Relation between QT interval variability and cardiac sympathetic activity in hypertension

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Running title: QT variability and sympathetic activity

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Abstract

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 nine normotensive control subjects. To assess beat-to-beat QT interval variability we calculated 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) as well as QTVi (-1.75 ± 0.36 vs. -1.42 ± 0.50, p = 0.05) were significantly increased in hypertensive patients compared to normotensive subjects. QTVN was significantly correlated with cardiac NE spillover ($r^2 = 0.31$, $p = 0.001$), RR variability ($r^2 = 0.20$, $p = 0.008$) and with systolic blood pressure ($r^2 = 0.16$, $p = 0.02$). Linear regression analysis identified the former two as independent predictors of QTVN. In conclusion, elevated repolarisation lability is directly associated with sympathetic cardiac activation in patients with essential hypertension.
Introduction

The QT interval of the body surface ECG reflects global depolarisation and repolarisation 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 non-cardiac conditions (5, 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 VT/VF events (33). Furthermore, QT variability was associated with an increased risk of VT/VF in patients enrolled in the MADIT II trial (17) and was predictive of sudden cardiac death in asymptomatic chronic heart failure patients with mild to moderate 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 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 (3).

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 relation between QT interval variability and cardiac sympathetic activation.

Methods

Subjects

The study cohort comprised a subsample of 23 patients with essential hypertension (EH) and 9 normotensive subjects (NT) 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, a history of stroke, renal insufficiency or diabetes mellitus. Previous use of antihypertensive therapy was reported in eleven hypertensive subjects. Antihypertensive therapy was discontinued for at least four weeks 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 >140/85 mm Hg. Blood pressure (BP) readings were taken according to WHO 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 two different occasions. These were confirmed by intra-arterial BP measurements during catheterisation (see
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 >12h 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, USA. 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 (10). Detailed results of the echocardiographic assessment have been presented previously (31).

**Cardiac NE spillover measurement**

This procedure has been previously described in detail (13). Participants received a tracer infusion of $^3$H-labeled norepinephrine (specific activity of 11-25Ci/mmol; New England Nuclear, USA) via a peripheral vein at 0.6 to 0.8 μCi/min, after a priming bolus of 12 μCi under local anaesthesia. The radial artery was cannulated for arterial blood pressure monitoring and blood sampling. A venous introducer sheath was placed in the antecubital fossa and a coronary sinus thermodilution catheter (Webster CCS 7/8U90A, Webster Laboratories, USA) was introduced via the venous sheath and 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 1000 Hz, using
PowerLab® and the LabChart® software (ADI Instruments, Australia). 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 (6):

\[ QTVi = \log \left( \frac{(QT_v/\text{mean QT}^2)}{(RR_v/\text{mean RR}^2)} \right) = \frac{QTVN}{RRVN}, \]

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

Results are presented as mean and standard deviation. 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. Further, stepwise multiple linear regression was conducted to identify predictors of QT interval variability.

Results

Demographic data, cardiovascular indices and serum biochemical data of the study cohort are presented in Table 1. Body-mass index, intra-arterial blood pressure and LV mass index were significantly higher in hypertensive patients compared to 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 to normotensive subjects. Coronary sinus plasma flow and fractional transcardiac \([^3]H\)NE extraction were comparable between both groups. Cardiac NE spillover was increased in hypertensive subjects and correlated with systolic BP \( (r^2 = 0.20, \ p = 0.009, \text{ Fig. 1}) \), but not with diastolic BP. However, when excluding the outlier this correlation became non-significant.
ECG parameters are detailed in Table 3. The QT variability index (QTVi) was significantly elevated in hypertensive patients compared to 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 ($r^2 = 0.31, p = 0.001$). 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 ($r^2 = 0.38, p = 0.002$, Fig. 2), but not in normotensive subjects. Further, QTVN was correlated with resting systolic BP (all subjects; $r^2 = 0.16, p = 0.02$, Fig. 1). There was no significant correlation between QTVi and cardiac NE spillover. Comparing QTVN to other ECG-based indices revealed moderate significant correlations with QTVI ($r^2 = 0.17, p = 0.02$), RRVN ($r^2 = 0.20, p = 0.008$), QTv ($r^2 = 0.94, p < 0.001$) and RRv ($r^2 = 0.25, p = 0.04$). 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 relation 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 as well as cardiac NE spillover were elevated compared to normotensive subjects, demonstrating that ventricular repolarisation lability as well as cardiac sympathetic activation are increased, which is in line with previous findings (26). Moreover, 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 blood pressure, 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, lack of homogeneity of β-adrenoceptors and variable arborisation 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 increased spatial QT dispersion (8). Beta-adrenoceptor activation by isoprotenerol has been
shown to increase beat-to-beat QT variability in healthy subjects during sinus rhythm (35), and β-adrenoceptor blockade with propranolol decreased QT variability during atrial pacing in patients without structural heart disease; observations suggestive that QT variability is modulated by the sympathetic nervous system (23). However, a study of left stellate-ganglion activity in healthy dogs showed no correlation with QT variability (28), indicating that spontaneous QT variability in the normal heart is not notably affected by the sympathetic outflow to the ventricular myocardium.

Our current data suggest a more differentiated picture. QT variability in humans appears to be associated with cardiac sympathetic activity, but not in resting subjects without an underlying cardiovascular condition. In agreement with our earlier work on patients with depression and panic disorder (3) the normotensive subjects in our current study did not show a relation between cardiac NE spillover and QT variability. However, the novel finding of this study is that in hypertensive patients QT variability was moderately correlated with cardiac NE spillover. Normotensive subjects might not display such a correlation because resting NE spillover levels are low and sympathetic activation might be required for the correlation between cardiac NE spillover and QT variability to occur. In support of this view, graded head-up tilt of healthy subjects has shown to progressively increase the fraction of QT variability that is independent of RR variability and respiration and is possibly related to sympathetic activation (30). Alternatively, additional change in the cardiac substrate might be necessary for the correlation between cardiac NE spillover and QT variability to occur. In line with this view, dogs displayed a relation 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.
The mechanisms by which subjects develop an association between cardiac sympathetic activity and QT variability are not clear. Results from selective versus combined pharmacological block of slow and rapid outward potassium currents in rabbits and dogs imply that reduction in repolarisation reserve may be an important mechanism for augmenting QT variability (21). A study of isolated canine myocytes found that isoprotenerol infusion during \( I_{Ks} \) block increased beat-to-beat variability of repolarisation (18). There are several lines of evidence for an association between sympathetic activation and subclinical organ damage in humans (19). Sympathetic activation promotes left ventricular hypertrophy (31) and LV diastolic dysfunction (16). In particular, the density and distribution of adrenoceptors throughout the ventricular myocardium might be altered. Global and regional cardiac (123)I-MIBG uptake was shown to be altered in hypertensive patients with left ventricular hypertrophy compared to normotensive subjects (15).

Although cardiac NE spillover was the main contributor to QT variability in our hypertensive patients, it explained only around 30 percent of its variance. Stepwise linear regression analysis further identified RRVN as an independent contributor to QT variability that accounts for a small portion of variance (≈15 percent) and most likely reflects electrical restitution (14). The relation between cycle length and action potential duration is complex and involves long-lasting adjustments (14) and therefore the association between QTVN and RRVN is rather weak. Dynamic linear parametric modelling of the RT-RR relation suggests that in particular very low frequency power of RT variability is largely independent of RR variability in normal subjects (29). Further, multiscale entropy and detrended fluctuation analyses of the QT time series...
revealed markedly different temporal organisation and complexity compared to the RR time series and provided additional evidence for the weak dependence of beat-to-beat QT variability on RR variability (2).

In clinical research, beat-to-beat QT variability is often considered in its ‘normalized’ form QTVi, 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 QTVi 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 (4, 24) the lack of association between QTVi 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. As QT variability is dependent on the recording site we consistently used lead III. Due to 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 QTVN in normal subjects. One subject in the hypertensive group had very high QTVN and cardiac NE spillover values and might have been the major driver of the significant correlation. However, the correlation between cardiac NE
spillover and QTVN remained significant when excluding this subject from the analysis.

Conclusions

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

Acknowledgements

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Figure 1. Relation between cardiac NE spillover and systolic blood pressure (A) and between systolic blood pressure and QTVN (B).

Figure 2. Relation between QT variability (QTVN) and cardiac NE spillover in hypertensive patients (A) and normotensive subjects (B).

Figure 3. Relation between RR variability (RRVN) and QT variability (QTVN) in hypertensive patients (A) and normotensive subjects (B).
### Table 1. Clinical characteristics of the study cohort

<table>
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<tr>
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<th>NT (n = 9)</th>
<th>EH (n=23)</th>
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<tbody>
<tr>
<td>Gender male/female</td>
<td>7/2</td>
<td>17/6</td>
</tr>
<tr>
<td>Age [years]</td>
<td>38 ± 13</td>
<td>44 ± 12</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>22.8 ± 3.9</td>
<td>28.1 ± 5.8*</td>
</tr>
<tr>
<td>Heart rate [bpm]</td>
<td>65 ± 6</td>
<td>62 ± 10</td>
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<tr>
<td>Intra-arterial systolic BP [mm Hg]</td>
<td>128 ± 12</td>
<td>166 ± 14*</td>
</tr>
<tr>
<td>Intra-arterial diastolic BP [mm Hg]</td>
<td>68 ± 7</td>
<td>84 ± 8*</td>
</tr>
<tr>
<td>LV mass index [g/m²]</td>
<td>89 ± 13</td>
<td>128 ± 29*</td>
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<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 ± 3</td>
<td>142 ± 2</td>
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<tr>
<td>Plasma potassium [mmol/l]</td>
<td>4.2 ± 0.3</td>
<td>4.3 ± 0.3</td>
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Data are presented as mean ± SD  
* p < 0.01

### Table 2. NE plasma kinetics.

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<th>NT (n = 9)</th>
<th>EH (n=23)</th>
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<tr>
<td>Arterial NE plasma concentration [pg/ml]</td>
<td>198 ± 42</td>
<td>260 ± 100</td>
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<tr>
<td>Coronary sinus NE plasma concentration [pg/ml]</td>
<td>194 ± 55</td>
<td>253.7 ± 104*</td>
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<tr>
<td>Coronary sinus plasma flow [ml/min]</td>
<td>82.6 ± 16.6</td>
<td>90.6 ± 29.2</td>
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<tr>
<td>Fractional transcardiac [³H]NE extraction [%]</td>
<td>0.69 ± 0.11</td>
<td>0.59 ± 0.15</td>
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<tr>
<td>NE plasma clearance [ml/min]</td>
<td>1302 ± 520</td>
<td>1557 ± 620</td>
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<tr>
<td>Whole body NE spillover</td>
<td>254 ± 115</td>
<td>402 ± 209*</td>
</tr>
<tr>
<td>Cardiac NE spillover [ng/min]</td>
<td>12.2 ± 6.5</td>
<td>20.7 ± 14.7*</td>
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Data are presented as mean ± SD  
* p < 0.05

### Table 3. QT interval variability.

<table>
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<th>NT (n = 9)</th>
<th>EH (n=23)</th>
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<tbody>
<tr>
<td>QTₘ [ms]</td>
<td>395 ± 51</td>
<td>397 ± 50</td>
</tr>
<tr>
<td>QTₙ [ms]</td>
<td>409 ± 39</td>
<td>403 ± 44</td>
</tr>
<tr>
<td>QT/Vi</td>
<td>-1.75 ± 0.36</td>
<td>-1.42 ± 0.50*</td>
</tr>
<tr>
<td>QT/RR coherence</td>
<td>0.49 ± 0.22</td>
<td>0.36 ± 18</td>
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<tr>
<td>QT/VN *1000</td>
<td>0.09 ± 0.06</td>
<td>0.13 ± 0.11</td>
</tr>
<tr>
<td>RR/VN *1000</td>
<td>5.02 ± 4.60</td>
<td>4.22 ± 5.63</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD  
* p < 0.05
A

\[ r^2 = 0.20, \ p = 0.009 \]

B

\[ r^2 = 0.16, \ p = 0.02 \]
A

$r^2 = 0.38, p = 0.002$

B

$r^2 = 0.20, p = 0.23$
A

$r^2 = 0.33, p = 0.004$

B

$r^2 = 0.09, p = 0.66$