Influence of age, the autonomic nervous system and anxiety on QT-interval variability

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ABSTRACT

As QT variability increases and heart rate variability diminishes, the QT variability index (QTVI) – a non-invasive measure of beat-to-beat fluctuations in QT interval on a single ECG lead – shows a trend towards positive values. Increased QT variability is a risk factor for sudden death. Aging lengthens the QT interval and reduces RR-interval variability. In the present study we investigated the influence of aging and the autonomic nervous system on QT-interval variability in healthy subjects. We studied 143 healthy subjects, and divided them into two age ranges (younger and older than 65 years). For each subject we measured two QTVIs: from the q wave to the end of the T wave (QTeVI) and to the apex of the T wave (QTaVI). Both indexes were calculated at baseline and after sympathetic stress. In 10 non-elderly subjects, both QTVIs were determined after β-adrenoreceptor blockade induced by intravenous infusion of propranolol or sotalol. The QTVI was higher in elderly than in younger subjects (P < 0.001). QTVIs obtained during sympathetic stress remained unchanged in the elderly, but became more negative in the younger group (P < 0.05). QTeVI and QTaVI at baseline were correlated positively with age (P < 0.01) and anxiety scores (P < 0.05), but inversely with the low-frequency spectral power of RR-interval variability (P < 0.001). QTVIs were higher in subjects with higher anxiety scores. In younger subjects, sotalol infusion increased both QTVIs significantly, whereas propranolol infusion did not. In conclusion, aging increases QT-interval variability. Whether this change is associated with an increased risk of sudden death remains unclear. The association of abnormal QT-interval variability with anxiety and with reduced low-frequency spectral power of heart rate variability merits specific investigation. In healthy non-elderly subjects, acute sympathetic stress (tilt) decreases the QTVI. β-Adrenoreceptor blockade inhibits this negative trend, thus showing its sympathetic origin. Because a negative trend in QTVI induced by sympathetic stress increases only in younger subjects, it could represent a protective mechanism that is lost with aging.

INTRODUCTION

The past 10 years have witnessed a flurry of studies on the dispersion of ventricular repolarization and its association with sudden death. Less information is available on temporal QT-interval (QT) variability in short-term recordings [1–3]. The QT variability index (QTVI) gives a non-invasive measure of beat-to-beat QT fluctuations on a single ECG lead [1–3]. It represents the relationship between QT and RR-interval (RR) variability. These two variables, even when considered singly, are good predictors of malignant ventricular arrhythmias that can induce sudden death [4,5]. Previous studies have confirmed that increased QT variability and low heart rate variability are...
predictive for sudden death [4,5]. However, QT and RR variance cannot be used as predictors of sudden death owing to their non-linear distribution in the general population [1]. Some investigators have sought to circumvent this problem by normalizing QT variance for RR variance [1–3]. In other words, increased QT variance and reduced RR variance, or both, increase the QTVI. An increased QTVI is correlated with the clinical severity of heart failure in patients with dilated cardiomyopathy [1] and is a risk factor for sudden death [2,3]. Normal subjects have a negative QTVI. Decreased QTVI negativity or a return to positive values therefore indicates a propensity for malignant ventricular arrhythmias [1–3].

Another advantage of normalizing QT data is that it avoids recourse to the various formulae that correct QT for heart rate, but often yield inappropriate results [6–8].

Because aging is associated with prolonged cardiac repolarization [9,10] and reduced RR variance [11–16] – in spectral analysis, termed total power – we investigated whether these ECG changes are accompanied in the elderly by an increased QTVI. Accumulating evidence also points to a greater risk of sudden death in subjects with high anxiety levels [17–19], altered autonomic cardiac modulation in subjects with anxiety [20–23], and increased QT dispersion in hypertensive subjects with anxiety [23]. Hence we also investigated the QTVI as a function of anxiety, of autonomic regulation studied by spectral analysis of RR, and of systolic blood pressure (SBP) variability, at baseline (rest) and after sympathetic stress (tilt test). Because the same oscillatory components contribute to variability in QT, RR and SBP, we determined all three variables during controlled respiration. Controlled breathing makes it easier to recognize the respiratory components of RRs and QTs, and thus determine their coherence.

We calculated QTs in two ways: from the q wave to the apex of the T wave, namely apex QT (QTa), and from the q wave to the end of the T wave, namely end QT (QTe). Because these two QT measurements reflect two distinct repolarization phases [22,24–26] they could differentially reflect age-related changes in autonomic nervous system function.

Finally, we studied the QTVI changes induced by the infusion of propranolol or sotalol. Because propranolol induces non-selective beta-receptor blockade, it lowers the heart rate but leaves cardiac repolarization unchanged. Although sotalol resembles propranolol in its beta-blocking properties, as a class III anti-arrhythmic agent it also prolongs cardiac repolarization.

METHODS

Study subjects

Apparently healthy adults were recruited from people presenting spontaneously to our outpatient clinic for preventative reasons. Before entering the study, all subjects underwent a complete medical history, physical examination, routine laboratory investigations, ECG, two-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 disease, electrolyte disorders, or a positive tilt test for vasovagal syncope. Other exclusion criteria included: diastolic blood pressure ≥ 90 mmHg and SBP ≥ 140 mmHg; body mass index > 26 kg/m²; current smokers; diabetes (presence of glycosuria, fasting glycaemia > 6.6 mmol/l or glycaemia > 11.1 mmol/l at 2 h after glucose loading); plasma cholesterol level > 5.7 mmol/l; arrhythmias or conduction abnormalities; ultrasound evidence of carotid stenosis of importance; or echocardiographic evidence of left ventricular wall-motion abnormalities or valvular disease. During echocardiography, data were obtained to determine the left ventricular mass index. 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. Echocardiographic left ventricular mass was then calculated from the Penn convention, according to the method described by Devereux and Reichek [26]. The left ventricular mass was then divided by the body-surface area to derive the left ventricular mass index. 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 attained at least 90% of the maximal age-corrected heart rate.

From among 556 outpatients observed over 24 months, 143 consecutive subjects (72 men and 71 women) were selected for study. The remaining 413 recruits were
excluded because they failed to meet the selection criteria. Eighteen subjects without a history of typical chest pain had significant ST-segment downsloping during exercise testing; 11 of these had coronary artery stenosis (> 50%) and underwent coronary angioplasty. In 27 recruits the tilt test had to be stopped because presyncope symptoms, accompanied by a fall in arterial blood pressure, developed during testing. None of the subjects had consumed caffeine on the morning of the examination.

All subjects had sedentary occupations. None of them had engaged in intense physical training before the study, and none had received medication for at least 2 months beforehand. All participants gave their informed consent to procedures, and the local ethical committee approved the study.

**Study protocol and data acquisition**

After a 15-min supine rest, each subject underwent a 12-lead ECG recording at a speed of 50 mm/s for the determination of QT dispersion. A 10-min simultaneous recording was then obtained for a single ECG lead (Telemetria Mortara Rangoni), beat-to-beat measurement of arterial pressure (Finapres; Ohmeda) and respiratory frequency (strain-gauge belt). During the last few minutes of this recording, subjects were instructed to breathe at 20 breaths/min (0.33 Hz) in time with a metronome. The 256-beat segment recorded under respiratory control (Figures 1 and 2) was used to determine RR, QTa and QTe, SBP and respiratory frequency (Figure 3). In each subject another ECG recording was obtained 15 min after head-up tilt (tilt), according to the study protocol described in detail elsewhere [11–15,20–23].

The three analogue signals (ECG, SBP and respiratory frequency) were acquired simultaneously and converted digitally with a custom-designed card (Keithley Metra-byte; DAS 1200 Series) at a sampling frequency of 500 Hz per channel with 12-bit precision.

For recognition and measurement of RR and QTa, SBP and respiratory rate, we used a software program developed in our laboratory and based upon an automated derivative/threshold algorithm. To calculate the QTe and to make the end of the T wave easier to identify, we used a software program based upon the algorithm for quantification of beat-to-beat fluctuations in QT variability proposed by Berger and co-workers [1,2].

In the second phase of the study, the Cornell Anxiety self-rated subscale proposed by Kawachi et al. [18,19], which elicits common symptoms of phobic anxiety, was administered to all participants [18–23]. The anxiety symptom scale therefore 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, the State–Trait Anxiety Inventory and the Crown–Crisp Index [18,19]. To validate the results of the Cornell Anxiety subscale proposed by Kawachi et al. [18], we also administered the Anxiety Scale Questionnaire [27] and the State Anxiety Inventory [28] to subjects.

Finally, we selected 10 young healthy subjects to undergo the same battery of recordings at rest and during tilt after intravenous infusion of propranolol (0.2 mg/kg body weight), placebo (glucose solution) and sotalol (1.5 mg/kg body weight). The three pharmacological tests took place at 1-week intervals. None of the subjects took other medications between tests. For ECGs obtained during these 3 weeks, identical leads were recorded using the same electrode placement.

**Offline power spectral analysis of RR and QT variability**

Stationary, 256-beat segments of ECG, blood pressure and respiratory recordings at rest and during tilt were analysed with an autoregressive algorithm (Figure 3). The power spectral densities of the recordings were computed by an autoregressive algorithm developed in our laboratory and described in detail elsewhere [11–15,20–23]. We then determined the total power of RRs and SBP and their total spectral density. For RR and SBP we calculated the following spectral components: a high-frequency power component (from 0.15 to 0.42 Hz), a low-frequency power (LF) component (from 0.03 to 0.15 Hz) and a very-low-frequency power component (below 0.04 Hz) [5,29] (Figure 3).

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 oscillations caused by respiratory sinus arrhythmia. The RR and respiratory signal recordings were also used for cross-spectral analysis. The software program automatically calculated the respiratory frequency for each cycle. The coherence function of the various spectral components and of the respiratory signal (the probability that the two signals vary simultaneously) was then estimated. Coherence expresses the fraction of power at a given frequency in either time series and is explained as a linear transformation of the other, and is thus an index of a linear association between the two signals [1,2]. The coherence function $\gamma (f)$ was then computed according to the formula:

$$\gamma (f) = |P_{xy} (f)|^2/P_{xx} (f) \cdot P_{yy} (f)$$

where $f$ is frequency, $P_{xx} (f)$ is the spectrum of a variable (RR spectrum for QTVI, or respiratory frequency spectrum for RR variability), $P_{xy} (f)$ the other variable (QT spectrum for QTVI, or RR spectrum for RR variability), and $P_{yy} (f)$ is the cross-spectrum. The coherence function provides a measure between zero and unity of the degree of linear interaction between heart rate and QT oscillations, or between respiratory frequency and RR fluctuations as a function of the frequency of those fluctuations. Mean coherence was measured by averaging $\gamma (f)$ over the frequency band from 0 to 0.42 Hz.

The QTVI was determined beat-to-beat by calculating the mean RR (RR_m) and its variance (RR_v) in 256 beats. Two distinct QTs were calculated: QTa (Figure 1), measured from the q wave to the apex of the T wave, and QTc (Figure 2), from the q wave to the end of the T wave. The QTa mean (QTa_m) and variance (QTa_v), and the QTc mean (QTc_m) and variance (QTc_v), were then computed from the respective time series for the 256-beat epoch, thus yielding two QTVIs (QTVI and QTcV)

$$\text{QTVI} = \log_{10} \left( \frac{(\text{QTa}_m)^2}{(\text{RR}_m)^2} \right)$$

$$\text{QTcV} = \log_{10} \left( \frac{(\text{QTc}_m)^2}{(\text{RR}_m)^2} \right)$$

**Measurement of QTs and dispersion**

The duration of the QT was measured at each lead of the 12-lead surface ECG for two consecutive cycles. Interval dispersion was calculated by the Perkiomaki method [23–25]. QTs were measured from the onset of the QRS complex to the end of the T wave by a tangential method. When U waves were present, the tangent was also used to measure the 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 corrected for heart rate (QTc). QTc dispersion was defined as the difference between the respective maximum and minimum QTc values, and the mean value of two consecutive cycles was calculated. Inter-observer measurement error was avoided by using measurements from the same trained operator. Intra-observer and measurement errors of QTc dispersion were defined.

**Statistical analysis**

All data were evaluated by use of database SPSS-PC+ (SPSS-PC+ Inc., Chicago, IL, U.S.A.). All results are expressed as means ± S.E.M. A $P$ value of $< 0.05$ was considered to indicate statistical significance.

Subjects were subdivided according to age into two groups: < 65 years and ≥ 65 years. One-way ANOVA was used to compare the general characteristics and QT data in the two groups.

Repeated-measures ANOVA was used to evaluate the differences between QT variables measured at rest and during tilt. Because spectral data expressed in absolute form have a non-linear distribution, we used the Mann–
Whitney test to compare them statistically. 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.

Subjects were also subdivided into three groups according to their scores on the anxiety symptoms scale: subjects with a score of 0, 1, and 2 or more [18,19,23]. A one-way ANOVA was used to compare the QT data in these three groups.

Repeated-measures ANOVA and Bonferroni’s test were used to evaluate the differences between QT variables measured during the pharmacological study.

Possible associations between variables were studied with a stepwise multiple regression analysis. To use spectral data with stepwise multiple regression analysis, we transformed the absolute power into the natural logarithm of the variables. Pearson’s correlation was used to assess relationships between variables.

RESULTS

No significant differences were found for general demographic characteristics, laboratory data (including sodium and potassium), anxiety scores, left ventricular mass or QTc dispersion in the elderly (mean age 77 ± 2 years) and non-elderly (mean age 41 ± 2 years) groups (Table 1).

QTVI and aging

QTc and QTa measured at rest and after tilt were significantly longer in healthy elderly than in younger subjects [QTc rest, 389 ± 11 and 354 ± 5 ms respectively (P < 0.05); QTc tilt, 378 ± 20 and 335 ± 6 ms respectively (P < 0.001); QTa rest, 316 ± 8 and 280 ± 4 ms respectively (P < 0.05); QTa tilt, 304 ± 15 and 251 ± 7 ms respectively (P < 0.001)]. QTc and QTa measured

Table 1 Baseline characteristics of study subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Younger subjects (&lt; 65 years)</th>
<th>Elderly subjects (&gt; 65 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>91</td>
<td>52</td>
</tr>
<tr>
<td>Male/female</td>
<td>47/44</td>
<td>25/27</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23 ± 0.6</td>
<td>24 ± 1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68 ± 1</td>
<td>67 ± 3</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>119 ± 3</td>
<td>125 ± 3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>73 ± 2</td>
<td>70 ± 2</td>
</tr>
<tr>
<td>Anxiety symptom score</td>
<td>1.3 ± 0.4</td>
<td>1.2 ± 0.3</td>
</tr>
<tr>
<td>Left ventricular mass index</td>
<td>113 ± 3</td>
<td>115 ± 3</td>
</tr>
<tr>
<td>QTc dispersion (ms)</td>
<td>40 ± 5</td>
<td>41 ± 3</td>
</tr>
</tbody>
</table>

Table 2 Data for the QTVI in the study subjects

Data are expressed as means ± S.E.M. Comparisons between groups were carried out by one-way and repeated-measures ANOVA. Significance of differences between values at rest and after tilt: *P < 0.05.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Younger subjects (&lt; 65 years)</th>
<th>Elderly subjects (&gt; 65 years)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTcVI</td>
<td>−0.97 ± 0.1</td>
<td>−0.29 ± 0.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QTaVI</td>
<td>−0.78 ± 0.1</td>
<td>−0.32 ± 0.2</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Mean coherence</td>
<td>0.45 ± 0.001</td>
<td>0.37 ± 0.006</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Tilt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTcVI</td>
<td>−1.37 ± 0.1*</td>
<td>−0.32 ± 0.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>QTaVI</td>
<td>−1.10 ± 0.2*</td>
<td>−0.08 ± 0.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean coherence</td>
<td>0.40 ± 0.009</td>
<td>0.32 ± 0.001</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Figure 4 Highly significant correlations (stepwise multiple regression) between QTc and QTa measured at rest were higher in elderly than in younger subjects [QTc, 54 ± 11 and 25 ± 2 ms² respectively (P < 0.05); QTa, 46 ± 14 and 21 ± 2 ms² respectively (P < 0.05)].

Both QTc and QTa measured at rest and after tilt differed significantly only in the younger subjects, in whom QTc and QTa values became significantly more negative after tilt (P < 0.05) (Table 2).
Figure 5 Highly significant inverse correlations (stepwise multiple regression) between QTeVI and RR LF, both at rest and after tilt.

The coherence function calculated between RR and QTe was significantly higher in younger than in elderly subjects (Table 2).

Aging and variability in RR and SBP
Although all RR spectral components were higher in younger subjects, differences in LF obtained at rest (younger, 510 ± 112 ms²; elderly, 327 ± 101 ms²; P < 0.05) and after tilt (younger, 1278 ± 484 ms²; elderly, 1381 ± 1225 ms²; P < 0.05) achieved the greatest statistical significance. Only in younger subjects did power expressed in absolute terms increase after tilt (from 510 ± 112 ms² to 1278 ± 484 ms²; P < 0.05).

No difference was observed between the two groups with regard to SBP variability.

QTVIs, QT dispersion and anxiety
The anxiety questionnaire identified three groups of subjects according to the severity of anxiety. Thus 49 subjects scored 0 (no anxiety), 25 subjects scored 1 (intermediate) and 69 subjects scored 2 or more (severe anxiety). No significant differences were found for general characteristics (including age, sex, body mass index and heart rate) among the three groups. The results of the Kawachi anxiety test correlated significantly with those from the Anxiety Scale Questionnaire (r = 0.83, P < 0.001) and the State Anxiety Inventory (r = 0.80, P < 0.001).

Subjects without anxiety (score 0) had significantly more negative QTeVI values than the group with an anxiety score of 2 or more (subjects scoring 0, −1.16 ± 0.1; subjects scoring 1, −1.23 ± 0.1; subjects with anxiety scores of 2 or more, −0.54 ± 0.1; P < 0.001). Similar differences were found for QTaVI.

Subjects without anxiety had significantly lower QT dispersion than the other two groups (subjects with score 0, 35 ± 0.1 ms; subjects with score 1, 50 ± 3 ms; subjects with score 2 or more, 55 ± 3 ms; P < 0.001).

Relationships between QTVI and other variables
Multiple regression analysis identified an association of QTeVI obtained at rest with age and with ln.LF at rest, and a weak association with the anxiety score (r² = 0.7, F = 16, P < 0.001; age: B = 0.01, β = 0.4, t = 3.2, P < 0.01; ln.LF, B = −0.2, β = −0.5, t = −4.0, P < 0.001; anxiety score: B = 0.1, β = 0.3, t = 2.1, P < 0.05) (Figures 4, 5 and 6). QTeVI after tilt also showed a significant
relationship with age and with lnLF after tilt ($r^2 = 0.7, F = 27, P < 0.0001$; age: $B = 0.1, \beta = 0.5, t = 3.5, P < 0.01$; lnLF, $B = -0.2, \beta = -0.4, t = -3.1, P < 0.01$) (Figures 4 and 5). No significant association was found between anxiety and QTDeVI after tilt (Figure 6). Although QTDeVI and QT dispersion differed significantly in subjects with high anxiety scores compared with those without, neither test yielded a significant correlation.

Pharmacological study

In subjects at rest, both QTDeVIs remained substantially unchanged after propranolol infusion (Figure 7). During tilt, both indexes decreased after placebo infusion, but not after propranolol infusion ($P < 0.05$) (Figure 8).

Sotalol infusion significantly reduced QTDeVI negativity at rest compared with placebo and propranolol [sotalol, $-0.72 \pm 0.1$ ($P < 0.001$); placebo, $-1.03 \pm 0.1$ ($P < 0.001$); propranolol, $-0.99 \pm 0.2$ ($P < 0.001$)] (Figure 7) and after tilt [sotalol, $-0.65 \pm 0.1$; placebo, $-1.31 \pm 0.1$ ($P < 0.001$); propranolol, $-1.14 \pm 0.2$, $P < 0.001$)] (Figure 8).

**DISCUSSION**

Our findings indicate that aging reduces the negativity of QTDeVI (QTDeVI and QTaVI) values obtained at rest. An increased QTDeVI is a marker of cardiac repolarization lability [1], and is correlated with an increased risk of sustained ventricular tachycardia and sudden death in subjects with heart disease [2]. A high QTDeVI value denotes an increase in temporal repolarization variability, whereas spatial variability – QT dispersion – seems uninfluenced by age. In the elderly, a prolonged action potential [9] arises chiefly from an increased duration of cardiac repolarization [9,10,30,31]. This phenomenon not only prolongs the mean duration of repolarization, but also induces heterogeneous repolarization in the single ventricular myocytes. The duration of the QT measured beat-to-beat is the sum duration of repolarization in all the ventricular myocardial cells. An asynchrony in the duration of repolarization could result in QT shortening and lengthening accompanied by larger QTDeVI variance and less negative QTDeVI values. The age-related reduction in RR variance [11–16] could therefore increase QTDeVI values (see the Methods section). Two typical disorders commonly seen in elderly patients prolong cardiac repolarization and diminish RR variability: myocardial ischaemia and hypertensive cardiopathy. Because we explicitly excluded elderly patients with these conditions, the prolonged QTDeVI in our elderly subjects is related to aging alone. Increased QTDeVI and QTaVI values might therefore be useful electrical markers of ventricular aging.

Because QTs and RRs oscillate around similar main frequencies, they invariably show good coherence. In the present study, the use of controlled respiration provided a precise respiratory frequency for reference. Having our subjects breathe at a rate of 20 breaths/min (0.33 Hz) yielded RR (high-frequency power) and QT spectral peaks at an identical frequency. Like the RR spectral peak [5,12,14,15,20–23,29], the QTDeVI is probably influenced by vagal activity [1]. In addition, the QT spectrum generally exhibits an additional oscillatory component that oscillates around 0.1 Hz and is coherent with a low-frequency spectral component of RR variability. Opinions differ as to the origin of the spectral component of RR variability. Some consider it a marker of sympathetic modulation [5,29], while others favour combined vagal (baroreceptor) and sympathetic sources [32,33]. Whatever its origin in the RR spectrum, in the QT spectrum it probably originates from the same source. The absolute QTDeVI values in the present study are lower than those originally reported by Berger et al. [1,2]. An explanation is that, unlike in the two previous studies, we recorded under conditions of controlled breathing, in order to enhance the single spectral components and thus obtain a more reliable assessment of autonomic control. Controlled breathing increases RR variance [5,29], thus...
increasing the denominator of the QTVI equation (see Methods section) and thereby resulting in a lower ratio.

Our results suggest that aging reduces RR and QT spectral coherence. This finding is consistent with a progressive age-related decrease in vagal QT modulation. Loss of coherence is typical of conditions associated with a chronic increase in sympathetic activity and concurrent vagal withdrawal, e.g. heart failure [1]. The same may hold true for aging, another condition generally associated with high plasma catecholamine concentrations and diminished vagal activity [14,15,34]. Further support for this observation comes from our data showing that acute sympathetic activation induced by tilt testing also reduced coherence between the two signals.

Another noteworthy observation is the negative trend in QTVI values in subjects under the age of 65 years – both QTVIs were invariably significantly more negative in this group than those determined in healthy elderly subjects under the same experimental conditions. Conversely, in elderly subjects, tilt testing left this index unchanged. In other words, in younger subjects, acute sympathetic stimulation shortens the mean RR and QT duration and reduces their variance, thus lowering QTeVI and QTaVI. Sympathetic stimulation in these subjects probably merely has the effect of accelerating diastolic depolarization (phase 4) in sinus node cells, thus increasing sinus heart rate and causing a relative increase in the speed of ventricular repolarization. In addition, the failure of propranolol-induced β-blockade to diminish the QTVI during tilt indicates that the lowering of these indexes is mediated by the sympathetic nervous system. In the elderly, despite enhancing diastolic depolarization, tilt is unable to adjust the speed of ventricular repolarization, probably owing to an age-related impairment in calcium-channel inactivation and a decrease in density of β-receptor dysfunction [34,40,41]. If the LF component depends predominantly on baroreflex activity, then the reduced function of age could reflect an age-related decrease in vagal activity. Hence the inverse relationship between QTeVI and LF could denote increased QT heterogeneity, related either to augmented sympathetic activity or to vagal reduction, both of which are age-related conditions.

Of importance in interpreting the relationship between anxiety level and QTMI is the five times higher risk of sudden death in subjects with anxiety than in those without [17–19]. An increased QTMI could be responsible for increasing susceptibility to ventricular arrhythmia. Unfortunately, owing to the widely dispersed data from the anxiety scales, we observed only a weak degree of correlation between the severity of anxiety and the QTMI (Figure 6). A more equal distribution (presence of subjects scoring 5 for anxiety) would probably increase the statistical significance of this association. Anxiety may therefore be able to alter the autonomic balance by increasing sympathetic modulation and reducing vagal modulation, or inducing both changes [20–23]. In elderly persons in whom cardiac repolarization is already altered, these pathophysiological changes could increase susceptibility to life-threatening ventricular arrhythmias. This hypothesis receives support from our observation that subjects with higher anxiety scores (subjects with two or more anxiety symptoms compared with subjects without anxiety) had higher (less negative) QTMI values.

Another interesting observation was that QT dispersion proved ineffective for assessing the effect of age on cardiac repolarization, probably because it is influenced predominantly by anatomical abnormalities, such as left ventricular mass (dilatation or hypertrophy). Conversely, variability in time (QTVI) correlates more closely with autonomic nervous system and neuroendocrine changes. In the present study we nonetheless confirm previous reports of greater QT dispersion in subjects with anxiety [22,23].

Finally, propranolol-induced sympathetic blockade (Figures 7 and 8) evidently had no effect on the QTMI because it caused proportionate increases in RR variance and mean duration (see the Methods section), but left QT duration and variance appreciably unchanged [42,43]. Conversely, sotalol, a drug that acts predominantly on repolarization (Ir blockade), increases the QTMI both at baseline and during sympathetic stress (Figures 7 and 8). This phenomenon arises from the significant increase in QT variance. The pathophysiological basis and the clinical importance of this behaviour is unknown. The Ir blockade and the diminished sympathetic nervous system modulation induced by sotalol could well amplify the vagally mediated respiratory oscillations in the QT (0.32 Hz), thus increasing QT variance, and ultimately increasing the QTMI. Nonetheless, we cannot automatically extend these results to other drugs in the same class, such as amiodarone. One reason is that drugs belonging to the same class may exert different actions.
For example, sotalol and amiodarone both increase the QT duration, whereas amiodarone – but not sotalol – reduces QT dispersion [44,45]. These observations make it necessary to study the predictive value of the QTVI in patients with heart diseases associated with a high incidence of ventricular arrhythmias receiving treatment with class III anti-arrhythmic agents. Although the efficacy of sotalol in preventing sudden death remains unproven [46–48], an increased QTVI seems to argue against this practice. The clinical implications arising from these observations nevertheless require further study, because we cannot extend conclusions drawn from data in healthy subjects to patients with heart disease at high risk of life-threatening arrhythmias.

In conclusion, aging is associated with an increased QTVI. Whether the observed alteration in QTVI is associated with a higher incidence of sudden cardiac death remains unknown. Insofar as an increased QTVI is correlated with degree of anxiety and with reduced LF spectral power – both conditions associated with sudden cardiac death – these issues should be addressed in a prospective study. Finally, after acute sympathetic stress (upright tilt) in healthy non-elderly subjects, QTVI values become negative. This negative trend is inhibited by β-adrenoceptor blockade, and therefore must originate from modulation of the sympathetic nervous system. Because QTVI values do not become negative during sympathetic stress in the elderly, this may represent a protective mechanism that is lost upon aging.

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