Transfer Function Gain between Heart Period and QT Variabilities Increases during Sympathetic Activation Induced by Head-up Tilt

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Abstract

The variability of the duration of the cardiac electrical activity, approximated by the onset of the Q-wave to the end of the T-wave (QT), computed in the low frequency (LF, from 0.04 to 0.15 Hz) band, is utilized as a marker of sympathetic modulation directed to the ventricles. However, the magnitude of QT variability might be affected by heart period (HP) variability as a consequence of the QT-HP relation. We hypothesize that the gain of the relationship between HP and QT in the LF band could be better suited than QT variability to infer the cardiac sympathetic control as a consequence of its intrinsic normalization by the magnitude of HP changes. In this study we assessed transfer function gain (TFG) from HP to QT as well as spectral QT and HP markers in 23 healthy young subjects (age 26±6 years, 11 males) undergoing head-up tilt test at 45° (T45) and 90° (T90). Results showed that QT variability in the LF band increased during T90. TFG increased as well but the raise was evident also at a lower tilt table inclination, namely during T45. H, the gain of the TFG in the LF band could be a more sensitive marker of the increased sympathetic drive than the LF power of QT variability.

1. Introduction

The duration of the cardiac electrical activity phase, approximated by the onset of the Q-wave to the end of the T-wave (QT) derived from the surface electrocardiogram, is monitored more and more frequently over time in clinical protocols because it was suggested that its variability could be exploited to infer cardiac sympathetic neural control [1,2]. The combined use of heart period (HP) and QT variability markers could provide a complete picture of the cardiac autonomic control given that parasympathetic control can be derived from the power of HP variability in the high frequency (HF, from 0.15 to 0.5 Hz) band [3] and sympathetic control could be inferred from QT variability in the low frequency (LF, from 0.04 to 0.15 Hz) band [4]. The LF power of the QT variability overcomes the limitation of the LF power of HP variability that is linked to both vagal and sympathetic modulations [5]. The concurrent analysis of HP and QT variability was shown to be helpful to investigate modifications of the cardiac neural control with physiological challenges [1,4,6], aging and pathology [7-10]. Unfortunately, QT variability can include a relevant confounding factor: it might be strictly related to the HP variability due to the QT-HP relation [11]. This dependence was limited via a modeling approach by computing the fraction of QT variability that is unrelated to HP variations [6,12]. However, the magnitude of the QT-HP transfer function could be an intrinsically normalized, and simpler, marker because it provides the amount of QT changes per unit variation of HP.

In this study we estimate the transfer function gain (TFG) from HP to QT variability via a bivariate linear model [12] in healthy subjects during the sympathetic activation induced by head-up tilt with different tilt table inclinations. We hypothesize that markers based on TFG could be more sensitive to the sympathetic stimulus than the LF power of QT variability.

2. Experimental protocol and data analysis

2.1. Experimental protocol

We exploited an historical database designed to assess neural control directed to the sinus node and ventricles [2]. We refer to [2] for a complete description of the experimental protocol. Briefly, 23 young healthy subjects

(age 26±6 years, 11 males) have been enrolled in this study. The study adhered to the principles of the Declaration of Helsinki for studies involving human subjects and was approved by the ethical review board of the "L. Sacco" Hospital, Milan, Italy. Subjects signed an informed consent before participating.

Subjects lied on the tilt table in supine position (T0) for 10 minutes, then the table was tilted at 45° and 90° (T45 and T90 respectively). Each session lasted 10 minutes. T45 and T90 were administered in a random order after 40 minutes of recovery. None of the subjects experienced presyncope signs. During the entire recording subjects were not allowed to talk and breathed spontaneously. Electrocardiogram was recorded from a modified lead II (Biosignal Conditioning Device, Marazza, Monza Italy). The sampling rate was 1 kHz.

2.2. Beat-to-beat series extraction

HP was derived as the temporal distance between two consecutive R-wave peaks located with minimum jitters with parabolic interpolation. QT interval was derived as the time interval between the second R-wave peak defining the HP and the end of its T-wave. The T-wave offset was detected automatically as the point where the first derivative calculated on the T-wave downslope became smaller than the 30% of the absolute value of the maximum derivative [13]. Stationary sequences lasting 300 beats were extracted from T0, T45, and T90 for HP and QT series. Ectopic beats or misdetections were manually corrected. Mean and variance of HP and QT series were extracted in all experimental conditions, labelled as μ_{HP}, μ_{QT}, σ^2_{HP} and σ^2_{QT} and expressed in ms, ms, ms^2 and ms^2 respectively.

2.3. Spectral analysis

Parametric spectral analysis was performed on HP and QT series [4]. Briefly, each series was modelled as a realization of an autoregressive process whose coefficients were estimated from the data and optimum model order was chosen in the range from 8 to 14 via the Akaike figure of merit. Power spectral density of HP and QT was decomposed into power spectral components [4], classifying each component as LF or HF if its central frequency was dropped in the LF or HF band [3]. The sum of the power of all components of HP in LF and HF bands was labelled as LF_{HP} and HF_{HP} respectively. The HF_{HP} power was taken as a marker of vagal modulation directed to the sinus node [3,5]. The sum of all the components of QT in LF and HF bands was denoted as LF_{QT} and HF_{QT}, the ratio between LF_{HP} and HF_{HP}, representing the sympathovagal balance, as LF_{HP}/HFHP. The LF_{QT} power was taken as a marker of sympathetic modulation directed to the ventricles [1,2,4]. All spectral indexes were expressed in ms^2.

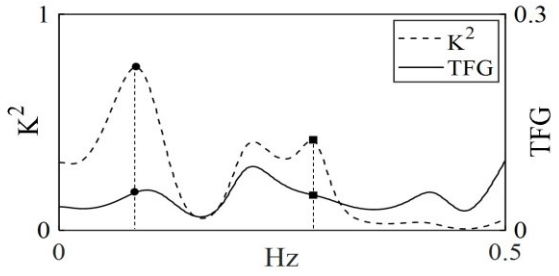

Figure 1. TFG (solid line) and K^2 (dashed line) between HP and QT derived from a representative subject during T0. TFG and K^2 are sampled at the maximum of K^2 marked with a solid circle in LF band and with a solid square in HF band.

2.4. Cross-spectral analysis

The relation between HP and QT variability series in frequency domain was computed via cross-spectral analysis [12]. The cross-spectrum was estimated via a parametric approach based on the computation of the coefficients of a bivariate autoregressive model with the model order fixed to 10 [14]. The TFG was computed as the cross-spectrum modulus between HP and QT divided by the power spectrum of HP. The Ph function was assessed as the phase of the cross-spectrum with negative phases indicating that QT changes lagged behind HP variations. The K^2 was calculated as the squared cross-spectrum modulus between HP and QT divided by the product of the power of HP and QT spectra. K^2 always ranged between 0 and 1, where 0 means null coupling and 1 indicates full coupling. TFG, Ph and K^2 were sampled at the maximum of K^2 in LF and HF band [15]. Markers were labelled as TFG_{LF}, TFG_{HF}, Ph_{LF}, Ph_{HF}, K^2_{LF} and K^2_{HF}. The percentage of subjects having K^2_{LF} and K^2_{HF} higher than 0.5, considered a threshold for a significant K^2 [14], was also assessed. Figure 1 shows TFG (solid line) and K^2 (dashed line) calculated in a representative subject during T0.

2.5. Statistical analysis

One-way repeated measures analysis of variance, or Friedman repeated measures analysis on ranks when appropriate, was applied for detecting differences among conditions (Dunnett's test for multiple comparisons). Statistical analysis was carried out using the commercial statistical program (Sigmaplot, v.14.0, Systat Software, Inc., Chicago, IL, USA). A $p<0.05$ was always considered as significant.

3. Results

Table 1 reports results relative to time and spectral

Table 1. Time and frequency domain markers derived from HP and QT series.

Index	T0	T45	T90
μ_{HP} [ms]	922.29±95.98	819.12±88.74 *	714.75±76.41 *,#
σ^2_{HP} [ms^2]	3652.14±2491.16	3478.64±2291.20	2307.69±1513.51
μ_{QT} [ms]	323.41±21.46	308.11±24.05 *	297.52±26.48 *,#
σ^2_{QT} [ms^2]	19.87±26.00	68.15±189.37	62.11±143.82
LF_{HP} [ms^2]	1287.47±917.47	1518.09±1610.27	1198.28±1052.50
HF_{HP} [ms^2]	1160.55±1144.27	531.07±520.34 *	184.88±163.61 *,#
LF_{HP}/HF_{HP}	2.42±4.07	5.02±5.23	11.35±10.73 *,#
LF_{QT} [ms^2]	5.04±9.81	13.77±32.77	23.85±74.54 *
HF_{QT} [ms^2]	10.23±17.29	33.20±98.42	16.19±18.79

μ_{HP}: HP mean; σ^2_{HP}: HP variance; μ_{QT}: QT mean; σ^2_{QT}: QT variance; low frequency: LF; high frequency: HF; LF_{HP}: power of HP in LF band; HF_{HP}: power of HP in HF band; LF_{QT}: power of QT in LF band; HF_{QT}: power of QT in HF band; T0, T45, T90: head-up tilt at 0°, 45°, 90° respectively. Results are reported as mean±SD The symbol * indicates $p<0.05$ versus T0. The symbol # indicates $p<0.05$ versus T45.

parameters derived from HP and QT series. μ_{HP} and HF_{HP} decreased in T45 and T90 compared to T0 and in T90 with respect to T45. μ_{QT} behaved analogously. LF_{HP}/HF_{HP} increased in T90 with respect to R and T45. During T90 LF_{QT} power increased compared to T0. σ^2_{HP}, σ^2_{QT}, LF_{HP} and HF_{QT} were not affected by postural challenge.

Table 2 shows K^2, Ph and TFG computed in LF and HF bands. K^2_{LF} remained stable, while K^2_{HF} decreased during T90 with respect to T0. Ph_{LF} and Ph_{HF} did not differ across experimental conditions. Conversely, both TFG_{LF} and TFG_{HF} were increased in T45 and T90 with respect to T0, but TFG markers were similar during T45 and T90. K^2_{LF} was higher than 0.5 in 70%, 61%, 52% of the subjects and K^2_{HF} in 52%, 39% and 30% of subjects respectively during T0, T45 and T90.

4. Discussion

The main findings of this work can be summarized as follows: i) the head-up tilt elicited the expected decrease of HF_{HP} power and the expected increase of the LF_{QT} power; ii) K^2_{LF} and K^2_{HF} were significant in the majority of the subjects during T0 and only K^2_{HF} was reduced during head-up tilt; iii) TFG_{LF} and TFG_{HF} increased during head-up tilt and the raise was already visible during T45.

This work investigated the dependence of QT on the HP variability via TFG as a marker of the sympathetic control during a graded head-up tilt. It is well-known that postural stimulus induces a sympathetic activation and vagal withdrawal [16,17] and this effect is reflected by the increase of the LF_{QT} power and the decrease of the HF_{HP} power [1,3-5]. The present study confirmed the findings present in literature [1,3-5]. The increase of LF_{QT} power were evident solely during T90, while HF_{HP} decreased already during T45. This finding might suggest a limited sensitivity of LF_{QT} power in detecting the effects of the postural stimulus on cardiac sympathetic control.

The analysis of the strength of the QT-HP coupling carried out with K^2 indicated that K^2_{LF} remained significant (i.e. higher than 0.5) in the majority of the subjects across the various experimental sessions of the protocol, thus suggesting that in the LF band the transfer function, comprising both magnitude and phase, is reliably estimated. Conversely, K^2_{HF} was reduced with tilt table angle, thus confirming the decoupling of HP and QT with the postural stimulus reported in [4]. Since the percentage of subjects with significant K^2_{HF} dropped below 50% during T45 and T90, we avoided to discuss

Table 2. Cross-spectral markers derived from HP and QT series.

Index	T0	T45	T90
K^2_{LF}	0.59±0.23	0.61±0.24	0.58±0.26
K^2_{HF}	0.53±0.24	0.49±0.22	0.41±0.20*
Ph_{LF} [rad]	-0.31±0.33	-0.39±0.58	-0.31±0.74
Ph_{HF} [rad]	-0.17±0.83	0.24±1.24	0.34±1.14
TFG_{LF}	0.04±0.01	0.07±0.09*	0.08±0.09*
TFG_{HF}	0.06±0.04	0.14±0.18*	0.17±0.21*

K^2; squared coherence function; Ph: phase function; TFG: transfer function gain; low frequency: LF; high frequency: HF; K^2_{LF}: K^2 in LF band; K^2_{HF}: K^2 in HF band; Ph_{LF}: Ph in LF band; Ph_{HF}: Ph in HF band; TFG_{LF}: TFG in LF band; TFG_{HF}: TFG in HF band; rad: radians; T0, T45, T90: head-up tilt at 0°, 45°, 90° respectively. Results are reported as mean±SD. The symbol * indicates $p<0.05$ versus T0.

between-condition differences of transfer function markers in the HF band. Remarkably, TFG_{LF} increased during postural challenge and this result confirms findings reported in [12]. The original finding of this study is that the TFG_{LF} significantly increased at lower magnitude of the sympathetic stressor (i.e. T45) compared to a more classical index such as the LF_{QT} power that raised only during T90. We suggest that the greater sensitivity of TFG_{LF} compared to LF_{QT} to sympathetic activation might be the result of the intrinsic normalization by the magnitude of the HP changes provided by any TFG marker given that TFG measures the amount of output variation in response to a unit change of input. Future studies might check whether further refinements could be obtained by accounting for nonlinear QT-HP interactions and their temporal directions [18,19]. Conversely, markers of phase shift between HP and QT were unable to reveal changes in experimental sessions and, thus, they appear to be insensible to modifications of the sympathetic drive.

5. Conclusions

This work evaluated the possibility of using markers of the dynamical dependence of QT on HP variability in the frequency domain to infer the sympathetic control directed to the ventricles. Since TFG_{LF} could detect the increased sympathetic activation induced by head-up tilt with a magnitude of the orthostatic stimulus smaller than LF_{QT} power, we suggest that an index based on transfer function might be more powerful than that derived from spectral analysis of QT variability. Results should be confirmed in a larger population and in different protocols challenging the autonomic regulation to understand its potentiality and its suitability to be introduced in clinical protocols.

References

[1] M. Baumert et al., "QT interval variability in body surface ECG: measurement, physiological basis, and clinical value: position statement and consensus guidance endorsed by the European Heart Rhythm Association jointly with the ESC Working Group on Cardiac Cellular Electrophysiology," *Europace*, vol. 18, pp. 925–944, 2016.

[2] B. De Maria et al., "Concomitant evaluation of heart period and QT interval variability spectral markers to typify cardiac control in humans and rats," *Front. Physiol.*, vol. 10, art. no. 1478, 2019.

[3] Task Force, "Heart rate variability. Standards of measurement, physiological interpretation, and clinical use," *Eur. Heart J.*, vol. 17, pp. 354–381, 1996.

[4] A. Porta et al., "Frequency domain assessment of the coupling strength between ventricular repolarization duration and heart period during graded head-up tilt," *J. Electrocardiol.*, vol. 44, pp. 662–668, 2011.

[5] B. Pomeranz et al., "Assessment of autonomic function in humans by heart rate spectral analysis," *Am. J. Physiol.*, vol. 248, pp. H151–H153, 1985.

[6] A. Porta et al., "RT variability unrelated to heart period and respiration progressively increases during graded head-up tilt," *Am. J. Physiol.*, vol. 298, pp. H1406–H1414, 2010.

[7] M. Baumert et al., "Cardiac repolarization variability in patients with postural tachycardia syndrome during graded head-up tilt," *Clin. Neurophysiol.*, vol. 122, pp. 405–409, 2011.

[8] A. Porta et al., "Autonomic control of heart rate and QT interval variability influences arrhythmic risk in long QT syndrome type 1," *J. Am. Coll. Cardiol.*, vol. 65, pp. 367–374, 2015.

[9] V. Bari et al., "Multiscale Complexity Analysis of the Cardiac Control Identifies Asymptomatic and Symptomatic Patients in Long QT Syndrome Type 1," *PLoS ONE*, vol. 9, art. no. e93808, 2014.

[10] M. Baumert et al., "Decoupling of QT interval variability from heart rate variability with ageing," *Physiol. Meas.*, vol. 34, pp. 1435–1448, 2013.

[11] H. C. Bazett, "An analysis of the time-relations of electrocardiograms," *Heart*, vol. 7, pp. 353–370, 1929.

[12] A. Porta et al., "Quantifying electrocardiogram RT-RR variability interactions," *Med. Biol. Eng. Comput.*, vol. 36, pp. 27–34, 1998.

[13] A. Porta et al., "Performance assessment of standard algorithms for dynamic RT interval measurement: comparison between RTapex and RTend approach," *Med. Biol. Eng. Comput.*, vol. 36, pp. 35-42, 1998.

[14] A. Porta et al., "Assessing baroreflex gain from spontaneous variability in conscious dogs: role of causality and respiration," *Am. J. Physiol.*, vol. 279, pp. H2558–H2567, 2000.

[15] V. Bari et al., "Comparison of causal and non-causal strategies for the assessment of baroreflex sensitivity in predicting acute kidney dysfunction after coronary artery bypass grafting," *Front. Physiol.*, vol. 10, art. no. 1319, 2019.

[16] W. H. Cooke et al., "Human responses to upright tilt: a window on central autonomic integration," *J. Physiol.*, vol. 517, pp. 617–628, 1999.

[17] A. Marchi et al, "Calibrated variability of muscle sympathetic nerve activity during graded headup tilt in humans and its link with noradrenaline data and cardiovascular rhythms, " *Am. J. Physiol.*, vol. 310, pp. R1134–R1143, 2016.

[18] V. Jacquemet et al., "Evaluation of a subject-specific transfer-function-based nonlinear QT interval rate-correction method," *Physiol. Meas.*, vol. 32, pp. 619–635, 2011.

[19] A. Porta et al., A network physiology approach to the assessment of the link between sinoatrial and ventricular cardiac controls, *Physiol. Meas.*, vol. 38, pp. 1472–1489, 2017.

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