



Cardiac repolarization variability in patients with postural tachycardia syndrome during graded head-up tilt

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ABSTRACT

Objective: The aim of this study was to assess cardiac ventricular repolarization in patients with postural tachycardia syndrome (POTS) and further the possible link between ventricular repolarization and sympathetic nervous system activity.

Methods: We recorded body surface ECGs together with plasma noradrenaline (NE) spillover, and muscle sympathetic nerve activity (MSNA) in twelve healthy control subjects (CON; 5 males; age: 23 ± 2 yrs) and 13 subjects with postural tachycardia syndrome (POTS; 4 males; 32 ± 13 yrs) during graded head-up tilt (0° – 20° – 30° – 40°). Ventricular repolarization was assessed by computing various measures of beat-to-beat QT interval variability and T wave amplitude.

Results: In patients with POTS, baseline heart rates were higher and MSNA increases during tilt were more pronounced than in CON. None of the QT variability measures was significantly affected by tilt or different between CON and POTS when corrected for heart rate. Contrary, the T wave amplitude flattened due to tilt ($p < 0.001$) and this effect was significantly more pronounced in POTS (32% at 40°) than in CON (21% at 40° ; $p = 0.03$).

Conclusions: Beat-to-beat variability of the QT interval is normal in patients with POTS. However, significantly more attenuated T waves during head-up tilt together with elevated MSNA levels suggest increased sympathetic outflow to the ventricular myocardium in patients with POTS.

Significance: Monitoring of the T wave during tilt test may provide a non-invasive tool for assessing excessive sympathetic outflow to the ventricular myocardium.

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1. Introduction

The postural tachycardia syndrome (POTS) is a form of orthostatic intolerance that was originally defined in adults by [Schondorf and Low \(Neurology, 1993\)](#) as an increase in heart rate by more than 30 beats per minute or an increase to a heart rate exceeding 120 beats per minute within 10 min when changing from supine to upright position. The functional distribution of central sympathetic outflow to the heart and vasculature has been suggested to be abnormal in POTS; circulating norepinephrine (NE) levels are increased ([Jordan et al., 2002](#)), muscle sympathetic nervous activity (MSNA) measurements, however, yielded equivocal results ([Bonyhay and Freeman, 2004](#); [Muentner Swift et al.,](#)

[2005](#)). Cardiac NE spillover levels were found to be elevated, suggesting an increased sympathetic neural outflow to the myocardium of patients with POTS ([Goldstein et al., 2002](#)). Other mechanisms that have been invoked in the pathogenesis include hypovolemia ([Fouad et al., 1986](#)), inadequate vasoconstriction, peripheral denervation ([Streeten, 1990](#)) and increased venous pooling ([Stewart, 2002](#)).

The aim of this study was to investigate ventricular repolarization variability in patients with POTS and the possible link to increased sympathetic outflow to the heart. The QT interval of the body surface ECG is a global marker of ventricular repolarization and the rate-corrected QT interval is traditionally used as a marker of arrhythmic risk ([Morita et al., 2008](#)). Recently, the elevation of beat-to-beat fluctuations in the QT interval—QT variability—was shown to be predictive of malignant arrhythmia and cardiac death in heart failure patients ([Berger et al., 1997](#); [Atiga et al., 1998](#); [Piccirillo et al., 2007](#); [Tereshchenko et al., 2009](#)).

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2. Methods

2.1. Subjects

The study comprised twelve healthy control subjects (CON; 5 males; age: 23 ± 2 yrs; BMI: 24 ± 4 kg m⁻²) and 13 subjects with POTS (4 males; 32 ± 13 yrs; 23 ± 4 kg m⁻²). The subjects with POTS underwent an exhaustive medical evaluation to exclude any other relevant medical condition. All patients with POTS shared the common clinical characteristics central to the diagnosis, such as recurrent episodes of presyncope while standing, absence of postural hypotension (decrease in systolic blood pressure while standing <20 mm Hg), and the presence of posture-related tachycardia (mean heart rate increase on standing recorded in the clinic = 41 ± 3 bpm). The most common symptoms of the POTS patients included fatigue, palpitations, cognitive impairment, syncope, and chest pain. All patients were unmedicated. They were either newly diagnosed and never treated or had stopped any medication for at least 7 days (7 days for β -adrenergic-blocking drugs, 21 days for fludrocortisone). The subjects were drawn from a previously published study on sympathetic nervous reactivity and norepinephrine transporter expression (Lambert et al., 2008)—ventricular repolarization has not been reported in these patients previously.

All subjects provided written informed consent to the study protocol that was approved by the Alfred Hospital Ethics Review Committee and conformed to the relevant guidelines of the National Health and Medical Research Council of Australia.

2.2. Experimental protocol and data acquisition

All subjects were tested in the morning after a light breakfast and with a void bladder. Participants were placed on a tilt table. After setting up the measuring equipment all participants rested at least for 30 min before the actual recording started. After rest, all subjects were gradually tilted at 20, 30 and 40 degrees and maintained in each position for 10 min. Most patients experienced symptoms during tilting including palpitations, clamminess and dizziness. The test was aborted at 40 degrees in two patients as the symptoms became intolerable.

2.3. QT interval variability analysis

Body surface ECG (lead III) was recorded at a sampling frequency of 1000 Hz, using PowerLab and the LabChart software (AD Instruments, Australia). The ECG waves were clearly defined. 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. (1997). 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 therefore sensitive to artefacts and noise. We computed the QT variability index (QTVi) was defined as in Berger et al. (1997):

$$QTVi = \log((QT_{var}/\text{meanQT}^2)/(RR_{var}/\text{meanRR}^2)),$$

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 RR intervals (RR_{var}) normalized to the squared mean RR interval (meanRR). The logarithm

is taken purely for statistical reasons, i.e. to ensure a normal distribution of the otherwise skewed QTVi distribution. In addition to QTVi, we also investigated QT_{var} , i.e. the variance of beat-to-beat QT intervals without any normalization.

Further, we applied a method proposed by Malik et al. (Malik et al., 2002; Pueyo et al., 2004) for individual-specific heart rate correction of the QT interval (QT_c). A parabolic function was used to describe the QT/RR relationship, i.e. $QT = \beta(\overline{RR})^\alpha$, where the regression coefficients α , β as well as the average heart period $\overline{RR}$ are individually estimated for each recording, minimizing the residual of the $[QT_i, \overline{RR}_i]$ regression fit. For details, see Malik et al. (2002) and Pueyo et al. (2004).

2.4. ECG waveform analysis

To assess tilt-related changes in the ECG waveform, we measured the amplitudes of all prominent waves (P, R and T). The average ECG waveform was obtained from 5 min artefact-free recordings for each tilt angle, using the LabChart® computer software (ADInstruments, Australia).

2.5. Direct assessment of sympathetic activity

To explore the relationship between QT variability and sympathetic nerve activity, we recorded multiunit sympathetic nerve firing rates in postganglionic fibres distributed to the skeletal muscle vasculature in the common peroneal nerve by using clinical micro-neurography as previously reported (Lambert et al., 2008). MSNA was recorded at 1000 Hz and expressed as bursts per minute.

In addition, plasma norepinephrine (NE) spillover was determined by the isotope dilution technique. Therefore, the radial artery was cannulated percutaneously under local anaesthesia and participants were infused with ³H-labeled NE via a peripheral venous cannula. The total NE spillover rate was determined as the ratio of [³H]NE infusion rate to plasma NE specific radioactivity. For details, see Esler and Kaye (1998).

2.6. Statistics

Baseline comparisons between normal subjects and patients with orthostatic intolerance were performed using student's *t*-test. Mixed model repeated measurement analysis was applied to test for tilt angle effects and group differences in the investigated measures. A first-order autoregressive covariance structure was chosen for the model. For post hoc comparisons between groups and tilt angles, confidence interval correction according to Sidak was applied. Normal distributions of variables were checked with the D'Agostino & Pearson test for both groups. Distributions were normal unless stated otherwise.

3. Results

3.1. Heart rate and blood pressure

Baseline heart rate was substantially elevated in the POTS group compared to controls (see Table 1). Heart rate increased significantly ($p < 0.001$) with increasing tilt angle, by 15% for CON and 18% for POTS (group $\times$ tilt angle interaction effect: $p = 0.04$, Table 1). Baseline systolic and diastolic blood pressure levels were not significantly different between CON and POTS. During tilting, systolic blood pressure remained stable in CON (-3%) but increased significantly in POTS (6% ; group $\times$ tilt angle interaction effect: $p = 0.06$, Table 1). Diastolic blood pressure levels were not significantly altered during tilt ($p = 0.06$, Table 1) and there was no significant group $\times$ tilt interaction effect ($p = 0.19$).

Table 1

Heart rate, blood pressure, QT variability and ECG waveform amplitudes of normal subjects (CON) and patients with postural orthostatic intolerance syndrome (POTS) measured during graded head-up tilt. Asterisks indicate significant between group differences.

Tilt angle	0°		20°		30°		40°	
	CON	POTS	CON	POTS	CON	POTS	CON	POTS
Heart rate [bpm]	65 ± 8	86 ± 18**	66 ± 8	91 ± 16***	71 ± 9	100 ± 18***	76 ± 9	102 ± 16***
Systolic BP [mmHg]	130 ± 15	135 ± 12	133 ± 17	146 ± 13	127 ± 17	147 ± 18	126 ± 21	143 ± 18
Diastolic BP [mmHg]	70 ± 9	72 ± 9	72 ± 9	77 ± 12	72 ± 11	80 ± 12	71 ± 13	77 ± 15
QT [ms]	352 ± 24	318 ± 37*	357 ± 32	312 ± 31**	358 ± 29	296 ± 38***	334 ± 30	296 ± 49
QT _c [ms]	365 ± 39	382 ± 41	373 ± 39	384 ± 49	390 ± 41	356 ± 56	364 ± 20	384 ± 77
QTVi [1]	−1.54 ± 0.38	−1.28 ± 0.46	−1.56 ± 0.18	−1.05 ± 0.32***	−1.47 ± 0.25	−1.05 ± 0.19***	−1.47 ± 0.25	−0.78 ± 0.39***
QTvar [ms ²]	38 ± 36	20 ± 20	25 ± 14	36 ± 24	27 ± 24	31 ± 16	22 ± 11	50 ± 32
P amplitude [mV]*	0.05 ± 0.02	0.09 ± 0.03	0.05 ± 0.03	0.10 ± 0.03	0.05 ± 0.03	0.11 ± 0.03	0.06 ± 0.03	0.11 ± 0.04
R amplitude [mV]*	0.49 ± 0.33	0.78 ± 0.35	0.48 ± 0.31	0.82 ± 0.37	0.50 ± 0.34	0.86 ± 0.38	0.51 ± 0.34	0.79 ± 0.42
T amplitude [mV]*	0.15 ± 0.09	0.16 ± 0.10	0.14 ± 0.09	0.15 ± 0.10	0.14 ± 0.09	0.12 ± 0.08	0.08 ± 0.06	0.12 ± 0.08

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

* Statistical test were performed for relative changes with regard to baseline, see text and Fig. 1.

3.2. QT interval variability

The uncorrected baseline QT interval was significantly shorter in the POTS group compared to controls (Table 1). Graded tilting resulted in QT interval shortening ($p < 0.001$) by, on average 5% for CON and 7% for POTS (group $\times$ tilt angle interaction effect: $p = 0.08$, Table 1). After covarying for heart rate ($p < 0.001$), neither group ($p = 0.98$) or tilting ($p = 0.49$) had a significant effect on the QT interval. In full agreement with this observation, the rate-corrected QT_c interval was not significantly different between groups ($p = 0.67$), not affected by tilt ($p = 0.79$) and there was no interaction effect between both ($p = 0.18$).

Uncorrected baseline beat-to-beat QT interval variability (QTvar) was log-transformed prior statistical analysis to achieve normal distribution. QTvar was not significantly different between groups (Table 1). Tilting had no significant effect on QT variability ($p = 0.12$, Table 1) and there was no significant interaction effect between group and tilt angle ($p = 0.07$) either.

QT variability normalized to heart rate variability, QTVi, was not significantly different between both groups at baseline. Tilting increased QTVi significantly ($p = 0.02$) by 5% for CON and 39% for POTS, on average, resulting in a significant group difference ($p < 0.001$, Table 1), although the group $\times$ tilt interaction effect was not significantly different ($p = 0.14$). After covarying for heart rate ($p = 0.005$), the group difference disappeared ($p = 0.15$) and tilting had no significant effect on QTVi any longer ($p = 0.38$). Covarying for MSNA ($p = 0.73$) and plasma NE spillover ($p = 0.38$) had no significant affect on QTVi.

3.3. Changes in the P, R and T wave amplitudes

To account for individual and lead-related differences in the P, R and T wave amplitudes, tilt-induced changes were considered with regard to the baseline measurement. There was a considerable between-subject variance in the magnitude of the waveform changes, which was not normal distributed over both groups. During tilt, the P wave amplitude showed a trend for increase ($p = 0.08$, Fig. 1), but no group difference ($p = 0.42$) or interaction effect ($p = 0.49$). The R wave amplitude was not affected by group ($p = 0.26$, Fig. 1) or tilt ($p = 0.36$).

The T wave flattened significantly with increasing tilt angle ($p = 0.001$, Fig. 1) by, on average, 21% for CON and 32% for POTS (group $\times$ tilt interaction effect: $p = 0.69$). In CON, there were six subjects with a T wave decrease of more than 10 percent. In POTS, there were eight patients with a T wave decrease of more than 10 percent. There was no significant group difference in the T wave

change ($p = 0.59$). After covarying for heart rate, tilt effects ($p < 0.001$) and group effects ($p = 0.03$) on T wave amplitude change were significant. Neither MSNA nor plasma NE spillover covaried significantly with the change in P or T wave amplitudes.

3.4. Sympathetic nerve activity

As previously reported, baseline MSNA was not significantly different between CON and POTS. MSNA increased continuously during graded tilt from the supine position to 40° ($p < 0.001$, Fig. 2). The increase in MSNA was significantly higher in the POTS group (123%) compared to CON (54%; group $\times$ tilt interaction effect: $p = 0.02$).

Baseline plasma NE spillover was not significantly different between CON and POTS either. During tilt, plasma NE spillover increased significantly ($p = 0.001$, Fig. 2). There was no interaction effect between group and tilt angle ($p = 0.59$).

4. Discussion

The major findings of this study are: (1) subjects with postural tachycardia show normal beat-to-beat QT interval variability, but pronounced T wave changes; (2) tilt-induced changes in the QT variability index are secondary to changes in heart rate.

Head-up tilt is a well-studied paradigm for orthostatic stress that is associated with sympathetic activation (Freeman, 2006). Accordingly, we observed a steady increase in systemic sympathetic outflow with increasing tilt angle as quantified by MSNA and plasma NE spillover. As previously reported, MSNA and plasma NE spillover were normal in patients with POTS during baseline recordings (Lambert et al., 2008). During tilt, MSNA increased significantly more in POTS patients than in controls, indicating enhanced sympathetic activation in the skeletal muscle vasculature of POTS patients, which was not evident in the total body NE spillover. The literature regarding sympathetic nervous activity in POTS is equivocal (see Lambert et al., 2008).

In agreement with the finding of other authors (Singer et al., 2003) our POTS patients showed increased baseline heart rate and furthermore, a pronounced heart rate response to tilt. One possibility includes increased cardiac sympathetic activation in this group of patients. This is supported by a study by Goldstein et al. (2002), who documented higher cardiac NE spillover to plasma in subjects with POTS than in controls and noted that increments in heart rate during yohimbine infusion correlated significantly positively with that in cardiac NE spillover. On the other hand, a loss of cardiac sympathetic neurons has been reported in a patient with

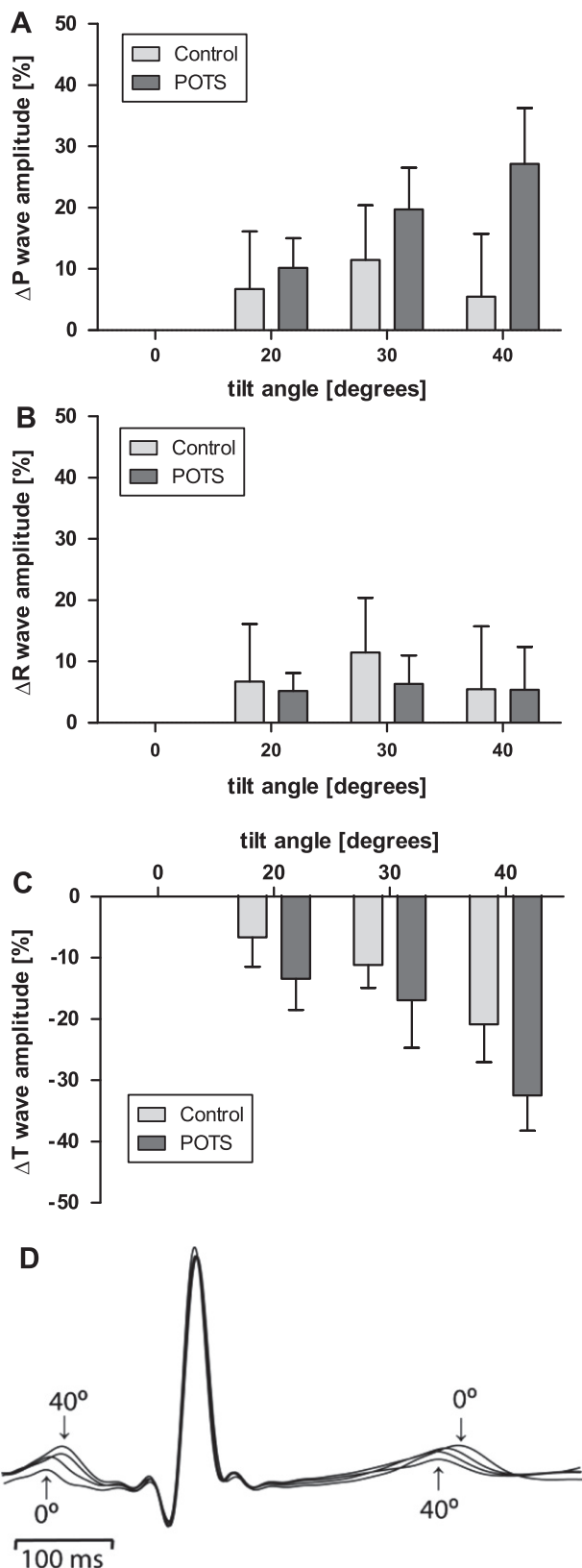


Fig. 1. The P wave magnitude (A) increases relative to the baseline amplitude with increasing tilt angle in control subjects and patients with postural tachycardia syndrome (POTS). Contrary, the T wave amplitude (C) decreases, while the R wave (B) remains unaffected. The example in D shows a subject's ECG waveforms for the different tilt angles (0°–20°–30°–40°) obtained from 5 min averages.

POTS (Haensch et al., 2008). Another possibility is decreased cardiac baroreflex function. The marked impairment of cardiac

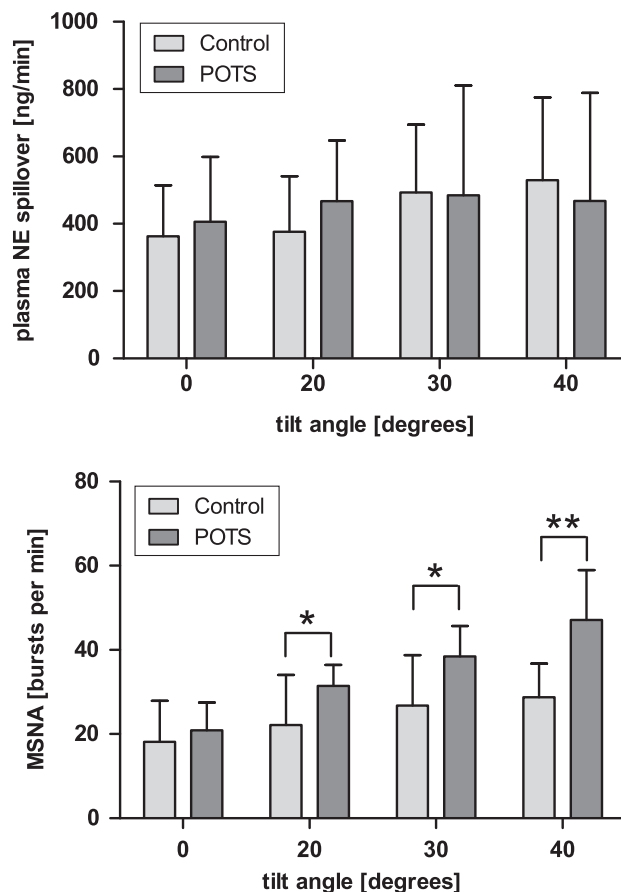


Fig. 2. Plasma norepinephrine spillover (top) and muscular sympathetic nerve activity (MSNA) increase significantly during graded head-up tilt in control subjects and patients with postural tachycardia syndrome (POTS). Asterisks indicate significant between group differences.

baroreflex sensitivity seen in patients with POTS when compared with healthy control subjects, described by Muentert Swift et al. (2005) and us (Lambert et al., 2008) suggests that vagal impairment also contributes to the excessive tachycardia seen in patients with POTS.

In agreement with Singer et al. (2003), we observed QT interval shortening in POTS, which can be largely attributed to restitution effects following heart rate acceleration—there were no significant QT interval changes during tilt or group differences after covarying for heart rate or in QT_c itself.

To assess ventricular repolarization dynamics in more detail, we studied beat-to-beat fluctuations in the QT interval during tilt. QT interval variability depends on heart rate and involves some complex long-lasting adjustments (Franz et al., 1988). Berger et al. (1997) proposed to relate QT variability to heart rate variability (QT variability index; QT_{Vi}), which is currently the standard metric for QT variability. Our results confirm the increase of QT_{Vi} during orthostatic challenge, but importantly, suggest that this increase in QT_{Vi} is largely the consequence of heart rate elevation—there was no significant change in QT_{Vi} after covarying for heart rate. Moreover, QT_{Vi} was not correlated with MSNA or plasma NE spillover, indicating that QT_{Vi} is not reflective of sympathetic activity (Baumert et al., 2008). Moreover, the difference in QT_{Vi}, which we initially observed between CON and POTS disappeared after heart rate correction.

Although the amount of beat-to-beat fluctuations in the QT interval was not altered with increasing tilt angles we observed a flattening of the T wave (Fig. 1C and D). This flattening is typically

caused by a change in the repolarization vector angle that does not appear to be directly related to the change in heart rate, implying that the neural outflow to the SA node is different from that to the ventricles (Paton et al., 2005). Morphological changes of the T wave have been observed after pharmacological sympathetic activation using isoproterenol (Magnano et al., 2002), suggesting that our finding might at least in part be indicative of increased sympathetic outflow to the ventricles. The parallel elevation of the P wave, reflecting vagal withdrawal, further suggests that the ECG waveform changes are primarily mediated by the autonomic nervous system. Interestingly, the T wave flattening was significantly more pronounced in POTS patients, after correcting for heart rate, indicating an abnormal ventricular repolarization process in POTS. Mayuga and Fouad-Tarazi (2007) found that the occurrence of tilt-induced T wave changes was directly correlated with an adverse test outcome. Our data suggest that the T wave amplitude rather than QT interval variability is sensitive to orthostatic stress and might provide insights into the autonomic effects on ventricular repolarization. A change in T wave amplitude, on the other hand, is likely to contribute to fluctuations in the QT interval and consequently to QT variability.

4.1. Limitations

Electrical noise and muscle activity potentially affect ECG and MSNA recordings. To minimize these adverse effects the subjects were resting for at least 30 min on the tilt table before the actual measurement started. Further, QT variability is dependent on the ECG electrode placement (Yeragani et al., 2002). As only a 1-lead recording system was at our disposal, we used consistently lead III. Further, the heart's electric dipole might have changed during tilt and caused changes in the projected ECG waveform. Also, we cannot exclude that changes in breathing patterns might have influenced the ECG waveform.

5. Conclusions

Beat-to-beat variability of the QT interval is normal in patients with POTS. The tilt-induced flattening of the T wave, however, was significantly more pronounced than in healthy control subjects, suggesting altered ventricular repolarization in patients POTS. Monitoring of the T wave changes during tilt test might provide a non-invasive means to assess excessive sympathetic outflow to the heart.

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