympathetic stimulation to the heart in hypertensive subjects. The technique we used could not confirm a sympathetic hyperactivity to either the heart or blood vessels. A reduced responsivity of the cardiac β-receptors and the baroreceptor influence on low-frequency RR could in part be responsible for this finding. Moreover, because power spectral analysis detects only nervous oscillatory components of heart rate and blood pressure variability, it could have missed tonic influences such as those exerted by humoral catecholamines. The high-frequency component RSA was not different in the two groups, despite an altered baroreflex control of heart rate in the hypertensive subjects. Because less than one fourth of the hypertensive subjects we studied had echocardiographic evidence of LVH, the cardiopulmonary reflexes, whose sensitivity has been found to be normal or even enhanced in hypertensive animals or subjects without LVH, could have played an important compensatory role in the origin of RSA, as previously suggested.

Effect of Tilting

In the tilt position, heart rate and DBP showed a similar increase in the two groups. During sympathetic activation, the low-frequency component RR and blood pressure were not higher in hypertensive than in control subjects in the tilt position.
subjects. Previous studies using power spectrum analysis found similar results at the cardiac level and different results at the vascular level. The possible presence of insulin resistance, the different protocol (5 versus 15 minutes upright, possibly different breathing pattern), and the patient population might explain the difference from our results. In the tilt position, the low-frequency component RR increased and the high-frequency component RR decreased significantly less in the hypertensive than in the control group, suggesting an overall lower autonomic reactivity. The observed impairment of the baroreceptor control of heart rate in hypertensive subjects, added to the recent observation of an increased sensitivity of the parasympathetic nerve activity in hypertensive subjects, could explain the reduced parasympathetic withdrawal and the reduced sympathetic activation in the tilt position. Moreover, an increased stimulation of the contractility-sensitive ventricular receptors in hypertrophied hearts in the upright position could lead to an increased vagal discharge to the heart. Despite the presence of a decreased BRS, we found a normal increase of sympathetic activity on the blood pressure signal in hypertensive subjects. The redundant control of the vascular resistances exerted from the carotid and aortic baroreceptors could have preserved the sympathetic activation on the vascular side. Moreover, because other reflex mechanisms could take part in the cardiovascular adjustment after tilting, cardiopulmonary reflexes could have played an important role in the increase of the peripheral sympathetic activity. In fact, when hypertensive subjects with and without LVH, and thus with and without impairment of cardiopulmonary reflexes, were compared, they did not show any difference in BRS, but the group with LVH failed to show a significant increase in sympathetic activity on the blood pressure.

Table 6. Effect of Tilting in Hypertensive Subjects With and Without Left Ventricular Hypertrophy

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR LF, NU</th>
<th>RR HF, NU</th>
<th>SBP LF, In-pw</th>
<th>SBP HF, In-pw</th>
<th>DBP LF, In-pw</th>
<th>DBP HF, In-pw</th>
<th>BRS&lt;sub&gt;LF&lt;/sub&gt;</th>
<th>BRS&lt;sub&gt;HF&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>38±7</td>
<td>55±6</td>
<td>1.63±0.22</td>
<td>1.44±0.13</td>
<td>1.19±0.17</td>
<td>0.75±0.12</td>
<td>5.06±0.83</td>
<td>8.45±1.21</td>
</tr>
<tr>
<td>Tilting</td>
<td>44±7</td>
<td>50±7*</td>
<td>2.68±0.27‡</td>
<td>2.11±0.26*</td>
<td>1.99±0.24‡</td>
<td>1.02±0.12</td>
<td>2.96±0.48*</td>
<td>4.78±0.92†</td>
</tr>
</tbody>
</table>

LVH indicates left ventricular hypertrophy; LF, low frequency; HF, high frequency; SBP, systolic blood pressure; DBP, diastolic blood pressure; and BRS<sub>LF</sub> baroreceptor sensitivity by power spectrum analysis. After passive tilting, hypertensive subjects with LVH do not show a sympathetic activation on blood pressure.

*P<.05, †P<.01, ‡P<.001 (paired t test).
The different characteristics of the vessels in hypertensive and control subjects could also play a role in maintaining the sympathetic response. Vascular remodeling in hypertension can increase the effect of sympathetic stimulation, so even a reduced sympathetic activation can be amplified (low-frequency component blood pressure), but further studies are needed to verify this hypothesis. Unlike in the blood pressure signal, we could not see a sympathetic activation at the skin arterioles in the hypertensive subjects (with or without LVH), while it was present in the control group. There are clear indications that skin flow takes part in the cardiovascular adjustments to postural change. It is possible that the high wall-radius ratio present in skin a-v anastomoses together with vascular hypertrophy has decreased the sympathetic discharge needed to increase the vascular resistance, so that this was no more detectable.

Respiratory-related vascular oscillations increased significantly in hypertensive subjects compared with control subjects. These oscillations are commonly thought to be due to the mechanical effect of respiration on cardiac output through an increase in venous return, which is augmented in the upright position. Therefore, in the presence of impaired autonomic control of the cardiac output, this mechanical effect could become more evident at the vascular level.

**Study Limitations**

The interpretation of the components of heart rate and blood pressure variability is complex and not fully explained. As we have outlined above, there is increasing evidence that the low-frequency variability seen on power spectrum analysis could be largely generated by the activity of the arterial baroreceptors. In addition, the blood pressure variability may reflect not only the autonomic modulation but also the vascular reactivity to autonomic stimulation. Further studies are needed to clarify this point. Moreover, static influences on blood pressure and heart rate such as those exerted by humoral catecholamines could not be detected by power spectrum analysis.

In conclusion, power spectrum analysis did not show evidence of increased sympathetic activity in the hypertensive subjects studied. After tilting, the hypertensive subjects showed a differing autonomic control at the heart and periphery. The decreased baroreceptor control of heart rate in the hypertensive subjects might have been responsible for the reduced autonomic changes at the heart. Cardiopulmonary reflex deactivation and vascular hypertrophy are among possible explanations for the preserved sympathetic activation at the periphery.

**References**


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