Autonomic Modulation and QT Interval Dispersion in Hypertensive Subjects With Anxiety

Gianfranco Piccirillo, Emanuela Viola, Marialuce Nocco, Elvira Santagada, Michele Durante, Carmela Bucca, Vincenzo Marigliano

Abstract—Anxiety is associated with an increased risk of sudden death. QT dispersion is a marker of cardiac repolarization instability and is seen in conditions of high risk of sudden death. The purpose of this study was to evaluate autonomic nervous system control and QT dispersion in hypertensive subjects with anxiety symptoms. In a recent preliminary study, we observed that hypertensive individuals reporting high scores on a self-assessment anxiety scale had more marked left ventricular hypertrophy. In 105 hypertensive subjects divided into 3 groups according to severity of anxiety, we evaluated autonomic control by short-term power spectral analysis of RR and arterial pressure variability at rest (baseline) and during sympathetic stress (tilt test), left ventricular mass index, and heart rate–corrected QT (QTc) dispersion. At baseline, hypertensive subjects with higher anxiety symptom scores had significantly lower high-frequency RR values expressed in absolute terms ($P<0.05$) and in normalized units ($P<0.05$) than their counterparts without anxiety symptoms. Hypertensive subjects with anxiety also had a higher mean left ventricular mass index ($P<0.001$) and greater QTc dispersion ($P<0.001$). Both indexes and high frequency ($P<0.05$) correlated with severity of anxiety. These findings suggest that anxiety is associated with autonomic imbalance. This condition could favor an increase in left ventricular mass. Myocardial hypertrophy alone or combined with neuroautonomic imbalance may lead to QT dispersion. (Hypertension. 1999;34:242-246.)

Key Words: autonomic nervous system ■ spectrum analysis ■ anxiety ■ death, sudden, cardiac ■ hypertension ■ hypertrophy, left ventricular ■ QT dispersion

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xiety,1–3 worry,4 and anger5 are among the psychological conditions associated with increased risk of death from coronary artery disease or indicated as a possible trigger of acute coronary episodes. Recent evidence also shows that depression can worsen the follow-up of postinfarction patients.6 Clinical studies and experiments in animals have shown that anxiety is associated with changes in neuroautonomic control.7–9 Spectral analysis of heart rate variability has confirmed increased indexes of sympathetic modulation,10–13 reduced indexes of parasympathetic modulation, or both10,11 in subjects with phobic anxiety. Similar changes have been described in subjects with expression of anger12 and panic attacks.13,14

In preliminary studies, we recently observed that subjects with hypertension and high scores on a self-rated anxiety scale had more marked left ventricular hypertrophy and decreased parasympathetic and increased sympathetic modulation of sinus activity.15 Hence, our aim in this study was to confirm these findings in a larger population of hypertensive subjects. Because subjects with high scores on the Cornell anxiety subscale proposed by Kawachi et al1 have a greater risk of sudden death, we also studied QT dispersion, a marker of electrical instability in subjects with left ventricular hypertrophy.16 Recent observations show that patients at high risk of sudden death have increased QT dispersion.17 Variability of QT duration among the 12 surface ECG leads depends on the differing recovery times of myocardial excitability16 and expresses electrical instability and greater susceptibility to malignant ventricular arrhythmias.17

We assessed autonomic nervous system by means of power spectral analysis at baseline (rest) and after sympathetic stress induced by the head-up tilt test (tilt).15,18–20 Because spectral analysis of RR and blood pressure variability is a noninvasive procedure that does not expose subjects to mental stress, it is ideal for studying neuroautonomic control over the cardiovascular system in these subjects. For the same reason, we induced stress by the tilt test, thus provoking an increase in sympathetic activity without stimulating the subjects psychologically.

Methods

Study Subjects

For this study from our outpatient clinic, we selected hypertensive subjects without cardiovascular complications. Hypertension was defined as diastolic blood pressure (DBP) ≥90 mm Hg.
On recruitment, hypertensive outpatients were unaware of their conditions; hence, none had received pharmacological treatment, and none had a history of other disorders or cardiovascular disease. No subject underwent restricted sodium intake. The subjects studied here are participating in a larger prospective study recently launched to study sudden death and hypertension. The high blood pressure values were confirmed ≥3 times during the past 6 months. Before entering the study, all subjects underwent a complete history, physical examination, routine laboratory investigations, ECG, 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 >106 μmol/L), liver, or gastrointestinal diseases or a tilt test positive for vasovagal syncope. Other exclusion criteria included DBP >110 mm Hg; body mass index (BMI) ≥26 kg/m²; age ≥65 years; smoking (≥5 cigarettes per day); diabetes (presence of glycosuria or fasting glycemia ≥6.6 mmol/L or 11.1 mmol/L at 2 hours after glucose loading); cholesterol plasma level >5.7 mmol/L; arrhythmias or conduction abnormalities; ultrasound evidence of carotid stenosis of importance; or echocardiographic evidence of wall motion abnormalities of the left ventricle or valvular disease. During echocardiography, data were obtained to determine the left ventricular mass index (LVM). Two-dimensional and M-mode echocardiograms were recorded from standard parasternal and apical windows by use of a commercially available ultrasound unit (Kontron Instruments). Each variable was measured according to the method described by Devereux and Reichek.21 LVM was then divided by body surface area to derive LVMI.

All selected subjects underwent Bruce protocol stress testing designed to eliminate subjects with silent myocardial ischemia. Tests were considered valid only if the subject reached ≥90% of the maximal age-corrected heart rate.

From 514 outpatients, 136 subjects (70 men and 66 women) were selected for study. The remaining 378 recruits were excluded because they failed to meet selection criteria. Fifteen subjects without a history of typical chest pain had significant ST-segment downsloping during exercise testing. Ten of these had coronary artery stenosis (≥50%) and underwent coronary angioplasty. In 46 recruits, the tilt test had to be stopped because presyncope symptoms accompanied by a fall in arterial blood pressure developed during testing.

**Study Protocol**

All selected subjects underwent a 12-lead surface ECG at a paper speed of 50 mm/s for QT evaluation and 10 minutes of baseline and head-upright tilt (90°) ECG (Telemedit Mortara Kangoni), beat-to-beat pressure (Finapres, Ohmeda), and respiratory (strain-gauge belt) recordings, RR interval, blood pressure, and respiratory recordings for spectral analysis in all subjects took place according to procedures used for other similar studies described elsewhere.10,15 These recordings were used for offline spectral analysis of RR interval and pressure variability.

Arterial pressure values were obtained manually by traditional mercury sphygmomanometer. The first measurement was discarded. Three additional measurements were obtained with a 3-minute interval between each, and the mean of 3 consecutive readings was used in data analysis.

In the second phase of study, the Cornell anxiety self-rated subscale proposed by Kawachi et al., which elicits common symptoms of phobic anxiety, was administered to all participants. The anxiety symptom scale ranged from 0 (no anxiety) to 5 (severe anxiety). 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, State-Trait Anxiety Inventory (STAI), and Crown-Crisp Index.2 To validate the results of the Cornell anxiety subscale proposed by Kawachi et al., we also administered the Anxiety Scale Questionnaire (ASQ)22 and the STAI to hypertensive subjects.23

**Offline Power Spectral Analysis and Data**

Stationary 10-minute segments of ECG, blood pressure, and respiratory recordings were analyzed with an autoregressive algorithm.18 The power spectral densities of the recordings were computed by an autoregressive algorithm developed in our laboratory and described in detail elsewhere.15,19,20 We then determined the total power (TP) of RR intervals and systolic blood pressure (SBP) and the total spectral density of these variables. For RR and SBP, we calculated the following spectral components: a high-frequency (HF) component (0.15 to 0.40 Hz Eq), a low-frequency (LF) component (0.04 to 0.15 Hz Eq), and a very-low-frequency (VLF) component (<0.04 Hz Eq).15,18,20

Spectra of the respiratory trace were analyzed on the signal sampled once every cardiac cycle. These spectra were used as a reference to identify heart rate oscillations 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 of ≥9 breaths per minute (0.15 Hz).19 The software program automatically calculated the respiratory frequency for each cycle. Recordings containing a respiratory frequency of <9 breaths per minute were discarded. 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 thus is an index of linear association between the 2 signals.

Because the resulting spectral data had a nonlinear distribution, we transformed them into normalized units (NUs).15–20 NUs were calculated as follows: LF NUs = LF power/TP – VLF power×100; HF NUs = HF power/TP – VLF power×100. Baroreceptor sensitivity was then calculated with the transfer function. This method yields 2 α indexes: α LF = (VLF RR×VLF SBP) and α HF = (VHF RR×VHF SBP).24

**Measurement of QT Intervals and Dispersion**

The duration of QT was measured at each lead of the 12-lead surface ECG for 2 consecutive cycles. Interval dispersion was calculated by the method of Perkiomaki et al.16,17 QT intervals were measured from the onset of QRS to the end of the T wave by a tangential method. When U waves were present, the tangent was also used to measure QT to the nadir of the curve between the T and U waves. Variables were measured manually by a trained operator blinded to each subject’s clinical and spectral data. Bazett’s formula was used to obtain QT intervals corrected for heart rate (QTC). QTC dispersion was defined as the differences between the respective maximum and minimum QTC values, and the mean value of 2 consecutive cycles was calculated. Interobserver measurement error was avoided by using measurements made by the same trained operator. Intraobserver and measurement errors of QTC dispersion were defined.

**Statistical Analysis**

All data were evaluated by use of database SPSS-PC+ (SPSS-PC+ Inc). All results are expressed as mean ± SE. Subjects were subdivided according to the symptom anxiety scale score into 3 groups: subjects with scores of 0, 1, and ≥2.1 One-way ANOVA and Bonferroni’s test were used to compare the general characteristics (including age, BMI, RR intervals, SBP, DBP, urinary and sodium plasma levels, QT dispersion, and LVM) and normalized spectral data of variables in 3 groups of hypertensive subjects. Repeated-measures ANOVA was used to evaluate the differences between baseline and after-tilt values of spectral variables. Because spectral data expressed in absolute form have a nonlinear distribution, we used the Kruskal-Wallis test to compare them statistically and the Dunn test to identify a possible significant difference between groups. The Wilcoxon test was used to assess the significance of changes in spectral variables expressed in absolute form and measured at rest and after tilt. Because of the nonlinear distribution of anxiety symptoms, the correlation between this and other variables was determined with Spearman’s rank test. Spearman’s rank corre-
Baseline Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Anxiety Symptom Score</th>
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<td></td>
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<tr>
<td>M/F</td>
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<td>Age, y</td>
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<td>BMI, kg/m²</td>
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<td>SBP, mm Hg</td>
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<td>DBP, mm Hg</td>
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<td>HR (Finapres), bpm</td>
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<tr>
<td>SBP (Finapres), mm Hg</td>
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<tr>
<td>DBP (Finapres), mm Hg</td>
<td>73.8±6.23</td>
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<tr>
<td>LVM, g/m²</td>
<td>105.2±9.1*</td>
</tr>
</tbody>
</table>

Comparison of the study subjects: composition of the groups, age, BMI, and other variables. Subjects were grouped according to anxiety symptom scores. RR (EGG), SBP (Finapres), and DBP (Finapres) are means of values used for spectral analysis. Data are expressed as mean±SE.

*p<0.05, subjects reporting no symptoms of anxiety vs subjects with anxiety scores ≥2 (Bonferroni’s test).

**Results**

The Kawachi et al anxiety questionnaire identified 57 hypertensive subjects (29 men and 28 women) who had no anxiety symptoms, 31 (16 men and 15 women) who had a single anxiety symptom, and 48 (25 men and 23 women) who had ≥2 symptoms (mean score, 2.92±0.2). The groups did not differ significantly in age, gender, and BMI (the Table).

Hypertensive subjects reporting ≥2 anxiety symptoms had significantly longer maximum QT than the group without anxiety symptoms (448.1±5.4 ms, *P<0.05). Hypertensive subjects with anxiety symptom scores of ≥2 had significantly broader QT and QTc dispersion than those scoring 0 and those with 1 anxiety symptom (60.1±2.1 ms, *P<0.001) (Figure). Subjects reporting 1 anxiety symptom also had significantly higher ASQ scores than groups without symptoms (9.1±0.26 versus 4.12±0.56, *P<0.001). Subjects reporting ≥2 anxiety symptoms also had significantly higher STAI scores (State subscale) than subjects reporting no symptoms (51.2±1.9 versus 28.3±1.5, *P<0.001).

HF RR obtained at rest and expressed in the absolute form (milliseconds squared) was significantly greater in subjects without anxiety than in subjects scoring ≥2 on the Cornell anxiety subscale (200±15 versus 134±21 ms², *P<0.05). The group scoring 1 point on this anxiety scale did not differ significantly from the other 2 groups (164±21 ms²). This result was confirmed by normalized data (44±2 versus 31±2 NUs, *P<0.05); again, no difference was found for HF NUs in the group with intermediate scores and the other 2 groups (37±3 NUs). Coherence between HF and the respiratory frequency was optimal at rest (0.92±1.5) and after tilt (0.85±1.0).

In nonanxious subjects, tilt induced an increase in SBP LF expressed both in the absolute form (4.9±1 mm Hg² at rest versus 27±10 mm Hg² for tilt, *P<0.05) and in normalized form (72±2 NUs at rest versus 79±2 NUs for tilt, *P<0.05). It also induced similar increases in subjects scoring 1 (6.6±1 mm Hg² at rest versus 20±13 mm Hg² for tilt, *P<0.05), and 77±4 NUs at rest versus 78±2 NUs for tilt, *P<0.05). Conversely, in subjects scoring ≥2, it induced no significant increase in SBP LF expressed either in absolute form (8±4 mm Hg² at rest versus 18±8 mm Hg² for tilt, *P=NS) or in normalized form (83±3 NUs at rest versus 79±2 NUs for tilt). SBP LF values during tilt did not differ in the 3 groups. No other significant differences were observed between the 3 groups for spectral variables expressed in absolute form.

**Relation Between Anxiety Symptom Scores and Other Variables**

Anxiety scores correlated significantly only with the QTc dispersion value (*r=0.65, P<0.001) and LVM (*r=0.62, P<0.001). During rest, HF, expressed in absolute form, and NUs correlated significantly with anxiety scores. In particular, RR HF (*r=−0.53, *P<0.05) and RR HF NUs (*r=−0.56, *P<0.05) correlated inversely with anxiety scores. During tilt, these variables did not correlate significantly with anxiety scores.
symptom scores. Multiple logistic regression analysis showed a significant association between anxiety score, QTc dispersion (t = 0.27, P < 0.001), LVMI (t = 0.26, P < 0.001), and HF (t = -1.38, P < 0.05) (anxiety score = 0.15 ms² + 0.07 g/m² - 0.001 ms⁻¹ 14.6). It found no significant relations between the other spectral and nonspectral variables. No significant difference was found between the 3 groups for baroreceptor sensitivity calculated with the transfer function.

STAI Study
Subdividing the subjects into 3 groups according to the STAI (State subscale) confirmed the statistical differences in the spectral data for QT dispersion (F = 23.0, P < 0.001) and the severity of myocardial hypertrophy (F = 7.3, P < 0.001) between the group with high anxiety levels and the group with no anxiety symptoms (P < 0.001). No significant differences were observed between the group with intermediate anxiety levels and the other groups.

Discussion
The assessment of autonomic regulation by power spectral analysis in hypertensive subjects remains controversial. Whereas some investigators reported a relative increase in LF (RR LF NUs and LF:HF) and a relative decrease in HF (RR HF NUs), others have failed to confirm this finding. Among the factors known to influence autonomic regulation and therefore spectral components are age, duration and severity of raised arterial pressures, gender, sodium sensitivity and intake, and presence of anxiety. Failure to account for these factors during the selection of subjects for study may have contributed to the discrepant findings. We would also underscore possible technical differences, including the type of recording (short term or 24 hour), breathing control, type of algorithm used, and subdivision into spectral bands.

Power spectral analysis during tilt and at rest provides a measure of cardiovascular autonomic regulation. HF power is influenced by respiratory activity. Hence, HF power of RR variability gives a specific index of vagal activity, whereas changes in LF power of arterial pressure, induced by tilt, provide an index of sympathetic nervous system cardiovascular modulation.

In this study, the hypertensive subjects with high anxiety symptom scores had lower RR HF NUs values expressed in absolute form and as NUs. These data were confirmed by the significant inverse relation between HF power and anxiety scores. This finding indicates a reduction in sinus vagal modulation. Although our preceding study yielded similar results, the data failed to reach statistical significance, probably owing to the small study sample.

During tilt, SBP LF, an index of sympathetic nervous system modulation, increased only in nonanxious and moderately anxious subjects (score = 1). Hence, only these 2 groups achieved a normal response to tilt. The inability to increase SBP LF during tilt probably arises from altered cardiopulmonary reflexes caused by the greater myocardial mass in subjects with high anxiety levels.

Multiple logistic regression analysis identified only 3 variables that correlated with anxiety scores, namely LVMI, HF, and QT dispersion. The fact that we explicitly excluded from the equation the other confounding variables (including BMI and blood pressure) likely to influence LVM shows that a direct correlation exists between QT dispersion, degree of anxiety, and reduced vagal activity independently from the other variables. The risk of sudden death for fatal ventricular arrhythmias in anxious subjects could be linked to the altered repolarization phase. The probable cause of dispersed cardiac repolarization in hypertensive subjects with anxiety is left ventricular hypertrophy. An altered repolarization phase in myocardial hypertrophy could be due to the potassium channel defect seen in hypertrophic myocardial cells. Another condition known to influence QT dispersion is the autonomic imbalance that we observed in subjects with anxiety. Recent reports describe a correlation between QT dispersion and autonomic imbalance in conditions of cardiac failure and acute myocardial infarction. This finding is indirectly confirmed by a reduction in QT interval dispersion during treatment with β-blockers.

Finally, in our subjects with arterial hypertension, arterial pressures did not correlate with myocardial mass. Independently from pressure values, therefore, anxiety could directly influence myocardial mass through a reduction in vagal modulation.

With the current available data, we postulate that chronic anxiety causes a stable change in the sympathovagal balance toward sympathetic hyperactivity and parasympathetic hypoactivity. This event could favor the increase in LVM. The potassium channel abnormalities induced by myocardial hypertrophy and the autonomic imbalance would then ultimately lead to QT dispersion. This cardiac repolarization disorder, along with autonomic imbalance, is probably responsible for lowering the ventricular fibrillation threshold.

Clinical Implications
These data raise matters of clinical interest. The Cornell anxiety subscale proposed by Kawachi et al, QTc dispersion, and RR variability might be useful for identifying subjects at risk of sudden death. An immediate question is whether these measures combined have predictive ability. Equally important is the type of hypertensive therapy. The end point of antihypertensive therapy probably should be not only to lower pressure levels and reduce myocardial mass and QT interval dispersion but also to reset the balance between sympathetic and vagal modulation. For this purpose, β-blocking agents seem most indicated, followed by ACE inhibitors and probably angiotensin II receptor inhibitors. Because diuretics can alter the electrolyte balance and therefore the repolarization phase and because dihydropyridine calcium channel antagonists augment sympathetic activity, neither drug class seems to have a place in the treatment of hypertensive patients with anxiety.

Study Limitations
Although QT dispersion is a widely used index, its real predictive value remains questionable. The principal technical problem is the method used to identify the end of the T wave. For this purpose, the tangential method used in this study is considered the most reliable. Only a prospective
study will definitively clarify the interrelations between anxiety, myocardial hypertrophy, altered polarization phases, and sudden death.

References

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