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Relation between QT interval variability and cardiac sympathetic activity in hypertension

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1School of Electrical and Electronic Engineering and 2Centre for Heart Rhythm Disorders, University of Adelaide, Adelaide; 3Neurovascular Hypertension and Kidney Disease Laboratory, 4Human Neurotransmitters Laboratory, and 5Heart Failure Research Group, Baker IDI Heart and Diabetes Institute, Melbourne; 6Faculty of Medicine, Nursing and Health Sciences, and 7Department of Physiology, Monash University, Melbourne; 8School of Biomedical Sciences and Pharmacy, University of Newcastle, Newcastle; and 9Department of Cardiology, Royal Adelaide Hospital, Adelaide, Australia

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Baumert M, Schlaich MP, Nalivaiko E, Lambert E, Ika Sari C, Kaye DM, Elser MD, Sanders P, Lambert G. Relation between QT interval variability and cardiac sympathetic activity in hypertension. Am J Physiol Heart Circ Physiol 300: H1412–H1417, 2011. First published January 21, 2011; doi:10.1152/ajpheart.01184.2010.—Elevated QT interval variability is a predictor of malignant ventricular arrhythmia, but the underlying mechanisms are incompletely understood. A recent study in dogs with pacing-induced heart failure suggests that QT variability is linked to cardiac sympathetic nerve activity. The aim of this study was to determine whether increased cardiac sympathetic activity is associated with increased beat-to-beat QT interval variability in patients with essential hypertension. We recorded resting norepinephrine (NE) spillover into the coronary sinus and single-lead, short-term, high-resolution, body-surface ECG in 23 patients with essential hypertension and 9 normotensive control subjects. To assess beat-to-beat QT interval variability, we calculated the overall QT variability (QTVN) as well as the QT variability index (QTVi). Cardiac NE spillover (12.2 ± 6.5 vs. 20.7 ± 14.7, P = 0.03) and QTVi (−1.75 ± 0.36 vs. −1.42 ± 0.50, P = 0.05) were significantly increased in hypertensive patients compared with normotensive subjects. QTVN was significantly correlated with cardiac NE spillover (r² = 0.31, P = 0.001), with RR variability (r² = 0.20, P = 0.008), and with systolic blood pressure (r² = 0.16, P = 0.02). Linear regression analysis identified the former two as independent predictors of QTVN. In conclusion, elevated repolarization lability is directly associated with sympathetic cardiac activation in patients with essential hypertension.

norepinephrine spillover

THE QT INTERVAL OF THE BODY surface ECG reflects global depolarization and repolarization in the ventricular myocardium and undergoes subtle beat-to-beat fluctuations (9). Elevated beat-to-beat QT interval variability has been demonstrated in various cardiac (6, 26) but also noncardiac conditions (4, 36). Importantly, QT variability has been shown to be elevated in dogs before pharmacologically induced Torsades de Pointes (32, 34) and in patients with structural heart disease before ventricular tachycardia/ventricular fibrillation events (33). Furthermore, QT variability was associated with an increased risk of ventricular tachycardia/ventricular fibrillation in patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial (MADIT) II (17) and was predictive of sudden cardiac death in patients with asymptomatic chronic heart failure with mild to moderate left ventricular (LV) diastolic dysfunction (27). However, the mechanisms contributing to beat-to-beat QT interval variability are incompletely understood. Besides electrical restitution, which reflects the intrinsic adaptation of the action potential duration to changes in cycle length (14), the autonomic nervous system is thought to play a key role in the genesis of beat-to-beat QT interval variability. Previous studies addressing this issue have provided conflicting results. A recent study in dogs showed that QT variability was related to left stellate-ganglion activity, but only after the dogs had developed heart failure (28). In healthy humans, pharmacological activation or blockade of β-adrenoreceptors augmented and reduced QT variability, respectively (23, 35). Cardiac norepinephrine (NE) spillover, the most direct index of cardiac sympathetic activity, had no association with QT variability in patients with panic disorder and depression, patients who were free of current underlying cardiovascular disease (2).

To gain further insight into the role of cardiac sympathetic activity in the genesis of QT interval variability in humans, we measured cardiac NE spillover and QT variability in patients with essential hypertension. Hypertension is associated with increased cardiac and vascular sympathetic activity as well as with an increased risk for arrhythmia (12, 16, 22) and therefore provides a suitable model to study the relationship between QT interval variability and cardiac sympathetic activation.

METHODS

Subjects. The study cohort comprised a subsample of 23 patients with essential hypertension and 9 normotensive subjects who were drawn from an earlier study examining sympathetic activation in hypertension (31). Demographic data are summarized in Table 1. None of the patients had accelerated hypertension, clinical coronary artery disease, heart failure, history of stroke, renal insufficiency, or diabetes mellitus. A previous use of antihypertensive therapy was reported in 11 hypertensive subjects. Antihypertensive therapy was discontinued for at least 4 wk before the study.

Normotensive subjects underwent careful clinical evaluation and serum biochemistry measurements to exclude renal and hepatic disease. None of the subjects had a history of incidental disease or blood pressure (BP) > 140/85 mmHg.

BP readings were taken according to World Health Organization recommendations (1). During screening, subjects were classified as normotensive if the average of four casual BP measurements taken in our outpatient clinic were <140 mmHg systolic and <90 mmHg diastolic on two different occasions. Subjects were classified as hypertensive if the mean of four casual BP measurements taken in the outpatient clinic was >140 mmHg systolic or >90 mmHg diastolic on...
Table 1. Clinical characteristics of the study cohort

<table>
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<tbody>
<tr>
<td>Age, yr</td>
<td>38±13</td>
<td>44±12</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>22.8±3.9</td>
<td>28.1±5.8*</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>65±6</td>
<td>62±10</td>
</tr>
<tr>
<td>Intra-arterial systolic BP, mmHg</td>
<td>128±12</td>
<td>166±14*</td>
</tr>
<tr>
<td>Intra-arterial diastolic BP, mmHg</td>
<td>68±7</td>
<td>84±8*</td>
</tr>
<tr>
<td>Left ventricular mass index, g/m²</td>
<td>89±13</td>
<td>128±29*</td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>4.80±0.77</td>
<td>5.40±0.95</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/l</td>
<td>2.98±0.57</td>
<td>3.41±0.86</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.31±0.34</td>
<td>1.26±0.36</td>
</tr>
<tr>
<td>Plasma sodium, mmol/l</td>
<td>142±2</td>
<td>142±2</td>
</tr>
<tr>
<td>Plasma potassium, mmol/l</td>
<td>4.2±0.3</td>
<td>4.3±0.3</td>
</tr>
</tbody>
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Values are means ± SD; n, number of subjects. NT, normotensive; EH, essential hypertensive. *P < 0.01.

To explain the data above, two different occasions. These were confirmed by intra-arterial BP measurements during catheterization. The study protocol was approved by the Alfred Hospital Ethics Review Committee, and all participants provided written informed consent.

The study commenced in the morning after an overnight fasting period >12 h with abstinence from smoking, alcohol, tea, and coffee.

Echocardiography. Two-dimensional-guided M-mode echocardiography was performed in all subjects, using a Sonos5500 (Agilent Technologies). LV dimensions and mass were quantified according to the recommendations of the American Society of Echocardiography (7). LV mass was corrected following the suggestions of Devereux et al. (10). Detailed results of the echocardiographic assessment have been previously presented (31).

Cardiac NE spillover measurement. This procedure has been previously described in detail (13). Participants received a tracer infusion of [¹³¹I]NE (specific activity of 11–25 Ci/mmol; New England Nuclear) via a peripheral vein at 0.6 to 0.8 µCi/min, after a priming bolus of 12 µCi under local anesthesia. The radial artery was cannulated for arterial BP monitoring and blood sampling. A venous introducer sheath was placed in the antecubital fossa, and a coronary sinus sheath was placed under fluoroscopic control in the coronary sinus for blood sampling. For the calculation of NE kinetics, coronary sinus blood flow was estimated based on previously published equations (13). Plasma concentrations of compounds required for the calculation of NE spillover were determined by high-performance liquid chromatography (20).

ECG analysis. Body surface ECG (lead III) was recorded at a sampling frequency of 1,000 Hz, using PowerLab and the LabChart software (ADInstruments). All ECG recordings were visually scanned to exclude artefacts. To obtain beat-to-beat QT intervals, we applied the algorithm proposed by Berger et al. (6). Here the operator defines a template QT interval by selecting the beginning of the QRS complex and the end of the T wave for one beat. The algorithm then finds the QT interval of all other beats by determining how much the template must be stretched or compressed in time to best match each T wave.

In this way, a relatively robust estimation of QT interval is achieved that takes into consideration the whole T wave instead of commonly applied threshold techniques that are based on determining the end of the T wave and are therefore sensitive to artefacts and noise. We computed the QT variability index (QTVI) defined as in Berger et al. (6):

\[
QTVI = \log \left( \frac{QTVN}{QTm} \right) / \log \left( \frac{RRVN}{RRm} \right) = QTVN/RRVN
\]

where the numerator (QTVN) contains the variance of all QT intervals (QTₜ) divided by the square of the mean QT interval (QTₚ). The denominator (RRVN) contains the variance of RR intervals (RRₚ) divided by the squared mean RR interval (RRₚ). The logarithm is taken for statistical reasons to ensure a normal distribution of the otherwise skewed QTVI distribution. Furthermore, we computed the coherence function between the power spectra of QT and RR interval time series as described in Berger et al. (6). In addition, we also computed the rate-corrected QT interval based on Bazett’s formula.

Statistics. Results are presented as means ± SD. Between-group comparisons of variables were carried out using Student’s t-test. Two-sided P < 0.05 was considered statistically significant. Associations between variables were investigated using Pearson’s correlation coefficient. Furthermore, stepwise multiple linear regression was conducted to identify predictors of QT interval variability.

RESULTS

Demographic data, cardiovascular indexes, and serum biochemical data of the study cohort are presented in Table 1. Body mass index, intra-arterial BP, and LV mass index were significantly higher in hypertensive patients compared with normotensive subjects. At the time of testing, 21 out of 23 patients had isolated systolic hypertension. There were no significant group differences in biochemical markers.

Parameters of NE kinetics are presented in Table 2. Mean arterial plasma NE concentration and average NE clearance were not significantly different between normotensive and hypertensive subjects. As noted previously (31), whole body NE spillover was elevated in hypertensive patients compared with normotensive subjects. Coronary sinus plasma flow and fractional transcardiac [¹³¹I]NE extraction were comparable between both groups. Cardiac NE spillover was increased in hypertensive subjects and correlated with systolic BP (r² = 0.20, P = 0.009, Fig. 1) but not with diastolic BP. However, when excluding the outlier, this correlation became nonsignificant.

ECC parameters are detailed in Table 3. The QTVI was significantly elevated in hypertensive patients compared with normotensive subjects. None of the other QT measures was significantly different between groups. Correlation analysis revealed a significant relationship between QT interval variability (QTVN) and cardiac NE spillover (r² = 0.31, P = 0.001). Subgroup correlation analysis, performed separately for the normotensive and the hypertensive group, showed a significant correlation between QTVN and cardiac NE spillover in hypertensive subjects (r² = 0.38, P = 0.002, Fig. 2) but not in normotensive subjects. Furthermore, QTVN was correlated with resting systolic BP (all subjects; r² = 0.16, P = 0.02, Fig. 1). There was no significant correlation between QTVI and cardiac NE spillover.

Comparing QTVN to other ECG-based indexes revealed moderate significant correlations with QTVI (r² = 0.17, P = 0.01).
Subgroup correlation analysis between QTVN and RRVN revealed a significant association between both in hypertensive patients ($r^2 = 0.33$, $P = 0.004$) but not in normotensive patients (Fig. 3). There was no significant correlation between RRVN and cardiac NE spillover.

Stepwise multiple linear regression analysis with QTVN as the dependent variable and all other measures obtained in this study as independent variables identified only cardiac NE spillover ($\beta = 0.54$, $t = 3.6$, $P < 0.002$) and RRVN ($\beta = 0.43$, $t = 2.8$, $P = 0.01$) as independent predictors, resulting in a significant model with an adjusted $R^2 = 0.51$ (ANOVA; $P < 0.001$).

**DISCUSSION**

Our major novel finding is the relationship between directly assessed cardiac sympathetic activity and beat-to-beat QT variability in humans. The amount of cardiac NE spillover is correlated to the magnitude of beat-to-beat fluctuations of the QT interval in patients with hypertension.

In our cohort of hypertensive patients, QTVi and cardiac NE spillover were elevated compared with normotensive subjects, demonstrating that ventricular repolarization lability and cardiac sympathetic activation are increased, which is in line with previous findings (26). Moreover, a correlation analysis of our data provides the first direct evidence that the magnitude of QT variability is related to cardiac sympathetic activation in hypertensive patients. QT variability was also partially correlated with systolic BP, possibly demonstrating the relationship between myocardial contractility and QT variability.
It is well established that the average QT interval of the body surface ECG is modulated by the autonomic nervous system (11, 37), and our data suggest that this autonomic influence extends to beat-to-beat fluctuations of the QT interval. Although the underlying mechanisms are currently unknown, the lack of homogeneity of β-adrenoceptors and variable arborization of the sympathetic nerves (25, 37) may contribute to spatial dispersion in the action potential duration in the ventricular myocardium and thereby increase QT interval variability during periods of higher sympathetic activity. In support of this view, patients with autonomic failure and heterogeneous autonomic denervation showed prolonged QT intervals and dogs displayed a relationship between left stellate-ganglion activity and QT variability, but only after they developed heart failure (28), suggesting that myocardial structural damage as well as sympathetic activation may be required.

Although cardiac NE spillover was the main contributor to QT variability in our hypertensive patients, it explained only around 30% of its variance. Stepwise linear regression analysis further identified RR variability as an independent contributor to QT variability that accounts for a small portion of variance (~15%) and most likely reflects electrical restitution (14). The relationship between cycle length and action potential duration is complex and involves long-lasting adjustments (14), and therefore the association between QT variability and RR variability is rather weak. Dynamic linear parametric modeling of the RT-RR relationship suggests that, in particular, very low frequency power of RT variability is largely independent of RR variability in normal subjects (29). Furthermore, multiscale entropy and detrended fluctuation analyses of the QT time series revealed markedly different temporal organization and complexity compared with the RR time series and provided additional evidence for the weak dependence of beat-to-beat QT variability in normal subjects (29).

Fig. 3. Relationship between RR variability (RRVN) and QTVN in hypertensive patients (A) and normotensive subjects (B).
variability on RR variability (M. Baumert, M. Javorka, A. Seeck, R. Faber, and A. Voss; unpublished observations).

In clinical research, beat-to-beat QT variability is often considered in its normalized form QTv, i.e., as the ratio of QT variability to RR variability, both divided by the squared means of QT and RR intervals, respectively. The interpretation of this simple index is rather difficult. Instead of removing the part of QT variability that is attributed to heart rate, RR variability is explicitly introduced into the equation. Consequently, a change in QT variability can be caused by a change in QT variability and/or RR variability. As the magnitude of RR variability is usually higher than that of QT variability and resting RR variability is not correlated with cardiac NE spillover (3, 24), the lack of association between QTv and cardiac NE spillover is not unexpected.

Technical considerations and limitations. Beat-to-beat fluctuations in the QT interval are typically small, and measurement noise might have a considerable impact on QT variability measures. In this study we were only able to record one ECG lead. Because QT variability is dependent on the recording site, we consistently used lead III. Because of the invasive nature of the study, the control group was relatively small, which limited the statistical power of our study. We therefore cannot exclude the possibility of a weak correlation between cardiac NE spillover and QTv in normal subjects. One subject in the hypertensive group had very high QTv and cardiac NE spillover values and might have been the major driver of the significant correlation. However, the correlation between cardiac NE spillover and QTv remained significant when excluding this subject from the analysis.

Conclusions. A cross-sectional analysis of patients with hypertension shows a moderate yet significant correlation between cardiac NE spillover and QT variability. QT interval variability in patients with cardiovascular disease may therefore partly reflect cardiac sympathetic activation.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

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