Cross-spectral analysis of cardiovascular parameters whilst supine may identify subjects with poor orthostatic tolerance

Giosuè GULLI, Victoria L. COOPER, Victoria CLAYDON and Roger HAINSWORTH
Institute for Cardiovascular Research, University of Leeds, Leeds LS2 9JT, U.K.

ABSTRACT

An easy and low-cost method for identification of subjects prone to orthostatic vasovagal syncope would be of clinical benefit. An orthostatic test with 60° head-up tilt and progressive lower-body negative pressure was performed on 79 patients with histories of unexplained syncope and 26 control subjects. The test was stopped at the onset of presyncope and time to presyncope was taken as a measure of orthostatic tolerance. Spectral and cross-spectral analysis was performed on the supine time series of the R–R interval (ECG) and systolic pressure (Finapres) recorded before the beginning of the test. According to reference values, 38 patients and 11 controls were classified as having poor orthostatic tolerance (PPT and CPT respectively), whereas 41 patients and 15 controls displayed normal orthostatic tolerance (PNT and CNT respectively). The central frequency of the low-frequency (LF ≈ 0.1 Hz.) oscillations in PNT and CNT was significantly higher than that in PPT and CPT. In addition, it was significantly linearly correlated with the time of presyncope. Using our test of orthostatic tolerance as a comparison, the LF central frequency allows the classification of subjects with poor or normal tolerance with 80% sensitivity and 82% specificity. These results suggest that the LF central frequency in the supine position may provide a useful index in the diagnosis of orthostatic intolerance.

INTRODUCTION

Syncope is a common clinical problem, which has severe medical, social and economic impacts. The Framingham study has indicated that syncope affects up to 3.5% of the general population and accounts for 3–5% of Emergency Department visits and 1–6% of hospital admissions in the U.S.A. [1–3]. Syncope due to orthostatic intolerance accounts for the majority of episodes of loss of consciousness that do not involve a cardiological, neurological or metabolic disorder. The most commonly used test for the identification of fainting-prone subjects is head-up tilting (HUT), but this test alone lacks sensitivity [4]. The sensitivity of HUT can be improved by adding infusion of isoprenaline or nitrate derivatives [5]. Unfortunately, the improvement in sensitivity is obtained at the expense of a loss in specificity of the test.

In our laboratory, we perform an entirely non-invasive test of orthostatic tolerance, which combines HUT with lower-body negative pressure (LBNP) [6]. This technique is successful in discriminating subjects with poor and normal orthostatic tolerance in a sensitive and repeatable manner [7]. However, the prompt diagnosis of vasovagal syncope still remains an important clinical problem. Patients undergo an array of expensive and
time-consuming tests and may even require days of hospitalization [8]. It would therefore be of considerable benefit if a diagnosis could be made by a simple, quick and cheap test. Recently, we observed [9] the unexpected result that patients with poor orthostatic tolerance, confirmed by the combined HUT and LBNP test, had a slower rhythm of low-frequency (LF) variability (normally approx. 0.1 Hz) of cardiovascular parameters whilst supine compared with patients with normal orthostatic tolerance.

The present study was undertaken to test the hypothesis that subjects with poor orthostatic tolerance, independent from their clinical status, have slower LF rhythm. Therefore we studied a further series of patients with histories of vasovagal syncope and compared the results obtained with those from a group of age-matched control subjects. The principal aim of our study was to determine in detail whether individuals prone to posturally related syncope could reliably be identified by simple cross-spectral analysis of beat-to-beat blood pressure and R–R interval (RR) variability recorded whilst supine. Successful discrimination of patients with poor tolerance to orthostatic stress would have considerable clinical benefit as the test is simple, does not require complex or expensive equipment and can be undertaken without medical supervision.

### METHODS

#### Patients

We studied 79 patients (29 male) aged 18–72 years (mean ± S.E.M., 37 ± 1.4 years) who underwent an orthostatic stress test, because of histories suggestive of posturally related syncope. All patients had undergone 12-lead ECG and Holter monitoring previously and some had also undergone other cardiovascular and neurological tests where clinically appropriate. Results of all tests were normal. No patient included in the study was receiving any medication with cardiovascular effects. The study was approved by the Research Ethics Committee of the Leeds Teaching Hospitals NHS Trust. All subjects gave their informed consent and all procedures carried out according to the Declaration of Helsinki.

#### Controls

We studied 26 healthy volunteers (16 male) aged 22–60 years (mean ± S.E.M., 35 ± 2.3 years) with no history of posturally related syncope. They did not display any clinical signs of cardiovascular, neurological or metabolic disorders and were not taking any medication.

The studies were performed in the mornings, in a temperature-controlled (22–24 °C) laboratory. Subjects were instructed to have only a light breakfast with no caffeine.

#### Combined HUT table and LBNP test

The combined HUT table and LBNP test has been described previously [6]. Briefly, subjects were positioned on the tilt table with an adjustable footboard positioned so that the iliac crest was aligned with the pivot of the table. A polypropylene cover was placed over the tilt table to make an airtight seal around the subject when a wooden board lined with neoprene foam was placed at the level of the iliac crest. The LBNP chamber was connected to a variable vacuum source, which allowed for the application of subatmospheric pressures.

The protocol was identical with that described previously [7] and included the following consecutive steps: 20 min of supine rest, 20 min of HUT at 60 ° alone (phase 1), then, while still tilted, 10 min at −20 mmHg LBNP (phase 2) and 10 min at −40 mmHg LBNP (phase 3). The test was stopped if presyncope occurred, which was defined as a drop in systolic pressure (SP) to below 80 mmHg and/or symptoms of impending syncope. The time from the start of HUT until presyncope was taken as the measure of orthostatic tolerance. Repeated measurements demonstrated a good repeatability of this test in terms of the time to presyncope (better than ±2 min). We divided subjects into those with normal or poor orthostatic tolerance on the basis of age and gender reference values [6,7]. These values indicate the time and stage of the orthostatic stress test at which presyncope occurs in 20% of asymptomatic control subjects.

#### Data analysis

We recorded the ECG (lead II) with a standard apparatus (model 78325C; Hewlett Packard, Boeblingen, Germany) and blood pressure with a photo-plethysmographic finger device (Finapres, Ohmeda, WI, U.S.A.) fitted to the right middle finger. Signals were continuously fed to a data-acquisition system (WinDAQ, sampling frequency 1000 Hz; Dataq Instruments, Akron, OH, U.S.A.) and stored for analysis later. The Finapres readings were calibrated every 2 min by comparison with an automatic sphygmomanometer (model 78325C; Hewlett Packard) placed on the left arm.

We performed off-line beat-to-beat analysis of the stored signals by extracting the time series of successive values of RR, SP, diastolic pressure (DP) and mean arterial pressure (MP) during the supine period. We corrected for ectopic beats by substituting their values by linear interpolation of adjacent beats. Almost all the supine time series were stable with no linear trends and, thus, did not require filtering operations to be optimally analysable. We fitted to each time series an autoregressive monovariate model [10] and automatically quantified the mean central frequency and the powers associated with each oscillatory component by computation of the residuals [11]. Two...
main oscillatory components were generally detected: one with the mean central frequency in the LF range (approx. 0.1 Hz), and one in the high-frequency (HF) range (related to the respiratory rate). We expressed the powers of the LF and HF oscillatory components of the RR variability in absolute and normalized units [12]. We also performed cross-spectral analysis of RR and SP, by a bivariate autoregressive model. This technique quantifies the frequency-related squared coherence, phase shift and transfer function gain (TFG) between two variables at a given frequency. Since this method provides a smooth estimate of the true cross-spectra, discrete values of phase shift and TFG between RR and SP were taken at the frequency corresponding to the highest coherence value, where the estimate error is minimal [13]. The central frequency of an oscillatory component estimated by cross-spectral analysis is defined by the discrete value of frequency in the x-axis corresponding to the highest coherence value.

We only accepted cross-spectral results when coherence values were above 0.5 (range 0–1), which was considered to indicate a statistically significant linear correlation between the two signals at all frequencies. A negative-phase shift indicates that changes in SP precede changes in RR. The TFG in the LF region was taken as an estimate of baroreflex sensitivity [14].

Statistical analysis
Statistical differences between groups were assessed using a one-way ANOVA. When appropriate, post-hoc comparisons between groups were made using unpaired Student's t tests. $P < 0.05$ was considered significant. Linear regression analysis was performed to evaluate the linear relationship between different parameters. $P < 0.05$ was considered significant. Effects and interactions of gender and age on the means of various groupings of single dependent variables were tested using the General Linear Model procedure. Test performance for the discrimination of subjects with normal or poor orthostatic tolerance on the basis of their LF central frequency was tested with the receiver operator characteristic (ROC) curve [15]. For all frequency cut-off values, we assessed specificity and sensitivity in the discrimination of subjects classified as having poor or normal tolerance by the orthostatic stress test. All values are reported as means ± S.E.M.

RESULTS
Presyncope was induced at some time during the procedure in 73 (92%) of the patients studied. On the basis of their orthostatic tolerance expressed as time to presyncope, the patients were divided into two groups. Patients ($n = 41$) with time to presyncope that was higher than that predicted for age- and sex-matched controls were assigned to the normal orthostatic tolerance (PNT) group. Of these patients, six tolerated the entire procedure. Patients ($n = 38$) with time to presyncope lower than that predicted were assigned to the poor orthostatic tolerance (PPT) group. Of the controls, 15 had a time to presyncope that was the same or better than predicted, and three of them tolerated the entire procedure and even a further level of LBNP. They were assigned to the control normal orthostatic tolerance (CNT) group. The remaining 11 control subjects had a time to presyncope earlier than predicted and were assigned to the control poor orthostatic tolerance (CPT) group. There were no significant age differences between the two patient groups or the control groups: PPT, 38 ± 2 years, PNT, 36 ± 2 years; CPT, 36 ± 4 years; and CNT, 34 ± 3 years. The gender ratio of males to females was 12:26 in PPT, 17:24 in PNT, 7:4 in CPT and 9:6 in CNT. There was a significant discrepancy in gender between controls and patients; however, gender did not influence the subgroup classification (normal compared with poor tolerance) or the differences in the time and frequency domain results between subjects with different orthostatic tolerance.

Time domain and spectral analysis results
Time domain and spectral analysis results are shown in Table 1. There were no significant differences in the mean RR between the four groups. Blood pressures were in the normal range in all groups; however, they tended to be higher in the controls than in patients.

There were no between-group significant differences in the absolute or in the normalized power of the HF or LF oscillations of RR. The only between-group difference was that PPT and CPT groups had smaller HF oscillations of SP in comparison with the PNT group. There were no significant differences in the mean and diastolic respiratory blood pressure oscillations (results not shown). We also found no significant differences in the LF oscillations of blood pressure.

Table 1 also shows the LF central frequency of RR and blood pressure variability obtained by monovariate spectral analysis of the single time series. Analysing the difference between subjects with different degrees of orthostatic tolerance, PPT and CPT groups had a tendency to have a lower LF central frequency than PNT and CNT groups. It should be noted that the mean LF central frequency value obtained from RR and that obtained from the blood pressure time series were not identical.

Cross-spectral analysis results
The central frequency in the LF range, identified by cross-spectral analysis whilst supine, showed differences between the groups (Table 2). PPT and CPT groups behaved similarly and had a mean central frequency of the LF oscillations around 0.09 Hz. PNT and CNT groups also behaved similarly, but they had a central frequency above 0.1 Hz.
Supine time domain and spectral analysis results in PPT, CPT, PNT and CNT groups

Supine cross-spectral analysis of cardiovascular parameters in PPT, CPT, PNT and CNT groups

These oscillations fell in the range generally classified as at a lower frequency (around 0.04). The frequency of these oscillations fell in the range generally classified as very-LF (‘VLF’) (Figure 1B). We did not find such a peak in any of the subjects with normal tolerance (PNT and CNT).

The CPT group constituted a smaller group and these subjects had more scattered results. In addition, two subjects from the CPT group reached presyncope at 29 min (borderline time to presyncope) and had cross-spectral characteristics typical of the normal tolerance subjects (LF central frequency above 0.1 Hz and no enlarged phase lag between SP and RR).

Figure 2(a) shows the distribution of the LF central frequency in the two patient and the two control groups.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>PPT</th>
<th>PNT</th>
<th>CPT</th>
<th>CNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (ms)</td>
<td>945.5 ± 19.3</td>
<td>929.9 ± 20.8</td>
<td>971.1 ± 44.3</td>
<td>945.4 ± 38.6</td>
</tr>
<tr>
<td>SP (mmHg)</td>
<td>130.9 ± 2.9*</td>
<td>137.9 ± 3.0</td>
<td>133.9 ± 4.4</td>
<td>144.6 ± 4.4</td>
</tr>
<tr>
<td>DP (mmHg)</td>
<td>62.2 ± 1.7*</td>
<td>65.5 ± 1.8*</td>
<td>67.7 ± 5.6</td>
<td>73.3 ± 3.0</td>
</tr>
<tr>
<td>MP (mmHg)</td>
<td>82.9 ± 1.9*</td>
<td>86.8 ± 2.1</td>
<td>87.1 ± 5.6</td>
<td>92.5 ± 3.1</td>
</tr>
<tr>
<td>LF RR (ms²)</td>
<td>924.0 ± 224.5</td>
<td>1348.3 ± 279.8</td>
<td>1874.1 ± 674.5</td>
<td>1414.5 ± 262.1</td>
</tr>
<tr>
<td>LF RR frequency (Hz)</td>
<td>0.100 ± 0.003</td>
<td>0.106 ± 0.002</td>
<td>0.100 ± 0.005</td>
<td>0.106 ± 0.004</td>
</tr>
<tr>
<td>HF RR (ms²)</td>
<td>793.0 ± 217.5</td>
<td>1242.8 ± 337.7</td>
<td>942.3 ± 309.6</td>
<td>1056.4 ± 310.2</td>
</tr>
<tr>
<td>LF/HF</td>
<td>2.8 ± 0.5</td>
<td>3.4 ± 0.9</td>
<td>3.5 ± 0.6</td>
<td>2.8 ± 0.6</td>
</tr>
<tr>
<td>LF (ms)</td>
<td>47.4 ± 3.8</td>
<td>51.5 ± 2.8</td>
<td>55.4 ± 5.5</td>
<td>47.7 ± 4.9</td>
</tr>
<tr>
<td>HF (ms)</td>
<td>30.9 ± 3.4</td>
<td>32.1 ± 2.2</td>
<td>22.0 ± 4.1</td>
<td>25.4 ± 3.5</td>
</tr>
<tr>
<td>LF SP (mmHg²)</td>
<td>3.6 ± 0.5</td>
<td>3.8 ± 0.5</td>
<td>7.2 ± 2.2</td>
<td>4.7 ± 0.7</td>
</tr>
<tr>
<td>LF SP frequency (Hz)</td>
<td>0.093 ± 0.004</td>
<td>0.103 ± 0.003</td>
<td>0.092 ± 0.007</td>
<td>0.104 ± 0.004</td>
</tr>
<tr>
<td>LF DP (mmHg²)</td>
<td>1.7 ± 0.3</td>
<td>1.9 ± 0.2</td>
<td>3.0 ± 0.7</td>
<td>2.5 ± 0.6</td>
</tr>
<tr>
<td>LF DP frequency (Hz)</td>
<td>0.090 ± 0.003†</td>
<td>0.096 ± 0.003</td>
<td>0.083 ± 0.005*</td>
<td>0.101 ± 0.004</td>
</tr>
<tr>
<td>LF MP (mmHg²)</td>
<td>2.1 ± 0.3</td>
<td>2.5 ± 0.3</td>
<td>3.8 ± 1.0</td>
<td>3.1 ± 0.9</td>
</tr>
<tr>
<td>LF MP frequency (Hz)</td>
<td>0.090 ± 0.003†</td>
<td>0.098 ± 0.003</td>
<td>0.083 ± 0.004*</td>
<td>0.100 ± 0.005</td>
</tr>
<tr>
<td>HF SP (mmHg²)</td>
<td>1.9 ± 0.2†</td>
<td>2.8 ± 0.4</td>
<td>1.5 ± 0.4†</td>
<td>1.9 ± 0.3</td>
</tr>
</tbody>
</table>

The PPT group also had a wider phase-shift between SP and RR fluctuations in the LF range. In terms of time, the phase lag in the PPT group corresponds to more than 2 s, whereas in the PNT, CNT and CPT groups, it corresponds to approx. 1.6 s (Table 2).

We also found that the PPT group has a lower coherence in the LF band between RR and SP oscillations in comparison with the other groups (Figure 1A). In two subjects from the PPT group and one from the CPT group, we found, together with an oscillation peak around 0.1 Hz processed in the results, another peak of coherence at a lower frequency (around 0.04). The frequency of these oscillations fell in the range generally classified as

Table 1 Supine time domain and spectral analysis results in PPT, CPT, PNT and CNT groups

Values are means ± S.E.M. *P < 0.05 compared with the CNT group, and †P < 0.05 compared with the PNT group, as assessed using post-hoc Student’s t test comparisons.

<table>
<thead>
<tr>
<th>Subjects</th>
<th>PPT</th>
<th>PNT</th>
<th>CPT</th>
<th>CNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>LF range</td>
<td>PPT</td>
<td>PNT</td>
<td>CPT</td>
<td>CNT</td>
</tr>
<tr>
<td>Frequency (Hz)</td>
<td>0.089 ± 0.002†</td>
<td>0.103 ± 0.003</td>
<td>0.091 ± 0.004†</td>
<td>0.104 ± 0.003</td>
</tr>
<tr>
<td>Coherence</td>
<td>0.69 ± 0.02†</td>
<td>0.74 ± 0.02</td>
<td>0.75 ± 0.04</td>
<td>0.76 ± 0.04</td>
</tr>
<tr>
<td>TFG (ms · mmHg⁻¹)</td>
<td>12.9 ± 1.4</td>
<td>14.6 ± 1.4</td>
<td>13.3 ± 1.9</td>
<td>14.9 ± 2.1</td>
</tr>
<tr>
<td>Phase shift (degree)</td>
<td>−68.8 ± 5.0°†</td>
<td>−56.4 ± 3.5</td>
<td>−55.7 ± 7.2</td>
<td>−56.1 ± 6.7</td>
</tr>
<tr>
<td>Converted phase shift (s)</td>
<td>2.2 ± 0.2°†</td>
<td>1.6 ± 0.2</td>
<td>1.7 ± 0.2</td>
<td>1.5 ± 0.2</td>
</tr>
</tbody>
</table>

Table 2 Supine cross-spectral analysis of cardiovascular parameters in PPT, CPT, PNT and CNT groups

Values are means ± S.E.M. *P < 0.05 compared with the CNT group, and †P < 0.05 compared with the PNT group, as assessed using post-hoc Student’s t test comparisons.

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Figure 1  Supine time series and spectral analysis in two subjects from the PPT group with atypical LF oscillations
From top to bottom, supine time series, spectral analysis of RR and SP, phase (thin line), coherence (thick line) and TFG in two subjects from the PPT group with atypical LF oscillations. In (A), note the absence of coherence in the LF range. In (B), note the additional presence of oscillations and a coherence peak around 0.04 Hz.

Figure 2(b) shows the ROC curve for the frequency of LF oscillations obtained by autoregressive spectral and cross-spectral analysis in the diagnosis of poor orthostatic tolerance. The resulting ROC curve shows that the best test is that based on the central frequency obtained by cross-spectral analysis. Indeed, this test has a larger area under the ROC curve [15]. At 0.095 Hz, the analysis provides a sensitivity of 80% and a specificity of 82%. In more detail, only eight subjects from the PPT group and three from the CPT group (false negatives) had values of LF higher than 0.095 Hz. On the other hand, seven subjects from the PNT group and four from the CNT group (false positives) had values of LF central frequency lower than 0.095 Hz. There was also a significant relationship between orthostatic tolerance (time to presyncope) and LF central frequency, which showed a linear significant correlation. (r = 0.49, P < 0.001).

DISCUSSION

The investigation of syncopal episodes remains a major clinical problem, which requires a huge expenditure of professional time and financial resources. The prompt diagnosis of vasovagal syncope is crucial to prevent unnecessary diagnostic testing and to allow the appropriate management of the disease. The aim of the present study was to prove the efficacy of an index that allows the identification of individuals likely to have poor orthostatic tolerance and, thus, who are prone to posturally related syncope. We have reported previously [9] that patients with poor orthostatic tolerance, as determined by early presyncope during an orthostatic stress test, had a lower LF central frequency. In the present report, the study of both new patients undergoing the orthostatic tolerance test and control subjects has confirmed our previous finding [9]. It has also verified
our present hypothesis: independent of clinical status, subjects with poor orthostatic tolerance had significantly lower LF central frequency compared with subjects with normal tolerance.

The most evident results concerning the LF central frequency were obtained by cross-spectral analysis and were also confirmed by the autoregressive analysis of single time series; however, this latter method provided more variable results. Moreover, coherence tended to be lower in the LF band between RR and SP oscillations in the PPT group in comparison with the other groups of subjects. We believe that this difference might be greater if we consider that, as described in the Methods section, we only included in the ROC curve the results of those subjects who had a coherence higher than 0.5. With this criterion, we had to exclude the analysis of five subjects from the PPT group and only two subjects from the PNT group (one of whom had a borderline normal orthostatic tolerance). Therefore we believe that the low value of coherence in the LF band is a characteristic distinguishing poor tolerance subjects.

The ROC curve showed that the LF central frequency obtained by the cross-spectral analysis gives the highest sensitivity and specificity in the discrimination of subjects with different degrees of orthostatic tolerance. The performance of the test is high since, for instance, at 0.095 Hz, the sensitivity is 82 % and the specificity is 80 %. Taking 0.095 Hz as a cut-off value, only 15 patients (19 %) would have been incorrectly diagnosed when compared with the orthostatic stress test. The significant linear correlation between LF central frequency and time to presyncope gives further strength to our finding. It does suggest that the higher the LF central frequency, the better the orthostatic tolerance.

Differences between poor tolerance and normal tolerance subjects would probably have gone overlooked if different methods for spectral analysis had been used. Fast-Fourier-analysis-based methods indicate a range of frequencies of interest, rather than a discrete value. As reported in the present study, the values of autoregressive analysis obtained from one time series do not always match those obtained from another. Therefore, for this purpose, we believe that the LF central frequency, estimated by the cross-spectral analysis in the point of maximal coherence, is more appropriate. At that point, the two variables share the highest proportion of non-random variance and, if coherence is higher than 0.5, RR and SP changes are considered to be statistically linearly correlated.

Few studies have addressed the physiological meaning of the actual frequency of non-respiratory rhythms. A leftward shift of the LF peak was found in healthy humans during HUT or exercise [16,17], whereas a rightward shift was detected in post-exercise recovery and after vagal stimulation with very low doses of atropine [16,18]. It is difficult to relate these observations to our results, since neither the patients nor the controls with poor orthostatic tolerance showed any clear sign of enhanced sympathetic activation or decreased vagal activity. We believe that such a shift may not be attributed to unspecified changes in the so-called ‘sympatho-vagal balance’, but rather to disrupted mechanisms of LF oscillations. This is also suggested by other findings. Patients with poor tolerance had a larger phase lag between SP and RR oscillations, which in supine control condition is around −55 degrees [14,19]. They also had lower values of coherence in the LF range, or in some cases the absence of coherence or the concomitant presence of VLF oscillations (Figure 1).

It is noteworthy that a leftward shift of the LF central frequency has also been reported in various abnormal conditions, such as autonomic neuropathies [12], α-blockade in humans [14] and anaesthesia and haemorrhage in dogs [20,21]. These findings were
attributed to changes in the pattern of the central sympathetic drive, possibly associated with blunted baroreceptor inputs to the cardiovascular medullary centres [22].

It is now almost unanimously accepted, although with different interpretations, that the origin of LF variability involves a dominant role of baroreflex mechanisms [14,23,24]. We did not find any differences between subjects with different degrees of orthostatic tolerance in the cardiac baroreflex sensitivity estimated by the TFG in the LF range. We have confirmed recently [25] this result by means of other techniques (neck-collar technique). Nevertheless, it may be emphasized that in a control system not only the static property (i.e., gain) of the input–output relationship, but also the dynamic property (time delay response) determines its efficiency. In a feedback control system, the delay in the effector response may generate an unstable state of regulation [26]. In a recent paper, Ringwood and Malpas [27] explained the decrease in LF of different animal species as a consequence of different input–output conducting time. In their model, they proposed that the larger the delay in the response, the lower the LF central frequency. This is in agreement with the larger phase shift observed in our PPT subjects.

Finally, we propose that the decrease or even the absence of coherence in PPT subjects may also be explained by impairment in the baroreflex function, as suggested by studies involving pharmacological autonomic blockade and baroreceptor deafferentation [23,28].

One secondary finding of our present study deserves a brief comment. Poor tolerance subjects showed lower values of supine blood pressure than normal tolerance subjects. Furthermore, poor tolerance patients had lower HF power of SP oscillations in comparison with normal tolerance patients. This is not related to the absolute values of SP, since we did not find significant correlations between SP and respiratory SP oscillations. Also, poor tolerance controls tended to have a lower power of respiratory SP. It is well known that the respiratory oscillations of SP are due to the mechanical effects of the intrathoracic pressure changes. These changes affect primarily the stroke volume and have therefore more effects on the SP changes rather than the DP ones. Differences in the respiratory SP oscillations may be explained by differences in central blood volume, which may also contribute to the lower blood pressure values in poor tolerance patients. A decreased blood volume in subjects with poor orthostatic tolerance has been demonstrated in previous studies and it also explains the beneficial effects of high salt intake in some of these subjects [29].

We wish to emphasize that our results were obtained in patients with no known cardiovascular or neurological diseases and who were not taking any cardiovascular drug therapy. In addition, values of LF central frequency were estimated while supine, as described above, by the cross-spectral analysis of a 20 min time series after a 15–20 min acclimatization period. Therefore we believe we have provided strong evidence for the use of LF central frequency for easy identification of patients with poor orthostatic tolerance. Also, the presence of low values of coherence, or even its absence in LF range, characterize these patients. These parameters, however, have been obtained in patients with suspected orthostatic intolerance with no other associated disorders and must not be extended to patients with other characteristics.

One legitimate question to our finding is why some patients with a history of unexplained syncope had normal tolerance to the combined HUT and LBNP test (false negative) and some asymptomatic subjects showed poor tolerance (false positive). It could be argued that this test lacks specificity; however, we believe that the results of the present study, on the contrary, support the specificity of the orthostatic stress test. Indeed, the PNT and CNT groups showed overlapping time and frequency domain results as well as the PPT and CPT groups. The absence of a positive result in the PNT group does not exclude their tendency to postural-related syncope. It might be that their syncopal episodes, which are characterized by different pathophysiological mechanisms [30], depend on occasional events that lower the threshold to a vasovagal attack [31]. On the other hand, it is possible that controls with poor tolerance do not faint in everyday life, because they have developed conscious or unconscious compensatory manoeuvres (for instance, muscle tensing), they have learned to avoid situations predisposing to syncope or they are not exposed to local environmental factors (heat, emotions, fever, exercise etc.). Their ‘sub-symptomatic’ status might be the reason, because they never have been referred for clinical investigations of syncope.

We have demonstrated a simple test based on cross-spectral analysis-derived parameters while supine, which could provide a helpful diagnostic tool and that is potentially suitable for low-cost examination. Primarily, patients with poor orthostatic tolerance may be identified with a good specificity and sensitivity from the frequency of the LF oscillations whilst supine. Secondarily, these patients are also characterized, although with less homogeneity, by low resting arterial blood pressure, enlarged phase shift and low (or in some cases its absence) values of coherence between RR and SP oscillations in the LF range.

The explanation of disrupted mechanisms of the LF cardiovascular variability falls into the highly debated interpretation of the LF origin and deserves specifically addressed investigations. At present, we can only speculate on the physiological mechanisms of this finding, but we think that it might be due to a disrupted baroreflex function.
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