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QT interval variability and cardiac norepinephrine spillover in patients with depression and panic disorder

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Baumert M, Lambert GW, Dawood T, Lambert EA, Esler MD, McGrane M, Barton D, Nalivaiko E. QT interval variability and cardiac norepinephrine spillover in patients with depression and panic disorder. *Am J Physiol Heart Circ Physiol* 295: H962–H968, 2008. First published July 3, 2008; doi:10.1152/ajpheart.00301.2008.—Suggestions were made that increased myocardial sympathetic activity is reflected by elevated QT variability (dynamic changes in QT interval duration). However, the relationship between QT variability and the amount of norepinephrine released from the cardiac sympathetic terminals is unknown. We thus attempted to assess this relationship. The study was performed in 17 subjects (12 with major depressive disorder and 5 with panic disorder). Cardiac norepinephrine spillover (measured by direct catheter technique coupled with norepinephrine isotope dilution methodology) was assessed before and 4 mo after treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants. The distribution of the cardiac norepinephrine spillover was bimodal, with the majority of patients having values of ≤ 10 ng/min. There was a positive correlation between cardiac norepinephrine spillover and corrected QT interval ($r = 0.7$, $P = 0.03$) but not with any of the QT variability measures. However, in a subgroup of five patients who had high levels of cardiac norepinephrine spillover (>20 ng/min) a tendency for a strong positive correlation with variance of QT intervals ($r = 0.9$, $P = 0.08$) was observed. There were significant correlations between the severity of depression and QT variability indexes normalized to the heart rate [QT/RR and QT interval/RR interval (QT/RR) coherence] and between the severity of anxiety and the QT/RR residual and regression coefficient, respectively. Treatment with SSRI antidepressants substantially reduced depression score but did not affect any of the QT variability indexes. We conclude that in depression/panic disorder patients with near-normal cardiac norepinephrine levels QT variability is not correlated with cardiac norepinephrine spillover and is not affected by treatment with SSRI.

sympathetic activity; antidepressants

AN EXCESSIVE CARDIAC SYMPATHETIC activity is a recognized risk factor for cardiac morbidity and mortality. In a range of clinical contexts, elevated cardiac sympathetic outflow has been demonstrated to contribute to ventricular arrhythmias (10), sudden death (6), myocardial stunning (21), and left ventricular hypertrophy (19). Direct assessment of norepinephrine (NE) spillover (the “gold standard” for assessing cardiac sympathetic activity) is a complex, invasive procedure, and cardiac sympathetic activity is still most frequently assessed by measuring mean heart rate or assessing its dynamic variability (1). Obviously, heart rate reflects autonomic influences only at the level of the cardiac pacemaker

region. Because different regions of the heart could be under independent autonomic control (7, 12, 13), it becomes increasingly evident that indexes reflecting sympathetic influences in the ventricular myocardium might be of better predictive and diagnostic value. In an attempt to assess these autonomic influences, QT variability (dynamic changes in QT interval duration, an index reflecting temporal changes in the duration of ventricular repolarization) was introduced a decade ago. Since then, a number of studies have presented evidence that increased myocardial sympathetic activity may be reflected by elevated QT variability (see DISCUSSION). To this juncture, however, there have been no studies that have compared QT variability values with directly measured NE release in the heart from the sympathetic terminals. This was the aim of the present study.

Using direct cardiac catheter techniques coupled with NE isotope dilution methodology, we recently demonstrated (2) that sympathetic activity in patients with major depressive disorder (MDD) follows a bimodal distribution, with some values being extraordinarily high and others being very low. Interestingly, after therapy with a selective serotonin reuptake inhibitor (SSRI), cardiac and whole body NE spillover was significantly reduced only in those subjects with the initially elevated sympathetic activity. Using a subset of patients from this previous study, we report here the relationship between cardiac NE spillover values and several indexes derived from beat-to-beat QT interval measurements. To overcome the traditional difficulties associated with the detection of the T-wave terminus, we used the template-matching algorithm developed by Berger et al. (4).

METHODS

Patients. Twelve patients with MDD (5 men, 7 women; age 45 ± 15 yr) and five patients with panic disorder (PD; 3 men, 2 women; age 32 ± 9 yr) were included in this study. All patients were screened for inclusion with two diagnostic instruments: the Mini International Neuropsychiatric Interview (MINI) and the Composite International Diagnostic Interview (CIDI). The Hamilton Depression Scale and Hamilton Anxiety Rating Scale (HamD and HamA, respectively), the Clinical Global Impressions scale (CGI), and the Beck Depression Inventory (BDI-1) were used to monitor progress. Subjects who met all of the following criteria were eligible for entry: HamD > 18 , BDI > 18 , positivity for MDD/PD on MINI and CIDI, and assessment as having a significant major depression or PD as the primary illness on interview by a psychiatrist.

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Initial studies were performed within 10 days of a confirmed diagnosis of MDD/PD. Patients then commenced treatment with a SSRI according to standard dosing ranges for antidepressants ($n = 13$ citalopram; $n = 1$ fluvoxamine; $n = 3$ sertraline). The choice of SSRI was based on clinical grounds and was made by the participating psychiatrist in consultation with the participant. No treatment other than SSRI was prescribed. Research studies were repeated after ~ 16 wk of therapy (116 ± 70 days). Patients were reviewed weekly for the purposes of the study, or more frequently if required on clinical grounds.

All investigations were performed with subjects in the supine position. Studies were conducted in the morning, and caffeinated beverages and tobacco smoking were prohibited for 12 h before the

study. Exclusion criteria included coexistence of any of the following: heart disease, diabetes, medicated hypertension, alcohol/drug abuse, infectious diseases, comorbid psychotic disorders, eating disorders, mental retardation, high suicide risk, personality disorders, and epilepsy. All patients provided written informed consent. The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Research and Ethics Committee of the Alfred Hospital, Melbourne, Australia.

ECG recording. Body surface ECG (lead III) was recorded before the NE spillover measurement over 5 min under resting conditions in the supine position at a sampling frequency of 1,000 Hz, with PowerLab and Chart software (AD Instruments). The patients rested for at least 20 min before the actual recording started.

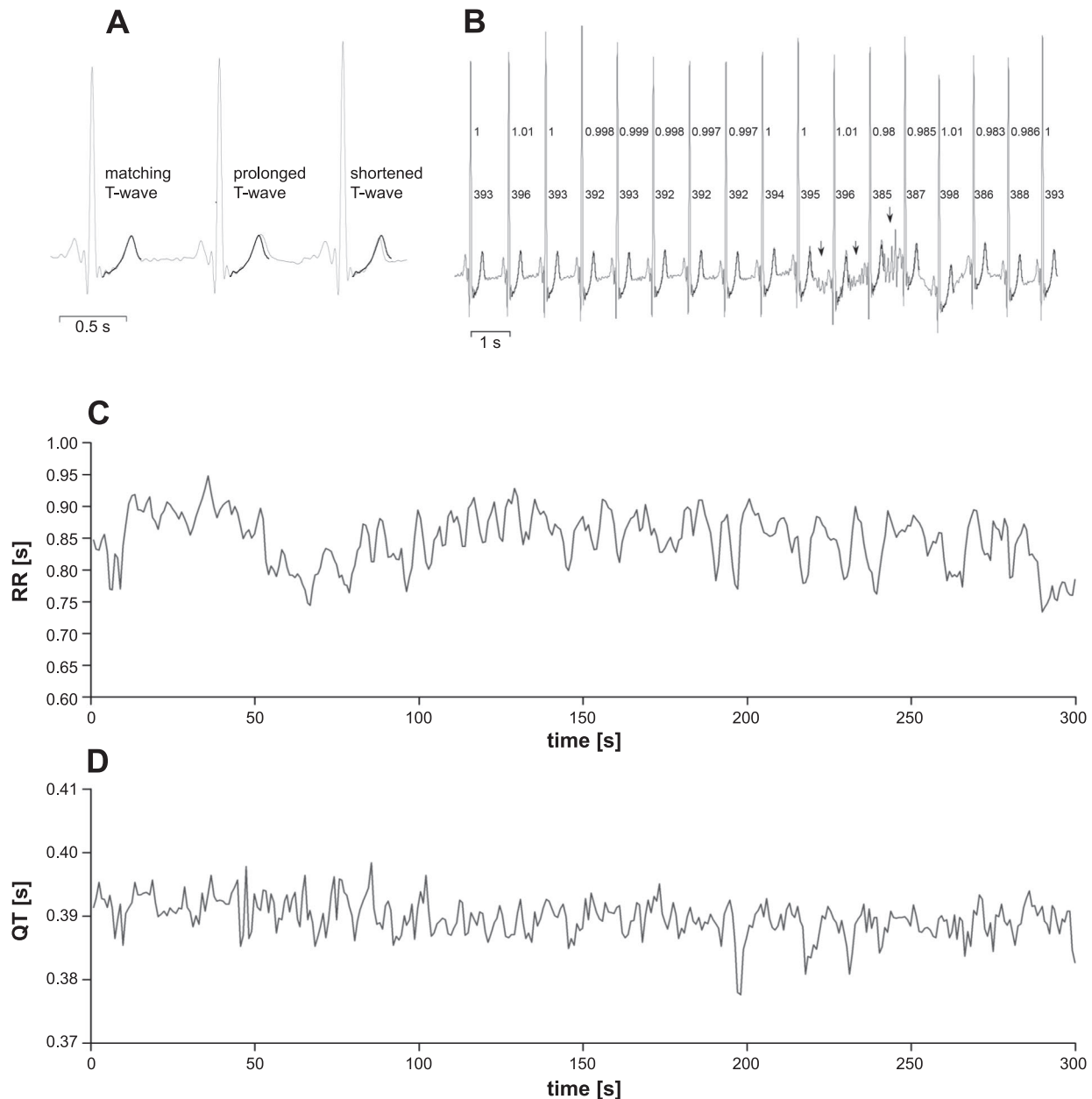


Fig. 1. Beat-to-beat QT interval measurement. **A:** an operator-defined template of the T wave (bold) is compared with the T wave of each heartbeat by cross-correlation (*top*). **B:** to measure the change in QT interval, the template is then compressed or dilated to maximize the match at each beat. The 15-s example ECG traces illustrates beat-to-beat changes in the QT interval, where the *top* values represent the compression/dilation factor and the *bottom* values the corresponding QT intervals (in ms). The algorithm is robust to artifacts and noise, as indicated by the arrows. **C:** R-R interval time series for the complete 5-min recording. **D:** QT interval time series for the complete 5-min recording.

Cardiac norepinephrine spillover. This procedure was described in detail previously (2). Briefly, a 6-F coronary sinus angiographic catheter (Cordis Europa, Roden, The Netherlands) was introduced via the antecubital venous sheath and placed under fluoroscopic control in the coronary sinus for blood sampling. Coronary sinus blood flow was estimated from the double product (systolic blood pressure $\times$ heart rate), as described previously (2). During the catheter study participants received a tracer infusion of ^3H -labeled NE (specific activity of 11–25 Ci/mmol; New England Nuclear, Boston, MA) via a peripheral vein at 0.6–0.8 $\mu\text{Ci}/\text{min}$, after a priming bolus of 12 μCi , for the measurement of NE kinetics by isotope dilution.

QT interval variability analysis. To obtain beat-to-beat QT intervals, we applied the algorithm proposed by Berger et al. (4). 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 each T wave must be stretched or compressed in time to best match the template (Fig. 1). 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 therefore sensitive to artifacts and noise. To assess QT variability, we computed the following measures.

QT variability index (QTVi) was defined as in Ref. 4:

$$\text{QTVi} = \log[(\text{QT}_{\text{var}}/\text{meanQT}^2)/(\text{RR}_{\text{var}}/\text{meanRR}^2)]$$

where the numerator contains the variance of all QT intervals (QT_{var}) normalized to the square of the mean QT interval (meanQT). The denominator contains the variance of R-R intervals (RR_{var}) normalized to the squared mean R-R interval (meanRR). The logarithm is taken purely for statistical reasons, i.e., to ensure a normal distribution of the otherwise skewed QTVi distribution.

QT_{var} , variance of beat-to-beat QT intervals without any normalization (in ms^2), indicates how much the beat-to-beat QT interval fluctuates around the mean QT interval.

QTc is QT interval (in ms) corrected for heart rate. We applied a method proposed by Malik et al. (9, 17) for individual-specific rate correction of the QT interval. A parabolic function was used to describe the QT/RR relationship, i.e., $\text{QT} = \beta(\text{RR})^\alpha$, where the regression coefficients α and β as well as the average heart period RR are individually estimated for each recording, minimizing the residual of the $[\text{QT}_i, \text{RR}_i]$ regression fit. RR is computed as the sum of weighted N previous R-R intervals

$$\overline{\text{RR}}_i = \sum_{j=-N+1}^0 w_j \text{RR}_{i+j}$$

where the weights w are individually estimated with a global optimization algorithm. Constraints of the optimizations are

$$\sum_{j=-N+1}^0 w_j = 1 \text{ and } 0 \leq w_j \leq 1$$

and $0 \leq w_j \leq 1$. N was set such that the R-R intervals of the previous 2 min were taken into consideration for estimating RR. Consequently, RR_i values were obtained for the last 3 min of the 5-min recordings.

QT/RR α , α coefficient of the parabolic $[\text{QT}_i, \text{RR}_i]$ fit, was computed with the optimum weight distribution.

Lag₉₀, hysteresis estimate of the QT rate adaptation, was derived from the index j_0 , where the cumulative sum $H(j)$ of individually optimized weights w_k reached 0.9, i.e.,

$$H(j) = \sum_{k=-n+1}^j w_k = 0.9, j = -N+1, \dots, 0$$

The hysteresis is then computed as $\text{Lag}_{90} = \text{RR}_{\text{mean}}(-j_0)$, reflecting the time down to which the RR history has an effective influence on the optimum $[\text{QT}_i, \text{RR}_i]$ fit (in s).

QT/RR r , global regression residual of the $[\text{QT}_i, \text{RR}_i]$ fit, was computed with the parabolic regression function and optimum weight distribution, i.e.,

$$r = \sqrt{\sum_{i=1}^{N_T} \frac{1}{N_T} [\text{QT}_i - \beta(\overline{\text{RR}}_i)^\alpha]^2}$$

reflecting the strength of the QT interval dependence on heart rate (in s); N_T is a total number of QT and RR pairs.

QT/RR coherence, the average coherence between the R-R and QT power spectrum in the frequency range of 0–0.2 Hz, reflects the similarity between slow oscillations in R-R and QT interval. It ranges between 0 (no similarity) and 1 (identical).

Statistics. To test treatment effects of SSRIs on cardiac NE spillover and QT variability measures we applied the nonparametric Wilcoxon test for paired measurements. Correlation analysis between QT variability measures and cardiac NE spillover was performed by applying the nonparametric Spearman correlation coefficient.

RESULTS

Effects of SSRI treatment on depression/panic symptoms. In the MDD group, depression symptom scores (as measured by the HamD and BDI scales) as well as anxiety scores were reduced significantly after treatment with SSRIs (Table 1). In the PD group, the HamA score was reduced significantly after treatment, but the anxiety trait and state scores were not altered by SSRI treatment (Table 1). These results have already been reported in a larger sample (2).

Correlation analysis. Correlation analyses between NE spillover and QT variability measures were performed on the data of the 17 patients (depressed and panic disorder) obtained before SSRI treatment. As described in our previous larger study from which the present data were selected (2), the distribution of the cardiac NE spillover was bimodal, with the majority of patients having values of ≤ 10

Table 1. Characteristics of patients with major depressive disorder and panic disorder before and after 16 wk of treatment with SSRIs

	MDD		PD	
	Pre	Post	Pre	Post
BMI, kg/m ²	26.9 $\pm$ 4.5	26.6 $\pm$ 4.3	25.8 $\pm$ 2.4	25.6 $\pm$ 1.1
HamD	26 $\pm$ 4	5 $\pm$ 4*		
HamA			24 $\pm$ 7	6 $\pm$ 5*
BDI	27 $\pm$ 4	8 $\pm$ 5*		
Anxiety trait	63 $\pm$ 7	46 $\pm$ 8*	47 $\pm$ 7	35 $\pm$ 8
Anxiety state	55 $\pm$ 11	38 $\pm$ 9*	43 $\pm$ 14	32 $\pm$ 12

Data are means $\pm$ SD for 5/7 (age 45 $\pm$ 15 yr) and 3/2 (age 32 $\pm$ 9 yr) men and women in major depressive disorder (MDD) and panic disorder (PD) groups, respectively, treated with selective serotonin reuptake inhibitors (SSRIs). Pre, before treatment; Post, after treatment; BMI, body mass index; HamD, Hamilton Depression Rating Scale; HamA, Hamilton Anxiety Rating Scale; BDI, Beck Depression Inventory. *Statistically significant changes after treatment within groups ($P < 0.05$).

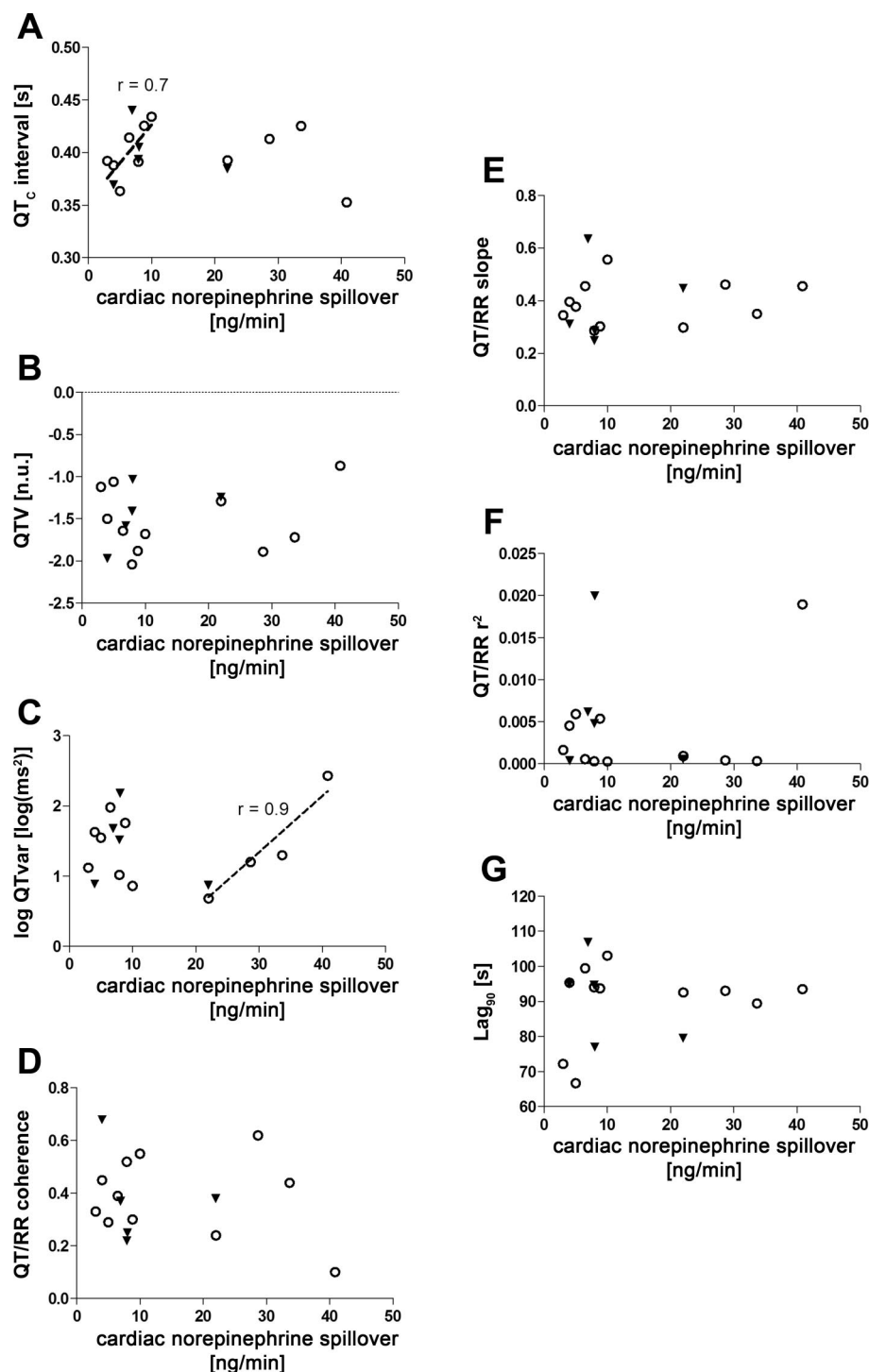


Fig. 2. Graphs showing correlation between cardiac norepinephrine (NE) spillover and QTc (A) and log QT_{var} (C) in 2 different subsets of patients and lack of correlation between cardiac NE spillover and other QT interval variability indices (B, D–G). Data from subjects with depressive (○) and panic (▼) disorders are shown. Note that for the majority of subjects, NE spillover values did not exceed 10 ng/min. QT variability measures are defined in METHODS.

ng/min (Fig. 2). We found a significant positive correlation between cardiac NE spillover and the rate-corrected average QT interval QTc ($r = 0.7$, $P = 0.03$) but no significant positive correlations between spillover and the QT variability measures when comparison was made for the group with low cardiac NE spillover (Fig. 2). The values of Spearman correlation coefficients were -0.3 for QTVi, -0.03 for log QT_{var}, -0.2 for QT/RR α , -0.06 for QT/RR r , -0.1 for QT/RR coherence, and 0.2 for Lag₉₀ ($P > 0.05$ in all instances). Interestingly, in a subgroup of five patients who

had high levels of cardiac NE spillover (>20 ng/min), a tendency for a strong positive correlation with QT_{var} ($r = 0.9$, $P = 0.08$) was observed (Fig. 2C).

Investigating possible relationships between cardiac parameters and psychological test scores, we found a negative correlation between HamD and QTVi and a positive correlation between HamD and QT/RR coherence (Table 2). Furthermore, there was a significant positive correlation between HamA and QT/RR r and a negative correlation between QT/RR hysteresis (Lag₉₀) and anxiety trait.

Table 2. Spearman correlation coefficients computed between psychological test scales and cardiac parameters in patients with major depressive disorder and panic disorder

	Cardiac NE Spillover	QTc	QTVi	log QT _{var}	QT/RR α	QT/RR r	Lag ₉₀	QT/RR Coherence
HamA	0.14	0.07	-0.31	0.37	-0.25	0.89*	0.13	-0.11
HamD	0.02	-0.13	-0.74*	0.16	-0.21	0.16	-0.08	0.72*
BDI	-0.49	-0.12	-0.51	0.07	-0.53	-0.11	-0.04	0.33
Anxiety trait	0.04	0.23	-0.10	-0.09	-0.26	-0.05	-0.68*	0.05
Anxiety state	-0.01	-0.15	0.15	0.43	-0.20	0.11	-0.24	-0.30

NE, norepinephrine; QTc, QT interval corrected for heart rate; QTVi, QT variability index; QT_{var}, variance of QT intervals; QT/RR, QT interval/R-R interval; α , r, α coefficient and global regression residual of parabolic [QT/RR]_i fit; Lag₉₀, hysteresis estimate of QT rate adaptation. *Significant correlation ($P < 0.05$).

Effects of SSRI treatment on norepinephrine spillover and on QT variability. Repeated NE spillover measurements (baseline and after 16 wk of treatment with SSRI) were available for 13 patients. There were no significant changes in cardiac NE spillover after medication (Table 3). Repeated ECG measurements before and after 16 wk of SSRI treatment were available for all 17 patients (MDD: $n = 12$; PD: $n = 5$). None of the investigated QT variability measures was significantly altered after SSRI treatment, either in the MDD or the PD group (Table 3).

DISCUSSION

This is the first study that has analyzed beat-to-beat QT variability in relation to directly assessed cardiac NE spillover. In a group of patients suffering from MDD and PD we found a significant correlation between NE spillover and the rate-corrected mean QT interval but no correlation between spillover and QT variability measures. Neither QT variability nor cardiac NE spillover changed significantly after treatment with SSRI.

QT variability and cardiac sympathetic tone. The physiological mechanisms underlying fluctuations in beat-to-beat QT variability are complex. The QT interval reflects the duration of ventricular repolarization. The latter depends on the heart rate. While introduced long ago, Bazett's formula for rate-corrected QT interval (3) is still in use. In a more recent human study by Franz et al. (5), it was revealed that the dynamic beat-to-beat relationship between cardiac cycle and QT duration is much more complex, with long-lasting adjustments. At present there is no transfer function allowing the prediction of the QT sequence from the cardiac cycle sequence. This situation is further complicated by the dependence of the duration of ventricular repolarization on sympathetic influences (11). While it is possible to assess global NE release from the heart (as we also did in the present study), the actual dynamics of NE

release from cardiac sympathetic terminals is unknown. Instead of using a simple standard correction such as Bazett's formula, we applied a sophisticated algorithm for rate correction of the QT interval proposed by Malik et al. (9), in which QTc is estimated specifically for each individual. In this way we were able to account for the high interindividual variability in rate dependence of the QT interval.

The evidence that beat-to-beat QT variability may reflect ventricular sympathetic tone comes from two kinds of studies. First, an elevated QTVi and elevated NE spillover have been independently found in postinfarction patients and in patients with PD and depression (2, 20, 22, 25). Second, activation of cardiac sympathetic activity (by orthostatic challenge or isoproterenol infusion) leads to increase in QTVi (23). In contrast to these findings, β -adrenergic blockade did not affect QTVi at rest or during tilt (14). The QTVi measure, which is the normalization of overall QT variance to overall R-R variance, has some significant shortcomings that might partly explain the discrepancy. First, it introduces into the equation vagally mediated components (respiratory sinus arrhythmia) that act at the pacemaker region and not at the ventricles. Consequently, QTVi might be altered because of changes in vagal tone and/or changes in sympathetic outflow to the sinoatrial node, i.e., R-R interval variability rather than changes in QT interval variability. Second, the QTVi measure does not account for the QT/RR hysteresis lag. The QT interval depends on a history of previous R-R intervals. Information on this complex relationship is lost when simply normalizing QT interval variability to R-R interval variability. Consequently, the physiological interpretation of QTVi is difficult.

Correlation between norepinephrine spillover and QT interval measures. The present data for cardiac NE spillover were drawn from our recent larger study in which we described a

Table 3. Cardiac norepinephrine spillover and QT variability measures in patients with major depressive disorder and panic disorder before and after 16 wk of treatment with SSRIs

	MDD		PD	
	Pre	Post	Pre	Post
Cardiac NE spillover, ng/min	17.3 $\pm$ 14.2	11.5 $\pm$ 11.5	5.9 $\pm$ 1.7	6.5 $\pm$ 3.7
QTc, ms	410 $\pm$ 33	408 $\pm$ 26	400 $\pm$ 33	435 $\pm$ 34
QTVi	-1.54 $\pm$ 0.42	-1.42 $\pm$ 0.52	-1.54 $\pm$ 0.49	-1.25 $\pm$ 0.42
log QT _{var} , log ms ²	1.27 $\pm$ 0.59	1.24 $\pm$ 0.4	1.43 $\pm$ 0.57	1.63 $\pm$ 0.37
QT/RR α	0.43 $\pm$ 0.16	0.40 $\pm$ 0.11	0.42 $\pm$ 0.14	0.68 $\pm$ 0.32
QT/RR r, ms	2.7 $\pm$ 5.3	3.5 $\pm$ 5.6	6.5 $\pm$ 8.1	7.0 $\pm$ 4.4
Lag ₉₀ , s	92.7 $\pm$ 7.7	86.2 $\pm$ 21.1	88.1 $\pm$ 16.0	99.3 $\pm$ 19.8
QT/RR coherence	0.39 $\pm$ 0.14	0.35 $\pm$ 0.16	0.46 $\pm$ 0.21	0.33 $\pm$ 0.19

Data are means $\pm$ SD.

bimodal distribution of the spillover values: in the majority of depressive/panic subjects, there was no difference compared with healthy subjects, whereas in a small subset of patients cardiac NE spillover was substantially elevated (2). We found a positive correlation between cardiac NE spillover and the rate-corrected QT interval in the major group of subjects whose spillover was normal. This is in line with a study by Magnano et al. (8) that describes the prolongation of QTc with the infusion of epinephrine in healthy subjects. In our study, however, no correlation between cardiac NE spillover and any of the QT variability indexes was observed when the comparison was made for the group with normal NE values. A trend for a strong positive correlation between spillover and QT variability was found in the subgroup of patients with high levels of cardiac NE release. In accord with this latter observation, a study by Satomi et al. (18) found an increase in QT variability after epinephrine infusion in patients with long QT syndrome (LQT1 subtype), but not in healthy control subjects. Pohl and Yeragani (16) reported an increase in QT variability after isoproterenol infusion, in particular in PD patients compared with healthy control subjects. The only potential explanation of this discrepancy with our data is that their cohort had an increased cardiac NE spillover. Three of the six patients reported panic attacks after isoproterenol infusion.

This may indicate that the QT variability/spillover dependence holds true only when NE spillover is elevated or when NE/QT relations are intrinsically altered (long QT syndrome). It is thus tentative to speculate that there exists a certain threshold of cardiac sympathetic activation below which QT variability is not sensitive enough to reflect this activation and above which QT variability becomes a sensitive indicator. On the contrary, the correlation between cardiac NE spillover and rate-corrected QT interval appears to exist only within normal ranges of spillover. Since we did not find a correlation between QT_{var} and QTc ($r = -0.03$), the former is not merely a consequence of the latter and thus provides additional information on repolarization dynamics.

It must be noted here that another catecholamine, epinephrine, may be also involved in β -adrenoreceptor-mediated changes in QT variability in depressed/panic patients. We recently demonstrated (20) elevated cardiac epinephrine spillover in panic patients that occurred presumably because of some alterations in its reuptake. Proving this hypothesis would require a separate study.

Effect of SSRI treatment on norepinephrine spillover and on QT variability. SSRI treatment did not affect cardiac NE spillover. We recently published this data in a larger study (2) and discussed it there in detail. In the present study we did not find differences in QT variability in patients with MDD or PD after treatment with SSRI. This is in accord with previous studies in which SSRI therapy did not affect QT variability in healthy volunteers (15) or in patients with anxiety disorders (24).

Correlation between psychological test scores and QT variability. In patients with MDD, we found a significant negative correlation between the HamD score and QT_{Vi} and a significant positive correlation between HamD score and QT/RR coherence. Since QT variability without normalization did not show any correlation with depression scores, we assume that heart rate variability is the primary cause for these relationships. Furthermore, there was a positive correlation between HamA and the QT/RR residual and a negative correlation

between the anxiety trait score and QT/RR hysteresis lag, indicating alterations in the rate dependence of QT.

Limitations. The major limitation of our study is the relatively small number of subjects but a substantial dispersion of NE spillover values, with a difference between minimal and maximal of more than one order that makes our conclusion quite convincing. Furthermore, our observation was limited to patients with MDD or PD and might not be generalized to the normal population, although most of the patients had normal spillover values. Finally, the 5-min ECG recordings might provide relative rather than absolute estimations of the QT/RR hysteresis lag. The short recordings might not cover a wide range of heart rates that would be needed for an accurate estimation of the rate dependence of the QT interval.

Conclusions. In patients suffering from depression or panic disorder, the rate-corrected QT interval, but not the beat-to-beat variability of the QT interval during rest, is correlated with cardiac NE spillover. Neither of these is affected by treatment with SSRI.

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