

Relation between QT interval variability and muscle sympathetic nerve activity in normal subjects

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El-Hamad F, Lambert E, Abbott D, Baumert M. Relation between QT interval variability and muscle sympathetic nerve activity in normal subjects. *Am J Physiol Heart Circ Physiol* 309: H1218–H1224, 2015. First published August 14, 2015; doi:10.1152/ajpheart.00230.2015.—Beat-to-beat variability of the QT interval (QTV) is sought to provide an indirect noninvasive measure of sympathetic nerve activity, but a formal quantification of this relationship has not been provided. In this study we used power contribution analysis to study the relationship between QTV and muscle sympathetic nerve activity (MSNA). ECG and MSNA were recorded in 10 healthy subjects in the supine position and after 40° head-up tilt. Power spectrum analysis was performed using a linear autoregressive model with two external inputs: heart period (RR interval) variability (RRV) and MSNA. Total and low-frequency power of QTV was decomposed into contributions by RRV, MSNA, and sources independent of RRV and MSNA. Results show that the percentage of MSNA power contribution to QT is very small and does not change with tilt. RRV power contribution to QT power is notable and decreases with tilt, while the greatest percentage of QTV is independent of RRV and MSNA in the supine position and after 40° head-up tilt. In conclusion, beat-to-beat QTV in normal subjects does not appear to be significantly affected by the rhythmic modulations in MSNA following low to moderate orthostatic stimulation. Therefore, MSNA oscillations may not represent a useful surrogate for cardiac sympathetic nerve activity at moderate levels of activation, or, alternatively, sympathetic influences on QTV are complex and not quantifiable with linear shift-invariant autoregressive models.

QT interval variability; muscle sympathetic nerve activity

NEW & NOTEWORTHY

QT interval variability in normal subjects does not appear to be significantly affected by the rhythmic modulations in MSNA following low to moderate orthostatic stimulation.

INCREASED SYMPATHETIC NERVOUS system activity contributes to the development and progression of cardiovascular disease, such as heart failure (17), and may even trigger ventricular arrhythmias (22). Therefore, quantification of the level of sympathetic outflow directed at the heart may be of diagnostic interest in clinical, as well as nonclinical, contexts (8, 15, 29).

Elevated beat-to-beat variability in ventricular repolarization duration, measured as changes in QT interval [QT variability (QTV)] on body surface ECG has been attributed to increased sympathetic outflow to the ventricles (32, 46). Although it is widely believed that QTV is predominantly driven by heart period (RR interval) variability (RRV) under normal conditions during rest (34), several studies across a range of condi-

tions, including healthy subjects (2), patients post-myocardial infarction (50), heart failure patients (25), and patients with diabetes mellitus (39), showed that a large part of QTV could not be solely attributed to RRV. An increased decoupling between RRV and repolarization variability was reported in healthy subjects following head-up tilt, a maneuver well known to increase sympathetic nerve activity (12), and QTV unrelated to RR and respiration (35) was shown to increase under similar experimental conditions. Correlations between QTV and cardiac norepinephrine spillover, a direct measure of sympathetic activity, recorded during rest were observed in patients with hypertension (6), but not in normal subjects or patients with panic disorder and depression (5). Also, QTV has been found to increase significantly during standing and isoproterenol infusion (46). Collectively, these findings suggest that heightened sympathetic neural modulation of the ventricular myocardium augments repolarization variability independent of RRV. Thus, measurement of QTV may allow evaluation of the effects of sympathetic activity on the ventricles and, thereby, yield a noninvasive index for quantification of sympathetic activity levels.

Muscle sympathetic nerve activity (MSNA) measured in the peroneal muscle using microneurography is a widely used technique to probe postganglionic sympathetic nerve activity (18). As the analysis of MSNA has been proven useful for investigating the autonomic regulation of sinoatrial node activity in conjunction with RRV (18, 24, 28), it may help quantify the relationship between QTV and sympathetic modulation of the ventricles.

The aim of this study was to investigate the extent to which QTV can be used to measure sympathetic activity. To address this question, we used an autoregressive model and power contribution analysis to study the relationship between QTV and MSNA in normal subjects following head-up tilt.

METHODS

Subjects and experimental protocol. We studied 10 healthy subjects (2 men and 8 women; 25.1 ± 5.9 yr of age, 23.5 ± 3.1 kg/m² body mass index) selected from a previously published study (19). After giving written informed consent, subjects were tested in the morning, with caffeine and alcohol consumption restricted ≥ 12 h before the study was initiated. After instrumentation, subjects rested for 30 min before the actual recording started. The experimental protocol was approved by the Alfred Hospital Ethics Review Committee.

ECG lead III, arterial blood pressure, and MSNA were recorded simultaneously for 10 min in the supine position in each subject and then for 10 min in the head-up tilt position at 20°, 30°, and 40° using PowerLab (ADInstruments, Bella Vista, NSW, Australia). Blood pressure was monitored through percutaneous cannulation of the radial artery. MSNA was recorded using microneurography, as described previously (19). Briefly, a tungsten microelectrode was in-

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serted into the common peroneal nerve to record nerve traffic from multiple postganglionic fibers. The MSNA signal was integrated using a resistor-capacitor circuit to obtain mean voltage of the multiunit nerve recording.

Data preprocessing. Recordings were visually inspected to identify artifact-free segments. Beat-to-beat series of the heart period (RR interval) were defined as the temporal distance between two consecutive QRS complexes. Beat-to-beat QT interval time series were obtained based on a recently proposed two-dimensional signal-warping algorithm (41). Briefly, the algorithm creates a template beat on which the QT interval is semiautomatically annotated and then morphed in both time and amplitude to match consecutive beats, thereby accounting for variations in the ECG waveform. Finally, the QT interval duration of each beat is obtained based on the scaled version of the annotated QT interval in the adapted template. The algorithm also incorporates rejection criteria for beats that are highly corrupted by noise.

Beat-to-beat systolic arterial pressure (SAP) and diastolic arterial pressure were defined as the local maximum and minimum, respectively, of the blood pressure signal enclosed by consecutive R peaks. Beat-to-beat values of MSNA were obtained by calculating the time average of the integrated MSNA signal between two consecutive diastolic arterial pressure time points.

For each subject, data segments of ~200 beats (~3 min) were selected for the analysis from both supine and 40° head-up-tilt positions. To simplify the analysis, intermediate tilt angles were not considered.

Beat-to-beat series of RR, QT, MSNA, and SAP were detrended using the smoothness priors method (43), comprising a time-varying finite-impulse response high-pass filter. A cutoff frequency of 0.04 Hz was chosen by setting the smoothing parameter to 22. The beat-to-beat series were normalized to zero mean and unit variance for frequency domain analysis.

Time domain analysis of QTV. Time domain analysis of RR, QT, MSNA, and SAP time series was performed to confirm the increase in variances expected with head-up tilt due to the increase in sympathetic activity. Mean RR interval (RRm), RR interval variance (RRv), mean QT interval (QTm), QT interval variance (QTV), MSNA variance (MSNAv), SAP variance (SAPv), and QT variability index (QTVi), given by

$$QTVi = \log_{10} \left[\frac{QT/(QTm)^2}{RRv/(RRm)^2} \right] \quad (1)$$

were calculated for each subject in supine and 40° tilt positions.

Frequency domain analysis. Power contribution analysis was performed using a linear autoregressive model with two external inputs (ARXX) (3). We assumed an open-loop structure, where QT is affected independently by RR and MSNA while QT does not exhibit an influence on MSNA and RR. The model assumes that the rhythm sources generating the three signals are uncorrelated. Thus the autoregressive model was defined as

$$A_1(z)QT(i) = B_1(z)RR(i) + B_2(z)MSNA(i) + e_{QT}(i) \quad (2)$$

where

$$A_1(z) = 1 + a_{1,1}z^{-1} + \dots + a_{1,n_{a1}}z^{-n_{a1}} \quad (3)$$

$$B_1(z) = b_{1,0} + b_{1,1}z^{-1} + \dots + b_{1,n_{b1}}z^{-n_{b1}} \quad (4)$$

$$B_2(z) = b_{2,0} + b_{2,1}z^{-1} + \dots + b_{2,n_{b2}}z^{-n_{b2}} \quad (5)$$

where A_1 , B_1 , and B_2 are polynomials of the parameters in the z domain that describe the effect of the samples of QT, RR, and MSNA up to a delay of n_{a1} , n_{b1} , and n_{b2} , respectively, on the one-step-ahead prediction of QT. Equation 2 describes QT as a function of its own past, past and present values of RR and MSNA, and a noise source that represents actual noise and rhythms originating from sources not included in the model.

On the other hand, RR and MSNA were modeled as separate autoregressive processes

$$A_2(z)RR(i) = e_{RR}(i) \quad (6)$$

$$A_3(z)MSNA(i) = e_{MSNA}(i) \quad (7)$$

$$A_2(z) = 1 + a_{2,1}z^{-1} + \dots + a_{2,n_{a2}}z^{-n_{a2}} \quad (8)$$

$$A_3(z) = 1 + a_{3,1}z^{-1} + \dots + a_{3,n_{a3}}z^{-n_{a3}} \quad (9)$$

where n_{a2} and n_{a3} are the AR model orders. Equations 6 and 7 describe MSNA and RR as a function of their own past and a noise source. Variables e_{QT} , e_{RR} , and e_{MSNA} are white noise sources with zero mean and σ_{QT}^2 , σ_{RR}^2 , and σ_{MSNA}^2 variance, respectively.

The goodness of fit was calculated to quantify the ability of the ARXX structure to represent the measured data (37). Model parameters were estimated using the least-squares method. The uncorrelation between noise sources was verified based on residual analysis. Frequency domain representations of the models were obtained by Fourier transform, where the power of QT can be represented through individual contributions (34)

$$P(f)_{QT} = \left| \frac{B_1(f)}{A_1(f) \times A_2(f)} \right|^2 \times \sigma_{RR}^2 + \left| \frac{B_2(f)}{A_1(f) \times A_3(f)} \right|^2 \times \sigma_{MSNA}^2 + \left| \frac{1}{A_1(f)} \right|^2 \times \sigma_{QT}^2 \quad (10)$$

where the first term is the power contribution from RR, the second term is the power contribution from MSNA, and the third term is the power independent of RR and MSNA that is attributed to noise and other sources not accounted for in the model. Here, $A_1(f)$, $A_2(f)$, $A_3(f)$, $B_1(f)$, and $B_2(f)$ are the Fourier transform polynomials of the model parameters. Both RR and MSNA total powers were computed as follows

$$P(f)_{RR} = \left| \frac{1}{A_2(f)} \right|^2 \times \sigma_{RR}^2 \quad (11)$$

$$P(f)_{MSNA} = \left| \frac{1}{A_3(f)} \right|^2 \times \sigma_{RR}^2 \quad (12)$$

SAP was modeled as an independent AR process similar to that adopted for RR and MSNA.

The squared coherence function was calculated to measure the linear relationship between QT and MSNA as a function of frequency (24) as

$$k^2(f) = \frac{|P_{QT-MSNA}(f)|^2}{P(f)_{QT} \times P(f)_{MSNA}} \quad (13)$$

To estimate the power contained in the low-frequency (LF) and high-frequency (HF) bands, each partial spectrum was decomposed into the spectral components of each pole, as described elsewhere (3). The power of the spectral component contributed by a pole was considered LF power if its central frequency fell in the frequency range 0.05–0.2 Hz and HF if its central frequency was in the range 0.2–0.4 Hz.

For model order selection and estimation, data segments were divided into two-thirds estimation data and one-third validation data. Model orders were selected from the range 4–12, minimizing the Akaike figure of merit (1). The model parameters were estimated using the least-squares method. Correlations within and across regression residuals were deemed negligible if no more than three points were outside the 95% confidence interval of the cross-correlation and autocorrelation plots.

Surrogate analysis. The method of surrogate data testing described by Faes et al. (10) was applied to test whether MSNA total and LF contributions are significant and to define the threshold for zero coherence. For each subject, 10 pairs of QT and MSNA surrogate

Table 1. Time domain measures in the supine position and following 40° head-up tilt

Variable	Position		P Value
	Supine	40° tilt	
RRm, ms	991 (904 to 1,177)	765 (743 to 858)	0.0020
RRv, ms ²	2,039 (1,813 to 4,805)	955 (382 to 1,743)	0.027
QTm, ms	368 (347 to 398)	338 (328 to 361)	0.0020
QTV, ms ²	2.6 (1.9 to 3.6)	3.9 (3.2 to 9.6)	0.0020
QTVi	-2.2 (-2.4 to -1.8)	-1.4 (-1.7 to -1.3)	0.0098
MSNAv, AU ²	0.00064 (0.00008 to 1.81)	0.002 (0.0003 to 3.8)	0.0488
SAPv, mmHg ²	5.2 (3.5 to 14.0)	6.9 (4.5 to 18.3)	>0.05

Values are medians (25th percentile–75th percentile). RRm, mean heart period; RRv, heart period variance; QTm, mean QT interval; QTV, QT interval variance; QTVi, QT variability index; MSNAv, muscle sympathetic nerve activity variance; SAPv, systolic arterial pressure variance; AU, arbitrary units.

series were generated by feeding the QT and MSNA models with 10 realizations of independent Gaussian white noise processes. MSNA total and LF power contributions and the maximum coherence between QT and MSNA in LF were computed for the generated surrogate series, resulting in 100 surrogate values for each variable across all subjects.

Statistical analysis. GraphPad Prism 6 software was used for statistical analysis. Data are presented as median (25th percentile–75th percentile). The paired two-tailed Wilcoxon test was used to test the change in time domain measures and frequency domain power estimates from the supine position to 40° head-up tilt. The Mann-Whitney test was performed to test whether MSNA power contributions estimated from measured data were significantly different from those obtained from the surrogate data. As proposed by Faes et al. (10), the threshold for zero coherence was set at the 95th percentile of the coherence sampling distribution computed from the surrogate data. $P < 0.05$ was considered statistically significant.

RESULTS

Time domain analysis. The time domain analysis results are summarized in Table 1. RRm, QTm, and RRv decreased significantly following 40° head-up tilt, while QTV, QTVi, and MSNAv increased significantly. However, SAP power did not change with tilt.

Frequency domain analysis. The goodness of fit of the ARXX model was 51% (41–56%) in the supine position and

41% (23–46%) following 40° head-up tilt. This reduction in goodness of fit was not statistically significant ($P > 0.05$).

Figure 1 shows the LF power of QTV and MSNA in the supine position and following 40° tilt. While LF power of QTV, measured in absolute units, increased significantly following 40° head-up tilt ($P = 0.037$), LF power of MSNA, measured in normalized units [LF/(LF + HF)], was not statistically significant between the two measurement conditions ($P > 0.05$). Furthermore, LF power of SAP was not affected by the tilt condition [0.12 (0.09–0.37) mmHg² and 0.24 (0.13–0.49) mmHg² in supine and standing positions, respectively, $P > 0.05$].

Figure 2 shows individual power contributions of RR and MSNA to QTV, as well as unexplained variance during the supine measurement and following 40° head-up tilt. In the supine position, RRv contributions to total and LF power of QTV were, on median, 38.8% and 45.5%, respectively. This contribution decreased significantly to ~20% of the total and LF power of QTV after head-up tilt ($P = 0.0195$, and $P = 0.0059$, respectively). The MSNA contribution to total and LF powers of QTV measured in the supine position during rest was, on average, 2.1% and 2.2%, respectively. Upon 40° head-up tilt, MSNA contributions tended to increase to 4.8% and 3.0% of the total and LF power of QTV; however, this increase was not statistically significant ($P > 0.05$). Surrogate data testing demonstrated that MSNA total and LF power contributions were significantly different from independent random processes ($P < 0.0001$ in the supine position and $P < 0.03$ following 40° head-up tilt).

In the supine position, total and LF power of QTV independent of RR and MSNA were ~59% and 54%, respectively, and increased significantly to ~74% and 76% following head-up tilt ($P < 0.02$).

Maximum coherence between LF oscillations in MSNA and QTV across all subjects was 0.05 (0.02–0.07) in the supine position, which tended to increase to 0.11 (0.04–0.17) after 40° head-up tilt ($P = 0.08$). For the surrogate data method, the threshold for zero coherence in the LF band was set at 0.5 in the supine position and 0.36 following 40° head-up tilt; hence, coherence values were not significant.

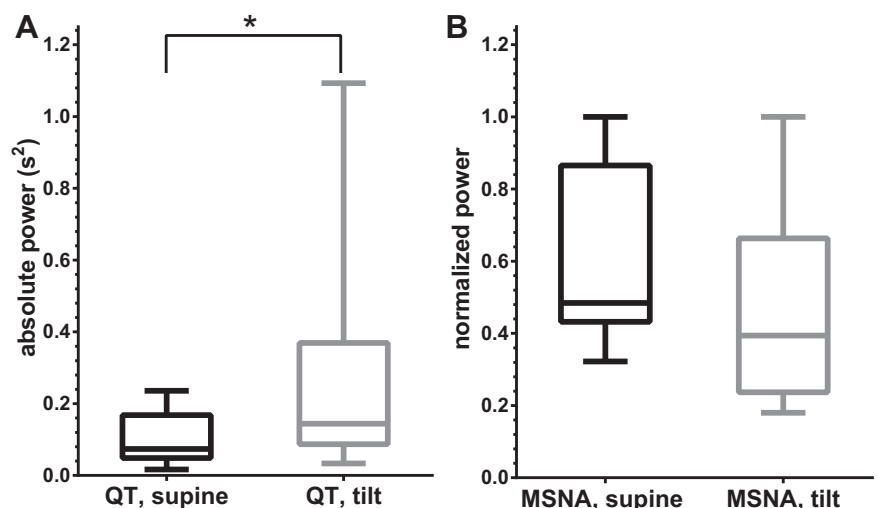


Fig. 1. Change in low-frequency (LF) power of QT (A) and muscle sympathetic nerve activity (MSNA; B) from the supine position to 40° head-up tilt. Bar plots represent median values and interquartile ranges. *Significant difference between supine and tilt.

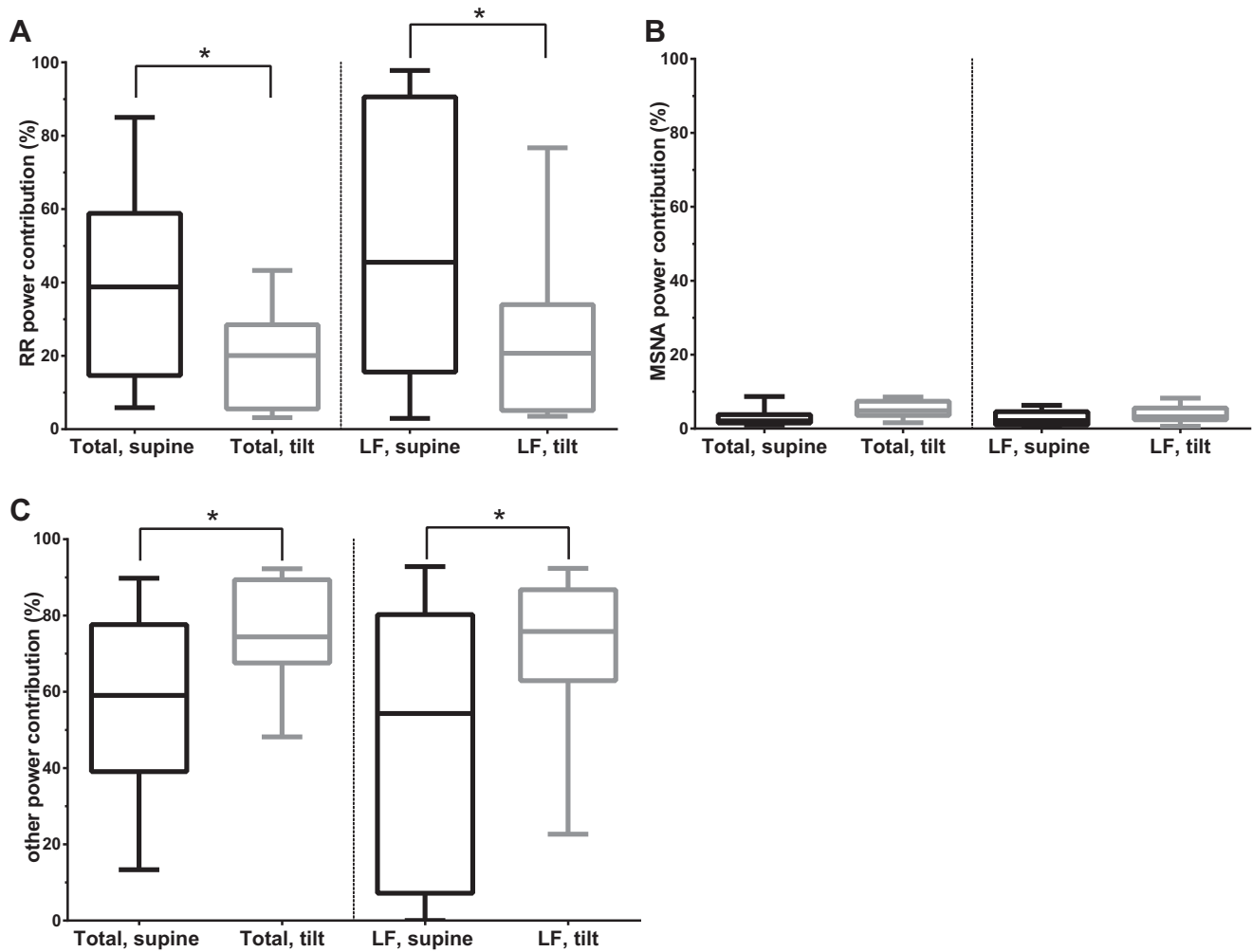


Fig. 2. Power contribution analysis results. A: heart period (RR interval) variability (RRV) contribution to QT interval variability (QTV). *Left*: RR contribution to total QT power; *right*: RR contribution to power in the LF band of QTV. B: MSNA contribution to QT power. *Left*: MSNA contribution to total QT power; *right*: MSNA contribution to power in the LF band of QT. C: QT power independent of RR and MSNA contribution. *Left*: total QT power independent of RR and MSNA. Bar plots represent median values and interquartile ranges. *Significant difference between supine and tilt.

DISCUSSION

The main finding of this study is that the oscillatory modulations in MSNA do not contribute significantly to QTV measured at rest or following moderate orthostatic stress.

The sympathetic nervous system influences the ventricular repolarization process. Within ventricular myocytes, the sympathetic nervous system can principally act on L-type calcium channels and the slowly activating delayed rectifier potassium current (I_{Ks}). The former affects myocardial contractility, while the latter affects the repolarization process. β -Adrenoceptor stimulation during I_{Ks} blockade was shown to increase variability in the cellular repolarization duration of canine myocytes (16). At the tissue level, transmural differences in action potential duration affect the T-wave morphology in body surface ECG (11). This may be altered during periods of sympathetic activation (21). Heterogeneous distribution of β -adrenoceptors, regional arborization of sympathetic nerves (48), and differential cardiac sympathetic control (49) may contribute to spatial dispersion in action potential duration across the ventricles during periods of high sympathetic activity.

Since the result of these effects can be observed on the averaged steady-state QT interval of the surface ECG (7), it has been suggested that the beat-to-beat variability of the QT interval carries information on sympathetic nerve activity. In normal subjects, studies have repeatedly shown increases in QTV in response to (graded) head-up tilt, the seated position, or the standing position (14, 31, 35, 46) suggestive of a sympathetic modulation of QTV. Increased QTV in response to sympathetic activation induced by acute hypoxia provides further evidence for the relationship between sympathetic nervous system activity and QTV in normal subjects (45). Spectral analysis of QTV in normal subjects during interview stress and physical exercise, both of which increased sympathetic activity, demonstrated increased LF oscillations in QTV (27). A subsequent study, in which QTV spectra were estimated during a mental stress test while the atria were paced at a constant rate to exclude heart rate variability-driven QTV, confirmed the increase in LF power during stress and suggests a direct, rate-independent influence of the sympathetic nervous system on QTV (26). Pharmacological β -adrenoceptor activation showed consistently an increase in QTV (25, 42, 45, 46).

Pharmacological β -adrenoceptor blockade, on the other hand, showed no effect on QTV when measured during resting conditions (25, 30) but a reduction in QTV when the effect of RRV was removed through constant atrial pacing (23). Correlations between QTV and cardiac norepinephrine spillover, a direct measure of sympathetic activity, recorded during resting were observed in patients with hypertension (6).

To provide quantitative evidence for the association between QTV and sympathetic activity, we studied the relationship between oscillations in QTV and MSNA, the latter being used as a marker of generalized sympathetic activity, following head-up tilt. Note that RRV was accounted for in the analysis, since its contribution to QTV is well established (34).

Consistent with results reported by others who studied QTV-involving protocols that induce of sympathetic activation, mean heart period, mean QT interval, and heart rate variability decreased significantly, while MSNA_v, QTV_i, and total QTV increased, after subjects were tilted from the supine position to 40° tilt. The LF power of QTV, measured in units of absolute power, also increased significantly with tilt. However, normalized LF power of MSNA, i.e., the relative amount of LF oscillations in MSNA, did not change with 40° tilt, in contrast to the previously reported increase in sympathetic burst rate (4) and the increase in normalized LF power of MSNA observed by Furlan et al. (13) following 70° head-up tilt. Furthermore, LF power in SAP did not increase following 40° tilt, contrary to findings of Pagani et al. (28), indicating that the orthostatic stimulus was insufficient in eliciting a significant sympathetic vasomotor response. However, since we observed an increase in QTV paralleled by a decrease in RRV (along with a total MSNA_v increase), the tilt angle appears sufficient to elicit a sympathetic cardiac response.

Although beat-to-beat changes in the QT interval of normal subjects are believed to be mainly driven by changes in heart period (34), our results show that RRV contributed <50% to QTV even at rest, when the sympathetic drive is low. Consistent with results reported in the literature, the RRV contribution to both total QTV and LF power of QT decreased with tilt, indicating a decrease in the coupling/correlation between RRV and QTV (33, 38). This suggests that other factors, such as sympathetic activity, play a role in generating QT oscillations during orthostatic stress. Surrogate data testing demonstrated that although the percentage of MSNA power contribution to total and LF power of QT was small, it was not negligible in our data. Yet these contributions did not increase significantly with tilt. In addition, the coherence between LF oscillations in MSNA and QTV was not significant in both supine and tilt conditions, further emphasizing the weak correlation between the two variables.

While we did not find a notable change in the power contribution from MSNA to QTV, others have reported a correlation between LF oscillations in MSNA and RR when blood pressure changes were induced pharmacologically (28, 40), suggesting that MSNA may be used as a surrogate for sympathetic activity directed at the heart. Because the correlation between RR and MSNA is partly mediated by the cardiac baroreflex and sympathovagal outflow to the sinoatrial node, no conclusions may be drawn regarding the level of sympathetic modulation of the ventricles. Furthermore, the correlation between SAP and MSNA is stronger than that reported between RR and MSNA (28), which appears to be

confirmed by the lack of change in LF power of both variables in our data.

The QTV power independent of RR and MSNA represented >50% of the total and LF power of QTV and increased significantly with tilt. While a fraction of this power might be attributed to the increase in measurement noise induced by muscle activity, this seems unlikely to account for >50% of QTV, especially in the supine position when body movement is at a minimum. Therefore, the possibility remains that other variables, including cardiac sympathetic activity, play a significant role in generating QTV.

Our study may suggest that MSNA oscillations measured in the efferent nerve fiber of the peroneal muscle do not provide a useful surrogate index of oscillations in sympathetic nerve activity directed to the heart, in particular to the ventricular myocardium. Possibly, orthostatic stress might cause an organ-specific sympathetic response, targeting the heart differently from skeletal muscles, as reported during isometric handgrip and mental stress maneuvers (44), in particular when the stimulus is only of moderate strength. In addition, MSNA itself responds inconsistently to different acute stressors (9). However, other measures of MSNA, such as single-unit muscle sympathetic nerve firing rate, have been associated with cardiac norepinephrine spillover in patients with hypertension and major depressive and panic disorders (20). Therefore, LF MSNA oscillations might not be associated with cardiac sympathetic activity, while other measures of MSNA might still be useful in this regard.

Our study has several limitations. In the experimental setup, ECG was recorded using lead III, which is not the optimum choice for capturing the cardiac repolarization process. Cardiovascular variables, as well as MSNA, are inherently non-stationary processes; however, to obtain quasi-stationary data, we removed slow trends and allowed the subjects to rest for 30 min before the actual recording started. A potentially relevant variable that affects QTV is respiration, which was not included in the model in favor of low complexity, yielding robustness in parameter estimation. However, additional modeling carried out with respiration as another exogenous input (data not shown) suggested that QT power independent of RR, MSNA, and respiration still represents almost half of QT power. In line with our observation, a previous study demonstrated a negligible effect of respiration on QTV that did not change with tilt (35).

In conclusion, beat-to-beat QTV in normal subjects does not appear to be significantly affected by the rhythmic modulations in MSNA during rest or moderate orthostatic stress. We suggest that MSNA may not be a useful surrogate for cardiac sympathetic activity if the levels are expected to be low and that sympathetic influences on QTV are complex and not quantifiable with linear shift-invariant autoregressive models.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

F.E.-H., E.A.L., and M.B. developed the concept and designed the research; F.E.-H. analyzed the data; F.E.-H., E.A.L., and M.B. interpreted the results of the experiments; F.E.-H. prepared the figures; F.E.-H. drafted the manuscript; F.E.-H., E.A.L., D.A., and M.B. edited and revised the manuscript; F.E.-H., E.A.L., D.A., and M.B. approved the final version of the manuscript; E.A.L. performed the experiments.

REFERENCES

1. Akaike H. A new look at the statistical model identification. *IEEE Trans Automat Contr* 19: 716–723, 1974.
2. Almeida R, Pueyo E, Martínez JP, Rocha AP, Olmos S, Laguna P. A parametric model approach for quantification of short term QT variability uncorrelated with heart rate variability. *Proc Comput Cardiol Conf, Thessaloniki Chalkidiki, Greece, 2003*, p. 165–168.
3. Baselli G, Porta A, Rimoldi O, Pagani M, Cerutti S. Spectral decomposition in multichannel recordings based on multivariate parametric identification. *IEEE Trans Biomed Eng* 44: 1092–1101, 1997.
4. Baumert M, Lambert E, Vaddadi G, Sari CI, Esler M, Lambert G, Sanders P, Nalivaiko E. Cardiac repolarization variability in patients with postural tachycardia syndrome during graded head-up tilt. *Clin Neurophysiol* 122: 405–409, 2011.
5. 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.
6. Baumert M, Schlaich MP, Nalivaiko E, Lambert E, Sari CI, 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.
7. Conrath CE, Ophof T. Ventricular repolarization: an overview of (patho)physiology, sympathetic effects and genetic aspects. *Prog Biophys Mol Biol* 92: 269–307, 2006.
8. Coumel P. Cardiac arrhythmias and the autonomic nervous system. *J Cardiovasc Electrophysiol* 4: 338–355, 1993.
9. DeBeck LD, Petersen SR, Jones KE, Stickland MK. Heart rate variability and muscle sympathetic nerve activity response to acute stress: the effect of breathing. *Am J Physiol Regul Integr Comp Physiol* 299: R80–R91, 2010.
10. Faes L, Pinna GD, Porta A, Maestri R, Nollo G. Surrogate data analysis for assessing the significance of the coherence function. *IEEE Trans Biomed Eng* 51: 1156–1166, 2004.
11. Franz MR, Bargheer K, Rafflenbeul W, Haverich A, Lichtlen PR. Monophasic action potential mapping in human subjects with normal electrocardiograms: direct evidence for the genesis of the T wave. *Circulation* 75: 379–386, 1987.
12. Freeman R. Assessment of cardiovascular autonomic function. *Clin Neurophysiol* 117: 716–730, 2006.
13. Furlan R, Porta A, Costa F, Tank J, Baker L, Schiavi R, Robertson D, Malliani A, Mosqueda-Garcia R. Oscillatory patterns in sympathetic neural discharge and cardiovascular variables during orthostatic stimulus. *Circulation* 101: 886–892, 2000.
14. Hnatkova K, Kowalski D, Keirns JJ, van Gelderen EM, Malik M. Relationship of QT interval variability to heart rate and RR interval variability. *J Electrocardiol* 46: 591–596, 2013.
15. Iellamo F, Legramante JM, Pigozzi F, Spataro A, Norbiato G, Lucini D, Pagani M. Conversion from vagal to sympathetic predominance with strenuous training in high-performance world class athletes. *Circulation* 105: 2719–2724, 2002.
16. Johnson DM, Heijman J, Pollard CE, Valentin JP, Crijns HJ, Abi-Gerges N, Volders PG. I_{Ks} restricts excessive beat-to-beat variability of repolarization during β -adrenergic receptor stimulation. *J Mol Cell Cardiol* 48: 122–130, 2010.
17. Kaye DM, Lefkovits J, Jennings GL, Bergin P, Broughton A, Esler MD. Adverse consequences of high sympathetic nervous activity in the failing human heart. *J Am Coll Cardiol* 26: 1257–1263, 1995.
18. Kingwell BA, Thompson JM, Kaye DM, McPherson GA, Jennings GL, Esler MD. Heart rate spectral analysis, cardiac norepinephrine spillover, and muscle sympathetic nerve activity during human sympathetic nervous activation and failure. *Circulation* 90: 234–240, 1994.
19. Lambert E, Eikelis N, Esler M, Dawood T, Schlaich M, Bayles R, Socratous F, Agrotis A, Jennings G, Lambert G, Vaddadi G. Altered sympathetic nervous reactivity and norepinephrine transporter expression in patients with postural tachycardia syndrome. *Circ Arrhythm Electrophysiol* 1: 103–109, 2008.
20. Lambert EA, Schlaich MP, Dawood T, Sari C, Chopra R, Barton DA, Kaye DM, Elam M, Esler MD, Lambert GW. Single-unit muscle sympathetic nervous activity and its relation to cardiac noradrenaline spillover. *J Physiol* 589: 2597–2605, 2011.
21. Litovsky SH, Antzelevitch C. Differences in the electrophysiological response of canine ventricular subendocardium and subepicardium to acetylcholine and isoproterenol. A direct effect of acetylcholine in ventricular myocardium. *Circ Res* 67: 615–627, 1990.
22. Meredith IT, Broughton A, Jennings GL, Esler MD. Evidence of a selective increase in cardiac sympathetic activity in patients with sustained ventricular arrhythmias. *N Engl J Med* 325: 618–624, 1991.
23. Mine T, Shimizu H, Hiromoto K, Furukawa Y, Kanemori T, Nakamura H, Masuyama T, Ohyanagi M. Beat-to-beat QT interval variability is primarily affected by the autonomic nervous system. *Ann Noninvasive Electrocardiol* 13: 228–233, 2008.
24. Nakata A, Takata S, Yuasa T, Shimakura A, Maruyama M, Nagai H, Sakagami S, Kobayashi KI. Spectral analysis of heart rate, arterial pressure, and muscle sympathetic nerve activity in normal humans. *Am J Physiol Heart Circ Physiol* 274: H1211–H1217, 1998.
25. Nayyar S, Roberts-Thomson KC, Hasan MA, Sullivan T, Harrington J, Sanders P, Baumert M. Autonomic modulation of repolarization instability in patients with heart failure prone to ventricular tachycardia. *Am J Physiol Heart Circ Physiol* 305: H1181–H1188, 2013.
26. Negoescu R, Dinca-Panaiteanu S, Filcescu V, Ionescu D, Wolf S. Mental stress enhances the sympathetic fraction of QT variability in an RR-independent way. *Integr Physiol Behav Sci* 32: 220–227, 1997.
27. Negoescu R, Skinner JE, Wolf S. Forebrain regulation of cardiac function: spectral and dimensional analysis of RR and QT intervals. *Integr Physiol Behav Sci* 28: 331–342, 1993.
28. Pagani M, Montano N, Porta A, Malliani A, Abboud FM, Birkett C, Somers VK. Relationship between spectral components of cardiovascular variabilities and direct measures of muscle sympathetic nerve activity in humans. *Circulation* 95: 1441–1448, 1997.
29. Parati G, Esler M. The human sympathetic nervous system: its relevance in hypertension and heart failure. *Eur Heart J* 33: 1058–1066, 2012.
30. Piccirillo G, Cacciafesta M, Lionetti M, Nocco M, Di Giuseppe V, Moise A, Naso C, Marigliano V. Influence of age, the autonomic nervous system and anxiety on QT-interval variability. *Clin Sci (Lond)* 101: 429–438, 2001.
31. Piccirillo G, Magnanti M, Matera S, Di Carlo S, De Laurentis T, Torrini A, Marchitto N, Ricci R, Magri D. Age and QT variability index during free breathing, controlled breathing and tilt in patients with chronic heart failure and healthy control subjects. *Transl Res* 148: 72–78, 2006.
32. Piccirillo G, Magri D, Ogawa M, Song J, Chong VJ, Han S, Joung B, Choi EK, Hwang S, Chen LS, Lin SF, Chen PS. Autonomic nervous system activity measured directly and QT interval variability in normal and pacing-induced tachycardia heart failure dogs. *J Am Coll Cardiol* 54: 840–850, 2009.
33. Porta A, Bari V, Badilini F, Tobaldini E, Gnecci-Ruscone T, Montano N. Frequency domain assessment of the coupling strength between ventricular repolarization duration and heart period during graded head-up tilt. *J Electrocardiol* 44: 662–668, 2011.
34. Porta A, Baselli G, Caiani E, Malliani A, Lombardi F, Cerutti S. Quantifying electrocardiogram RT-RR variability interactions. *Med Biol Eng Comput* 36: 27–34, 1998.
35. Porta A, Tobaldini E, Gnecci-Ruscone T, Montano N. RT variability unrelated to heart period and respiration progressively increases during graded head-up tilt. *Am J Physiol Heart Circ Physiol* 298: H1406–H1414, 2010.
37. Porta A, Tobaldini E, Magagnin V, Bassani T, Gnecci-Ruscone T, Montano N. Open loop linear parametric modeling of the QT variability. *Proc Annu Int Conf IEEE Eng Med Biol Soc, Minneapolis, MN, 2009*, p. 6453–6456.
38. Porta A, Tobaldini E, Montano N, Gnecci-Ruscone T. The strength of QT-RR coupling decreases during graded head-up tilt. *Proc 29th Annu Int Conf IEEE Eng Med Biol Soc, 2007*, p. 5958–5961.
39. Sacre JW, Franjic B, Coombes JS, Marwick TH, Baumert M. QT interval variability in type 2 diabetic patients with cardiac sympathetic dysinnervation assessed by ^{123}I -metaiodobenzylguanidine scintigraphy. *J Cardiovasc Electrophysiol* 24: 305–313, 2013.

40. Saul JP, Berger RD, Albrecht P, Stein SP, Chen MH, Cohen RJ. Transfer function analysis of the circulation: unique insights into cardiovascular regulation. *Am J Physiol Heart Circ Physiol* 261: H1231–H1245, 1991.
41. Schmidt M, Baumert M, Porta A, Malberg H, Zaunseder S. Two-dimensional warping for one-dimensional signals—conceptual framework and application to ECG processing. *IEEE Trans Signal Processing* 62: 5577–5588, 2014.
42. Seethala S, Shusterman V, Saba S, Mularski S, Nemec J. Effect of β -adrenergic stimulation on QT interval accommodation. *Heart Rhythm* 8: 263–270, 2011.
43. Tarvainen MP, Ranta-aho PO, Karjalainen PA. An advanced detrending method with application to HRV analysis. *IEEE Trans Biomed Eng* 49: 172–175, 2002.
44. Wallin BG, Esler M, Dorward P, Eisenhofer G, Ferrier C, Westerman R, Jennings G. Simultaneous measurements of cardiac noradrenaline spillover and sympathetic outflow to skeletal muscle in humans. *J Physiol* 453: 45–58, 1992.
45. Xhaet O, Argacha JF, Pathak A, Gujic M, Houssiere A, Najem B, Degaute JP, Van de Borne P. Sympathoexcitation increases the QT/RR slope in healthy men: differential effects of hypoxia, dobutamine, and phenylephrine. *J Cardiovasc Electrophysiol* 19: 178–184, 2008.
46. Yeragani VK, Pohl R, Jampala V, Balon R, Kay J, Igel G. Effect of posture and isoproterenol on beat-to-beat heart rate and QT variability. *Neuropsychobiology* 41: 113–123, 2000.
48. Yoshioka K, Gao DW, Chin M, Stillson C, Penades E, Lesh M, O'Connell W, Dae M. Heterogeneous sympathetic innervation influences local myocardial repolarization in normally perfused rabbit hearts. *Circulation* 101: 1060–1066, 2000.
49. Zaza A, Malfatto G, Schwartz PJ. Sympathetic modulation of the relation between ventricular repolarization and cycle length. *Circ Res* 68: 1191–1203, 1991.
50. Zhu Y, Lee PJ, Pan J, Lardin HA. The relationship between ventricular repolarization duration and RR interval in normal subjects and patients with myocardial infarction. *Cardiology* 111: 209–218, 2008.

