Autonomic modulation of heart rate and blood pressure in hypertensive subjects with symptoms of anxiety

Gianfranco PICCIRILLO, Santagada ELVIRA, Emanuela VIOLA, Carmela BUCCA, Michele DURANTE, Paolo RAGANATO and Vincenzo MARIGLIANO
I Clinica Medica, Policlinico Umberto I, 00161 Rome, Italy

ABSTRACT

1. The influence of anxiety symptoms on autonomic nervous system cardiovascular control has never been studied in hypertensive subjects. This study was designed to verify the presence of sympathetic hyperactivity in hypertension associated with anxiety symptoms.

2. Neuroautonomic cardiovascular control was evaluated using short-time power spectral analysis of RR and arterial pressure variability at baseline and after the head-up tilt test. The two spectral components principally influenced by the autonomic nervous system are the low-frequency (LF) component, mainly though not exclusively due to sympathetic modulation, and the high-frequency (HF) component, due to parasympathetic activity. The ratio of LF to HF powers (LF:HF) provides an index of the sympathovagal sinus balance.

3. We studied 33 hypertensive subjects (mean age 47 ± 1 years; M:F = 19:14) and 37 normotensive control subjects (mean age: 47 ± 2 years; M:F = 20:17) divided into four subgroups: hypertensive subjects who scored 2 or more on a 5-item anxiety symptom scale, hypertensive subjects who scored 0, normotensive controls who scored 2 or more and normotensive controls who scored 0. LF:HF and LF during rest were significantly higher (P < 0.05) in hypertensive and normotensive groups with an anxiety score of 2 or more compared with the two groups who scored 0. HF of systolic blood pressure was significantly lower in the hypertensive group who scored 2 or more than in the hypertensive group who scored 0 (P < 0.05). Tilt in both hypertensive groups reporting anxiety symptoms left the indexes of sympathetic modulation unchanged. Tilt in hypertensive subjects reporting anxiety symptoms also induced a significant fall in arterial pressure (P < 0.05). The mean left ventricular mass index was significantly higher in the hypertensive subjects who had anxiety scores of 2 or more than in those scoring 0 (144.7 ± 3.0 versus 133.4 ± 2.31, P < 0.05).

4. In conclusion, normotensive and hypertensive subjects reporting anxiety symptoms showed increased sympathetic modulation of heart rate at rest. Higher anxiety scores seem to be associated with the development of left ventricular hypertrophy.

INTRODUCTION

Anxiety [1–5], hypertension, especially in the early stages [6–8], and left ventricular hypertrophy [7,9,10] are clinical conditions associated with sympathetic hyperactivity. They are also risk factors for sudden death [11,12]. The influence of acute mental stress on cardiovascular reactivity in patients with borderline hypertension has...
been widely studied [13–18], but data are lacking on the influence of anxiety symptoms on cardiovascular neuro-autonomic control in arterial hypertension.

Our aim in this preliminary study was to assess autonomic nervous system function by power spectral analysis of RR and arterial pressure variability in hypertensive subjects with and without self-reported symptoms of anxiety.

To assess levels of phobic anxiety we chose the 5-item self-reported anxiety symptom scale constructed by Kawachi et al. [11,12]. Two studies assessing anxiety with this scale found that subjects reporting two or more anxiety symptoms had a higher risk of sudden cardiac death independent of all other coronary risk factors [11,12]. Because it is simple to administer and provides prognostic indications, this scale is useful for rapid assessment of a patient’s psychological profile.

We assessed autonomic nervous system activity at baseline (rest) and after sympathetic stress induced by the head-up tilt test (tilt) [19–22]. Because spectral analysis of RR and blood pressure variability is a non-invasive procedure that does not expose subjects to mental stress, it is ideal for studying neuroautonomic control over the cardiovascular system. For the same reason we induced stress by the tilt test, thus provoking an increase in sympathetic activity without stimulating the subjects psychologically.

Power spectral analysis distinguishes three main components (Figure 1); two primarily reflect autonomic nervous system modulation. The first, high-frequency (HF), component centres around 0.26 Hz and provides an index of the influence of respiratory activity on heart rate and arterial pressures [19–22], whereas HF of RR variability is an index of parasympathetic sinus modulation, and HF of pressure oscillations seems to be influenced more by ventilatory mechanics [23–25]. The second or low-frequency (LF) component centres around 0.1 Hz and is primarily influenced by sympathetic activity. The ratio of LF to HF powers (LF : HF) of heart rate variability provides an index of cardiac sympathovagal balance [19–22]. Specifically, LF is considered to result from a slow response of the sympathetic system to baroreceptor stimuli [26,27]. Although opinions may differ, reasonable evidence justifies considering LF, especially normalized LF, as an index of relative sympathetic modulation [28].
METHODS

Study subjects

For this study from our outpatients clinic we selected normotensive apparently healthy subjects and hypertensive subjects without cardiovascular complications. Hypertension was defined as a diastolic blood pressure (DBP) equal to or greater than 90 mmHg. On recruitment, hypertensive subjects were unaware of their condition; hence none of them had received pharmacological treatment, and none had a history of other disorders or cardiovascular disease. Their clinical attendance depended solely on a family history of hypertension or cardiovascular disease. None of the subjects underwent restricted sodium intake.

Before entering the study, all subjects underwent a complete history, physical examination, routine laboratory investigations, electrocardiography, a 2-dimensional echo Doppler study of the vessels and echocardiography. Subjects were excluded if they had a history or demonstrable evidence of cardiovascular, respiratory, renal (presence of proteinuria and creatinine monosodium), hepatic or gastrointestinal diseases. Other exclusion criteria included DBP > 114 mmHg; body mass index > 26 kg/m²; age > 65 years; smoking (> 5 cigarettes/day); diabetes (presence of glycosuria or fasting glycaemia > 120 mg/dl or 110 mg at 2 h after glucose loading); cholesterol plasma level > 220 mg/dl; arrhythmias or conduction abnormalities, ultrasound evidence of significant carotid stenosis or echocardiographic evidence of wall motion abnormalities of the left ventricle or valvular disease. The only electrocardiographic abnormalities allowed were signs of left ventricular hypertrophy. During the echocardiographic examination data were obtained to determine the left ventricular mass index (LVMI). All subjects underwent Bruce protocol stress-testing designed to eliminate from the study subjects with silent myocardial ischaemia. Tests were considered valid only if the subject reached at least 90% of the maximal age-corrected frequency. Two-dimensional and M-mode echocardiograms were recorded from standard parasternal and apical windows using a commercially available ultrasound unit (Kontron Instruments). Each variable was measured according to the convention of the American Society of Echocardiography [29]. Echocardiographic left ventricular mass was then calculated from the Penn convention, according to the method described by Devereux and Reichek [30]. The LVMI was calculated for each subject by dividing left ventricular mass by body surface area. On the same day, before echocardiography, a blood sample was drawn for measurement of plasma sodium.

All subjects had sedentary occupations. No subject had taken part in a programme of intense physical training before the study. None had received medication for at least 2 months beforehand.

All participants gave their written, informed consent to the study procedures, which had the approval of the hospital ethics committee.

Study protocols

All selected subjects underwent an electrocardiographic recording of heart rate (TElemetria M ortara) and beat-to-beat blood pressure (Finapres, Ohmeda) at baseline (rest) and after sympathetic stress (tilt). These recordings were used for off-line spectral analysis of RR and blood pressure variability.

Heart and blood pressure recordings for spectral analysis in all subjects took place according to the following protocol: at 08:30 h, after blood pressure measurement, the subject rested supine in a quiet, comfortable environment (24 °C) for at least 30 min before undergoing a 10-min electrocardiographic, beat-to-beat blood pressure and respiratory signal recording (rest). Respiratory activity was measured with a strain gauge. Afterwards subjects underwent head-upright tilt testing, a passive orthostatic manoeuvre achieved with a motorized tilt table. After 15 min upright (90 °) the subject underwent a second 10-min electrocardiographic, beat-to-beat blood pressure and respiratory recording (tilt). Transit from 0 ° to 90 ° took about 15 s. If hypotension [a systolic blood pressure (SBP) fall of 20 mmHg] or symptoms indicating the onset of vasovagal syncope, nausea or heartburn developed during tilt, testing was stopped and the subject was excluded from the study. To minimize the possible influence of emotional effects on heart rate and blood pressure recordings we avoided drawing blood during this procedure. The values of 24-h urinary sodium excretion reported are those obtained 24 h before the autonomic examination. Plasma and urinary sodium levels were measured by standard laboratory methods.

Arterial pressures were measured by traditional mercury sphygmomanometry at rest and after tilt. Systolic pressures were recorded at Korotkoff phase I; diastolic pressures at Korotkoff phase V. The first measurement was discarded. Three further measurements were obtained with a 3-min interval between each and the mean of three readings was used.

In the second phase of study, the self-rated scale of Kawachi et al. [11] which elicits common symptoms of phobic anxiety was administered to all participants. The scale comprised five items: ‘Do strange people or places make you afraid?’; ‘Are you considered a nervous person?’; ‘Are you constantly keyed up and jumpy?’; ‘Do you often become suddenly scared for no good reason?’; and ‘Do you often break out in a cold sweat?’.

A negative response to any of the questions scored 0; a positive response scored 1. The anxiety symptom scale therefore ranged from 0 to 5 (no anxiety to severe anxiety). According to the score obtained, we subdivided...
the subjects into two groups: subjects with scores of 0 and those with 2 or more [11]. Although the items included in this scale were taken from the Cornell Medical Index they are also found in other indexes including the Brief Symptom Inventory, the State-Trait Anxiety Inventory and the Crown-Crispin Index [11]. To validate the results of the Kawachi scale in hypertensive subjects we also administered the Anxiety Scale Questionnaire (ASQ) [31] and the State-Trait Anxiety Inventory (STAI) [32].

Off-line power spectral analysis and data

Stationary, 10-min segments of electrocardiographic, blood pressure and respiratory recordings were analysed with an autoregressive algorithm [33]. The power spectral densities of the recordings were computed by an autoregressive algorithm developed in our laboratory and described in detail elsewhere [1,6,7]. We then considered the total power (TP) of R–R intervals (RR), SBP and DBP and the total spectral density of these variables. For RR, SBP and DBP we calculated the following spectral components: an HF component (0.15–0.40 Hz Eq), an LF component (0.04–0.15 Hz Eq) and a VLF (very-low frequency) component (< 0.04 Hz Eq) [19]. For LF and HF in addition to power we also measured the central frequency. Although the validity of VLF power in shorttime recordings remains controversial [19] some evidence shows that a recording lasting a maximum of 5 min yields VLF power values that are significantly related to those from a 24-h recording and hence sufficient for estimating this spectral component [19,34]. All of our recordings lasted at least 10 min.

Spectra of the respiratory trace were analysed on the signal sampled once every cardiac cycle. These spectra were used as a reference to identify heart rate oscillation caused by respiratory sinus arrhythmia. The RR interval and respiratory signal recordings were also used for cross-spectral analysis. To avoid respiratory events that might influence LF power, we checked that subjects breathed at a rate faster than 9 breaths per minute (0.15 Hz) [7].

The coherence function of the various spectral components and of the respiratory signal was then estimated. Coherence expresses the fraction of power at a given frequency in either time series that can be explained as a linear transformation of the other and is thus an index of linear association between the two signals.

The resulting spectral data were transformed into the natural logarithm of the variable (ln) [19,26,34], and LF and HF power into normalized units (NU) [19,20,35]. Transforming data into NU also helped to accentuate sympathovagal balance [6,19]. NU were calculated as follows: LF NU = LF power/TP – VLF power × 100; HF NU = HF power/TP – VLF power × 100. The last calculation was the ratio of LF and HF powers of heart rate (LF:HF) [19]. Because these data had a non-linear distribution they were also transformed into ln.

Statistical analysis

All data were collected by use of database 1-2-3 (Lotus Development Corporation) and evaluated with two software packages: Primit (McGraw-Hill, Italy) and SPSS-PC + (SPSS-PC + Inc, Chicago, IL, U.S.A.). All results are expressed as means ± S.E. Student’s unpaired t-test was used to compare the general characteristics (including age, body mass index, RR intervals, SBP, DBP, urinal and sodium plasma levels, anxiety symptoms and LVMI) in two groups: hypertensive and normotensive subjects.

We then divided the subjects into subgroups according to their total phobic anxiety symptom scale scores. This resulted in four groups: hypertensive subjects with anxiety scores of 2 or more; hypertensive subjects who scored 0; normotensive subjects with anxiety scores of 2 or more and normotensive subjects who scored 0. One-way analysis of variance (ANOVA) and Bonferroni’s test were used to compare spectral data and other variables in the two hypertensive and normotensive groups.

Repeated-measures ANOVA was used to evaluate the differences between baseline and post-tilt values of arterial pressure, mean RR interval, blood pressure and spectral analysis.

The possible association between LVMI and other spectral and non-spectral variables was assessed by the stepwise multiple regression analysis. In this correlation we also included the data for subjects reporting only one anxiety symptom.

Spearman’s rank correlation coefficients were calculated to compare the scores obtained with the Kawachi, ASQ and STAI scales.

A P value of < 0.05 was considered to indicate statistical significance.

RESULTS

From among 354 outpatients, 70 subjects (39 men and 31 women) were selected for study. Ten subjects without a history of typical thoracic pain had significant ST-segment downsloping during exercise testing. Five of these had coronary artery stenosis (> 50%) and underwent coronary angioplasty. In 76 recruits the tilt test had to be stopped because presyncope symptoms accompanied by a fall in arterial blood pressure developed during testing. The remaining 198 recruits were excluded because they did not fulfill the selection criteria.

The anxiety questionnaire of Kawachi et al. [11,12] showed that 24 subjects [12 hypertensive (M:F, 8:4) and 12 normotensive (M:F, 7:5)] had no self-reported anxiety
Table 1  Clinical characteristics of study subjects

<table>
<thead>
<tr>
<th></th>
<th>Hypertensive subjects (n = 33)</th>
<th>Normotensive subjects (n = 37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M:F)</td>
<td>19:14</td>
<td>20:17</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.8 ± 1.52</td>
<td>47.16 ± 1.88</td>
<td>NS</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.52 ± 0.23</td>
<td>23.49 ± 0.37</td>
<td>NS</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>147.12 ± 2.2</td>
<td>117.30 ± 2.28</td>
<td>0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>94.55 ± 1.01</td>
<td>73.38 ± 1.44</td>
<td>0.001</td>
</tr>
<tr>
<td>Anxiety symptom score</td>
<td>1.76 ± 0.28</td>
<td>1.59 ± 0.22</td>
<td>NS</td>
</tr>
<tr>
<td>Plasma sodium (mmol/l)</td>
<td>140.09 ± 0.56</td>
<td>139.40 ± 0.59</td>
<td>NS</td>
</tr>
<tr>
<td>Sodium excretion (mmol/day)</td>
<td>171.83 ± 14.92</td>
<td>152.29 ± 6.07</td>
<td>NS</td>
</tr>
<tr>
<td>LVMI (g/m²)</td>
<td>139.42 ± 2.26</td>
<td>98.84 ± 1.16</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 2  Heart rate and blood pressure in study subjects

Results are given as means ± S.E. *P < 0.05: hypertensive subjects who scored 2 or more on the anxiety symptom scale versus hypertensive subjects who scored 0 (one-way ANOVA and Bonferroni test). ††P < 0.05: normotensive subjects who scored 2 or more on the anxiety symptom scale versus normotensive subjects who scored 0 (Bonferroni test). ‡‡P < 0.001: hypertensive subjects who scored 2 or more on the anxiety symptom scale versus normotensive subjects who scored 0 (Bonferroni test). 9.5 P < 0.001: hypertensive subjects who scored 0 on the anxiety symptom scale versus normotensive subjects who scored 0 (Bonferroni test). ††P < 0.05, ‡‡P < 0.001: rest versus tilt (repeated-measures ANOVA).

<table>
<thead>
<tr>
<th></th>
<th>Hypertensive subjects</th>
<th>Normotensive subjects</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety symptom score</td>
<td>2 or more</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>(n = 19; M:F = 10:9)</td>
<td></td>
<td>(n = 12; M:F = 8:4)</td>
<td></td>
</tr>
<tr>
<td>Rest RR interval (ms)</td>
<td>858.02 ± 28.05</td>
<td>877.61 ± 44.57</td>
<td></td>
</tr>
<tr>
<td>Tilt RR interval (ms)</td>
<td>796.42 ± 22.68‡</td>
<td>732.04 ± 36.21‡†‡</td>
<td></td>
</tr>
<tr>
<td>Rest SBP (mmHg)</td>
<td>147.37 ± 2.58##‡</td>
<td>145.83 ± 4.4759†</td>
<td></td>
</tr>
<tr>
<td>Tilt SBP (mmHg)</td>
<td>131.58 ± 6.71††</td>
<td>148.75 ± 5.4495†</td>
<td></td>
</tr>
<tr>
<td>Rest DBP (mmHg)</td>
<td>94.21 ± 1.39##‡</td>
<td>94.17 ± 1.0455‡</td>
<td></td>
</tr>
<tr>
<td>Tilt DBP (mmHg)</td>
<td>87.37 ± 3.30†††</td>
<td>103.75 ± 4.4055§‡‡</td>
<td></td>
</tr>
</tbody>
</table>

symptoms, 5 subjects [2 hypertensive (M:F, 0:2) and 3 normotensive (M:F, 2:1)] had 1 symptom, and 41 subjects [19 hypertensive (M:F, 10:9) and 22 normotensive (M:F, 11:11)] had 2 or more symptoms (mean scores 2.95 ± 0.22 in hypertensive and 2.55 ± 0.17 in normotensive subjects). The groups did not differ significantly in terms of age, sex or body mass index (Table 1).

Even though none of the subjects underwent a restricted sodium diet before the study their 24-h sodium excretion values did not differ significantly. Hence we assume that salt intake did not differ in the four groups analysed and therefore had no influence on their spectral data [7].

Hypertensive subjects had significantly higher baseline values of SBP, DBP and LVMI (Table 1). In all subjects heart rate increased significantly during tilt (Table 2). In hypertensive subjects reporting anxiety symptoms SBP and DBP fell significantly during tilt; whereas in normotensive subjects reporting anxiety symptoms both arterial pressures rose significantly (Table 2). DBP after tilt was significantly lower in the hypertensive subjects with anxiety symptoms scores of 2 or more than in those who scored 0.

The ASQ and STAI scores correlated significantly with the Kawachi test scores (ASQ 0.803, P < 0.001; STAI 0.799, P < 0.001). The groups who scored 2 or more had significantly higher ASQ scores than groups scoring 0 (8.7 ± 0.26 versus 4.75 ± 0.75, P < 0.001). A STAI scores of 7 or more indicate high anxiety levels. Subjects with anxiety symptoms scores of 2 or more also had significantly higher STAI scores than subjects scoring 0 (50.9 ± 1.9 versus 29.1 ± 1.3, P < 0.001).

Spectral data of RR variability

LF: HF and RR LF NU during rest were significantly higher in the hypertensive group who had anxiety scores of 2 or more than in the normotensive group who scored 0 (P < 0.05) (Table 3). RR HF expressed in NU and as absolute power (ln ms²) during rest was significantly

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lower in the hypertensive group who had anxiety symptoms scores of 2 or more than in the normotensive group who scored 0 (P < 0.05) (Table 3). LF:HF and RR LF NU during rest were significantly higher but RR HF was significantly lower in the normotensive group with anxiety scores of 2 or more than in those who scored 0 (P < 0.05) (Table 3). In both hypertensive groups and in the normotensive group reporting no anxiety symptoms tilt caused a significant decrease in RR HF. In hypertensive and normotensive groups reporting no anxiety symptoms tilt also significantly increased the LF:HF ratio (P < 0.05) and RR LF NU (P < 0.05) but decreased RR HF NU (Table 3).

No significant differences were found among the groups for RR TP or RR VLF during rest or after tilt. Coherence between HF and the respiratory frequency was optimal at rest (0.91) and after tilt (0.85).

Spectral data for SBP variability
In all groups except the hypertensive group reporting phobic anxiety symptoms tilt induced a significant increase in SBP LF, whereas in all groups it induced a significant increase in SBP HF (Table 4). Expressed in relative terms (NU) SBF LF increased significantly after tilt only in normotensive controls: from 62.9 ± 3.8 during rest to 79.3 ± 3.2 after tilt (P < 0.001) in those who had anxiety symptom scores of 2 or more, and from 67.6 ± 4.7 during rest to 85.7 ± 2.5 after tilt (P < 0.001) in those who scored 0. SBP HF NU increased significantly after tilt only in hypertensive subjects who had anxiety scores of 2 or more (from 18.0 ± 3.1 at rest to 29.7 ± 4.4 after tilt). No significant differences were found among groups for SBP TP or DBP VLF at rest or during tilt.

Spectral data of DBP variability
DBP LF and DBP HF increased significantly during tilt in normotensive groups. DBP LF expressed in relative terms (NU) increased significantly only in the group reporting no anxiety symptoms: from 71.4 ± 4.3 at rest to 91.2 ± 1.4 during tilt (P < 0.001). DBP HF NU decreased significantly in both normotensive groups: from 14.6 ± 2.4 at rest to 7.9 ± 0.9 after tilt (P < 0.05) in those who had anxiety symptoms scores of 2 or more, and from 18.1 ± 2.6 at rest to 9.1 ± 1.3 (P < 0.05) in those who scored 0. These changes were not seen in the hypertensive groups. No significant differences were found for DBP TP or DBP VLF among groups.

Left ventricular mass index
The mean LVMI was significantly higher in hypertensive subjects who had anxiety symptoms scores of 2 or more...
Table 4  Spectral data for SBP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypertensive subjects</th>
<th>Normotensive subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 or more</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>(n = 19)</td>
<td>(n = 12)</td>
</tr>
<tr>
<td>Rest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP LF (ln mmHg²)</td>
<td>1.35 ± 0.22</td>
<td>1.59 ± 0.15</td>
</tr>
<tr>
<td>SBP LF CF (Hz)</td>
<td>0.08 ± 0.00</td>
<td>0.07 ± 0.00</td>
</tr>
<tr>
<td>SBP HF (ln mmHg²)</td>
<td>−0.26 ± 0.12</td>
<td>0.33 ± 0.20</td>
</tr>
<tr>
<td>SBP HF CF (Hz)</td>
<td>0.29 ± 0.01</td>
<td>0.31 ± 0.03</td>
</tr>
<tr>
<td>Tilt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP LF (ln mmHg²)</td>
<td>1.90 ± 0.20</td>
<td>2.46 ± 0.29</td>
</tr>
<tr>
<td>SBP LF CF (Hz)</td>
<td>0.08 ± 0.01</td>
<td>0.08 ± 0.01</td>
</tr>
<tr>
<td>SBP HF (ln mmHg²)</td>
<td>0.87 ± 0.19</td>
<td>1.37 ± 0.33</td>
</tr>
<tr>
<td>SBP HF CF (Hz)</td>
<td>0.28 ± 0.01</td>
<td>0.33 ± 0.03</td>
</tr>
</tbody>
</table>

Table 5  Multiple regression for LVMI in hypertensive subject with and without self-reported anxiety symptoms

<table>
<thead>
<tr>
<th>Partial regression coefficient</th>
<th>Standard error</th>
<th>Standardized regression coefficient</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety symptom scores</td>
<td>4.89</td>
<td>0.69</td>
<td>0.60</td>
<td>7.00</td>
</tr>
<tr>
<td>LF:HF tilt (ln)</td>
<td>−13.14</td>
<td>3.35</td>
<td>−0.93</td>
<td>−3.91</td>
</tr>
<tr>
<td>SBP LF rest (mU)</td>
<td>−0.16</td>
<td>0.05</td>
<td>−0.26</td>
<td>−2.82</td>
</tr>
<tr>
<td>Intercept</td>
<td>193.01</td>
<td>11.76</td>
<td>16.40</td>
<td>16.40</td>
</tr>
</tbody>
</table>

compared with those who scored 0 (144.7 ± 3.0 versus 133.4 ± 2.31, P < 0.05) and compared with both normotensive groups (104.7 ± 1.7, P < 0.001; 95.3 ± 1.2, P < 0.001). Multiple regression in the hypertensive subjects detected a significant association between the following variables (Table 5): self-reported anxiety symptoms (B: 4.89, P < 0.0001), LF:HF after tilt (B: −13.14, P < 0.0001), SBP LF and SBP NU during rest (B: −0.16, P < 0.01).

DISCUSSION

Hypertensive and normotensive subjects with high anxiety symptom scores had a higher LF:HF and higher RR NU during rest than subjects who scored 0 (Table 3). This result indicates that these two groups have more predominant baseline sympathetic sinus modulation than normotensive subjects reporting no anxiety symptoms. Because normotensive and hypertensive subjects reporting anxiety symptoms had similar spectral indexes of sympathetic modulation their manifest sympathetic sinus hyperactivity could depend upon their anxiety state. The differences in these spectral indexes in hypertensive subjects reporting anxiety symptoms and those who did not probably failed to reach statistical significance because of the small study sample.

Previous studies using spectral methods to assess autonomic sinus control in arterial hypertension have yielded discordant results [6,7,26,36–41], probably owing to the non-homogeneous enrolment criteria and experimental conditions. Particularly in the normotensive controls studied, sinus sympathetic activity was strictly influenced by the presence of anxiety. Hence we speculate that the contradictory results from studies of sinus autonomic modulation in arterial hypertension stem also from the failure to select subjects with similar arterial pressures. Our present results imply that studies investigating autonomic sinus control must take into account all the following variables: sodium intake [7], age [6] and the presence of anxiety.

Apart from its theoretical value, the concept of sympathetic sinus-node hyperactivity offers promising therapeutic developments. Our findings suggest that individuals in the early stages of hypertension who manifest more conspicuous sympathetic sinus activity are...
those reporting one or more anxiety symptoms. These subjects should in theory benefit more than others from β-blocking drugs. This option also receives support from the higher risk of sudden death in subjects reporting two or more symptoms of anxiety [11,12].

Anxiety in our subjects did not seem to influence sympathetic modulation of resting SBP. In normotensive and hypertensive subjects who scored 0 on the anxiety symptoms scale tilt induced a physiological increase in the spectral indices of sympathetic modulation (RR LF NU and LF:HF), but it decreased parasympathetic measures obtained from RR interval variability (RR HF, RR and HF NU) (Table 3) [1,6,19,22,42]. In all subjects this spectral pattern was accompanied by a concomitant increase in heart rate. When tilt induced an increase in heart rate, sympathetic activity increased while parasympathetic activity decreased (vagal withdrawal) (Table 2) [22,43,44]. Using relative terms (NU) rather than absolute numbers (ms²) emphasizes this behaviour because normalization neutralizes the effect of the low total power of spectral variability that often accompanies the increased heart rate [19]. Our results therefore indicate that because hypertensive and normotensive individuals reporting anxiety symptoms already have enhanced sympathetic sinus node activity at baseline they increase their heart rate during tilt primarily by vagal withdrawal. A diminished ability to increase sympathetic sinus node modulation during postural stress is typical of physiological conditions associated with enhanced sympathetic or elevated blood catecholamine levels or both, for example hypertension [6,7,36], heart failure [45], obesity [46] and aging [6]. In reducing the ability to augment RR LF we surmise the intervention of two phenomena. The first is the failure of the sinus node – already over-saturated with sympathetic impulses – to maintain a rhythmic modulation of heart rate [47,48]. The second is the reduced β-receptor responsiveness induced by the excessive catecholamine levels [49,50].

The real difference between the hypertensive and normotensive groups with self-reported symptoms of phobic anxiety lies in their arterial pressure responses to tilt. In the normotensive subjects reporting anxiety symptoms arterial pressures rose significantly, whereas in the hypertensive subjects reporting anxiety symptoms they fell (Table 2). We attribute this phenomenon to the scarce ability of the hypertensive subjects with anxiety to increase sympathetic pressure modulation. This group alone failed to increment SBP LF significantly during tilt (Table 4). Our finding receives partial confirmation from a recently published study reporting an inverse correlation between increased LF during mental stress and scores obtained in a test assessing anger [51].

In nearly all groups, although tilt induced significant changes in SBF LF and HF, it predominantly changed LF. Conversely, the hypertensive group reporting anxiety symptoms exhibited an increase in SBP HF measured in absolute values (ln ms²) and in relative values (NU) that the significant increase in LF left unopposed. We conclude that hypertensive individuals who are anxious fail to adapt their arterial pressures to orthostatic stress because they cannot augment sympathetic vascular modulation. Because SBP HF is influenced more by ventilatory mechanics and less by the autonomic nervous system [23–25] the SBP LF increase probably also reflects these subjects' loss of autonomic control over arterial pressure.

Another finding closely related to anxiety was the larger left ventricular mass (Table 5). The subgroup of hypertensive subjects with high anxiety symptom scores had a significantly larger mean left ventricular mass than the hypertensive subjects who scored 0. The significant association between LVMI and anxiety symptom scores in our hypertensive subjects could also indicate that at least in the early stages of hypertrophy these two variables have a linear relationship (Table 5). Hence the presence of a larger left ventricular mass in the anxious subjects suggests that even though the psychic asset may not per se stimulate left ventricular hypertrophy it does contribute to its development. In addition, multiple regression analysis detected an inverse correlation between LVMI sympathetic sinus (LF:HF) and pressure modulation (SBF LF NU) during orthostatic stress. In other words, the higher the degree of hypertrophy the greater is the failure of sympathetic activation during sympathetic stress [26]. This observation could be explained by two known phenomena in subjects with myocardial hypertrophy. First is the association of increased left ventricular mass with β-receptor dysfunction [10] and second, the hypertrophy reduces sympathetic responses to deactivation of cardiopulmonary receptors [52,53].

A final interesting point is that two consecutive epidemiological studies have now reported an association between anxiety and sudden cardiac death in persons scoring 2 or more on the Kawachi anxiety symptom scale [11,12]. Whether anxiety might further increase the risk of sudden cardiac death in hypertensive subjects remains a conjectural yet attractive notion that merits future assessment in a large cohort.

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evidence of decreased cardiac sympathetic responsiveness.

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