Transfer Function Gain Between Heart Period and QT Interval Variability Decreases at a 10-year Follow-up in Half-Marathon Runners

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Abstract

In the last years there is increasing interest in the study of the effects of physical activity on the cardiovascular control of athletes by heart period (HP) and QT interval (QT) variability analysis. However, the relation between HP and QT variability in athletes has been poorly investigated. Therefore, we aimed at estimate transfer function gain (TFG) to typify the relationship between HP and QT variability in athletes. We acquired electrocardiogram in 18 half-marathon runners while supine (REST) and during active standing (STAND) at baseline (B) and at a 10-year follow up (FU). The TFG was computed as the ratio between the modulus of the cross-spectral density between HP and QT divided by the power spectral density of HP in low frequency (LF, 0.04-0.15 Hz, TFG_{LF}) and high frequency (HF, 0.15-0.4 Hz, TFG_{HF}) bands. We found that TFG_{HF} was lower at FU compared to B both at REST and during STAND. TFG_{LF} increased during STAND compared to REST only at FU. The present work supports the use of the linear approach in the frequency domain to typify the cardiac control of athletes. In addition, the findings suggest that a moderate and regular physical activity through the years is beneficial as it favors a decrease of the cardiac sympathetic modulation.

1. Introduction

In the last years the topic of the right dose of physical exercise is an open issue. The debate regards both primary and secondary prevention in healthy subjects and patients [1,2]. Indeed, from one hand physical exercise is strongly recommended to reduce the overall cardiovascular risk, but from the other hand even more evidences are suggesting that the type and amount of physical exercise are factors that need to be considered to reach a proper and positive effect of physical activity on the cardiovascular system [3,4]. In this scenario, there is increasing attention in addressing this topic studying the effect of physical exercise on the cardiovascular system exploiting the heart period (HP) variability analysis [4-6]. More recently, the evaluation of QT interval (QT) variability analysis has been proposed as a complementary evaluation with respect to the more traditional HP variability one to better typify the cardiac sympathetic modulation also for the study of the cardiac control of athletes [7,8].

However, the relationship between HP and QT variability in athletes has been poorly investigated. Indeed, it is well established that a portion of the QT variability is dependent on the HP variability and it is also well known that indexes of the HP and QT variability relation are helpful in identifying aspects of the cardiac control that cannot be captured via the separate computation of HP and QT variability indexes [9-16]. Among the several methods useful to study the relation between HP and QT variability, the transfer function gain (TFG), quantifying the amount of QT changes per unit variation of HP [11], is a simple one that could be applied to sport medicine to investigate the cardiac control of athletes.

Therefore, the aim of this study is to apply the TFG method to evaluate the relation between HP and QT variability in a group of half-marathon athletes who have

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performed regular exercise for 10 years and who have been studied by active standing protocol. We hypothesize that the TFG is a marker sensible to the modulation induced by physical exercise in the cardiac neural control.

2. Experimental Protocol and Data Analysis

2.1 Experimental Protocol

The full experimental protocol and studied population were described in [5,6]. Briefly, 18 amateur half-marathon runners (17 males) were studied at baseline (B) and after a 10-year follow-up (FU). The mean age at FU was 52.3±8.0 years and the body mass index was 23.1±1.7 kg·m^2. The group of athletes reduced the overall physical activity from B to FU (from 14.6±2.9 to 6.5±3.1 hours per week). Both at B and at FU the athletes were studied by active standing test. They were studied in the morning after a good night sleep, avoiding alcoholic and caffeinated beverages in the 24 hours preceding the test and far from a session of physical exercise. Electrocardiogram (ECG) from modified lead II (AT-MIO 16E2, National Instrument at B and LAB3, Marazza, Monza Italy at FU) was recorded for 5 minutes while supine in resting condition (REST) and for 4 minutes during active standing (STAND). The sampling rate was 300 Hz at B and 1000 Hz at FU. Attention was paid to position electrodes to minimize noise during the acquisition of the ECG and to avoid biphasic T-waves.

The experimental protocol adhered to the principles of the Declaration of Helsinki and was approved by the Ethics Committee of ICS Maugeri (number of approvals 2277CE). Each subject signed a written informed consent before the start of the experimental session.

2.2. Beat-to-beat Time Series Extraction

From the recorded ECG, beat-to-beat time series of HP and QT were extracted using a method based on a threshold on the first derivative. R wave position was fixed by means of parabolic interpolation. The *n*th HP was approximated as the time interval between two consecutive R-wave peaks detected on the ECG signal. The QT interval was approximated as the time interval between the second R-wave peak delimiting the *n*th HP and the end of the following T-wave [17]. The end of the T wave was fixed where the absolute value of the first derivative calculated on the T-wave downslope became smaller than the 30% of the value of the steepest slope of the T-wave [17]. All the fiduciary points were detected by an automatic algorithm and visually checked to avoid detection errors. Correction of the HP and QT time series was implemented in case of ectopic beats, which never exceeded 5% of the series length. Linear interpolation between the HP and QT interval values with time index preceding and following those directly influenced by ectopies was applied. For each athlete stationary segments of 300 consecutive HPs and QTs were selected for further analysis at REST and during STAND. After linear detrending of the series, mean and variance of the HP and QT series were calculated and named as μ_{HP} and σ^2_{HP}, μ_{QT} and σ^2_{QT}, respectively. μ_{HP} and μ_{QT} were expressed in ms, while σ^2_{HP} and σ^2_{QT} in ms^2.

2.3. Cross-spectral Analysis of HP and QT Interval Series

The relation between HP and QT variability series was quantified by the model-based cross-spectral method in the frequency domain [11,18]. The method is based on the estimation of the coefficients of a bivariate autoregressive model identified via least squared approach [18]. The model order was fixed at 10 [18]. The TFG was computed as the ratio between the modulus of the cross-spectral density between HP and QT divided by the power spectral density of HP. The squared coherence function K^2 was calculated as the ratio between the square cross-spectral density modulus between HP and QT, to the product of the power spectral densities of QT and HP series. TFG and K^2 were sampled in correspondence of the weighted central frequency of the HP components in low frequency (LF, 0.04-0.15 Hz) and high frequency (HF, 0.15-0.4 Hz) bands, where the weights were the powers of the components [18,19]. Markers in the LF and HF bands were

Table 1. Time domain indexes of HP and QT series.

Index	REST		STAND	
	B	FU	B	FU
μ_{HP} [ms]	930.31±194.69	1069.67±155.87*	765.90±192.34#	856.07±141.02#
σ^2_{HP} [ms^2]	2711.12±1713.96	1727.56±717.73	2577.85±1720.54	1811.14±957.48
μ_{QT} [ms]	348.81±39.06	373.96±36.27*	326.63±39.20#	338.78±38.63#
σ^2_{QT} [ms^2]	22.66±9.12	10.63±8.99*	40.22±23.27#	18.25±18.67*

REST: supine in resting condition; STAND: active standing; B: baseline condition; FU: after a 10-year follow-up; HP: heart period; μ_{HP}: mean of HP; σ^2_{HP}: variance of HP; QT: QT interval; μ_{QT}: mean of QT; σ^2_{QT}: variance of QT. The symbol * indicates $p<0.05$ B vs FU. The symbol # indicates $p<0.05$ REST vs STAND.

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

Index	REST		STAND	
	B	FU	B	FU
K^2_{LF}	0.31±0.25	0.21±0.18	0.31±0.29	0.51±0.23*#
K^2_{HF}	0.23±0.19	0.21±0.17	0.21±0.23	0.25±0.22
TFG_{LF}	0.03±0.01	0.02±0.01	0.04±0.02	0.05±0.02#
TFG_{HF}	0.09±0.09	0.03±0.02*	0.11±0.13	0.05±0.03*

REST: supine in resting condition; STAND: active standing; B: baseline condition; FU: after a 10-year follow-up; HP: heart period; K^2: squared coherence function; LF: low frequency; K^2_{LF}: K^2 in LF band; HF: high frequency; K^2_{HF}: K^2 in HF band; TFG: transfer function gain; TFG_{LF}: TFG in LF band; TFG_{HF}: TFG in HF band. The symbol * indicates $p<0.05$ B vs FU. The symbol # indicates $p<0.05$ REST vs STAND.

indicated as TFG_{LF} and K^2_{LF}, or TFG_{HF} and K^2_{HF}, respectively. K^2_{LF} and K^2_{HF} ranged from 1 (full correlation between HP and QT variability) to 0 (null QT-HP correlation). All markers were dimensionless.

2.4. Statistical analysis

Two-way repeated measure analysis of variance (Holm-Sidak test for multiple comparison, one factor repetition) was applied to test the differences between the two experimental conditions (i.e. REST and STAND) within the same time point (i.e. B or FU) and between the two time points within the same experimental condition. Data are reported as mean±standard deviation. All the statistical analyses were performed using the commercial software Sigmaplot (version 11.0, Systat Software, Inc., Chicago, IL). A $p<0.05$ was always considered as significant.

3. Results

Table 1 shows the results of the time domain analysis of HP and QT variabilities in the two periods of observation (i.e. B and F) in both the experimental conditions (i.e. REST and STAND). μ_{HP} and μ_{QT} decreased during STAND compared to REST both at B and FU and were higher at FU compared to B at REST. σ^2_{QT} decreased at FU compared to B both at REST and during STAND conditions and increased from REST to STAND only in B. σ^2_{HP} did not change across periods of observation and experimental conditions.

Table 2 shows the results of the cross-spectral analysis between HP and QT in the two periods of observation (i.e. B and FU) in both the experimental conditions (i.e. REST and STAND). K^2_{LF} increased from REST to STAND at FU and was higher at FU compared to B during STAND. K^2_{LF} remained stable across periods of observation and experimental conditions. TFG_{HF} was lower at FU compared to B both at REST and during STAND and it did not exhibit variations in response to STAND. TFG_{LF} did not change between B and FU and increased during STAND in FU but not in B.

4. Discussion

In the present study we assessed the relation between HP and QT variability in a group of half-marathon runners at a 10-year follow up. We found that: i) the variance of the QT variability is reduced at FU compared to B; ii) the TFG from HP to QT in the HF band is reduced at FU compared to B with a stable value of K^2; iii) the increase of the TFG from HP to QT in the LF band during STAND compared to REST was detectable only at FU and was accompanied by the concomitant increase of K^2.

The results of the present study support the possibility to use the cross-spectral analysis to study the cardiac control of athletes. In previous studies the application of transfer function analysis during sympathetic activation induced by an orthostatic challenge detected an increase of the gain of the QT-HP transfer function in healthy untrained subjects [11,20]. Therefore, we interpret the lower gain of the QT-HP relationship in the HF band at FU compared to B as a sign of a reduced sympathetic control. This finding suggests that in the group of studied athletes the maintenance of regular physical exercise through the year, moving from strenuous to moderate activity, resulted in a lower sympathetic control. This observation is in keeping with previous studies [6,7] pointing out that reduction of physical exercise from strenuous to moderate implies a reduced sympathetic regulation and enhanced vagal cardiac modulation at FU, lowering the overall cardiovascular risk. This trend is opposite to those occurring with physiological ageing [21]. Remarkably, the lower gain of the QT-HP relationship at FU compared to B was detected not only during STAND and also at REST, thus suggesting that sympathetic control was modified even in absence of the stimulus. No difference was observed in the LF band between the two time points even though the expected increase of the QT-HP transfer function gain in response to STAND was detected only at FU. This suggests that the usual reactivity to an orthostatic stimulus is better preserved at FU than B and this finding can be taken again as a positive feature of the FU time point compared to the B one.

We conclude that the cross-spectral analysis between HP and QT variabilities provides additional and complementary information with respect to the more traditional univariate analyses in the study of the cardiac control of athletes.

5. Conclusion

This study focused on characterization of the relation between HP and QT variabilities in a group of half-marathon runners evaluated at baseline and at a 10-year follow up. The observed decrease of the TFG through the years supports that a moderate and regular physical activity is beneficial as it causes a decrease of the sympathetic cardiac modulation contributing to lower the overall cardiovascular risk. The present work also supports the use of the cross-spectral methods, in addition to the more traditional time domain indexes, to typify the cardiac control of athletes. We recommend to extend the present analysis to untrained or less-trained population as well to complement more usual tools utilized to monitor the aging process [22].

References

[1] A. Pelliccia et al., "2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease," *Eur. Heart J.*, vol. 42, pp. 17-96, 2021.

[2] L. Galiuto et al., "Personalized Exercise Prescription for Heart Patients," *Curr. Sports Med. Rep.*, vol. 18, pp. 380-381, 2019.

[3] G. Tesema et al., "Does chronic high-intensity endurance training have an effect on cardiovascular markers of active populations and athletes? Systematic review and meta-analysis," *BMJ Open*, vol. 9, art. no. e032832, 2019.

[4] L. A. Dalla Vecchia et al., "Can strenuous exercise harm the heart? Insights from a study of cardiovascular neural regulation in amateur triathletes," PLoS ONE, vol. 14, art. no. e0216567, 2019.

[5] L. Dalla Vecchia et al., "On site assessment of cardiac function and neural regulation in amateur half marathon runners," *Open Heart*, vol. 1, art. no. e000005, 2014.

[6] B. De Maria et al., "Ten-year follow-up of cardiac function and neural regulation in a group of amateur half-marathon runners," *Open Heart*, vol. 8, art. no. e001561, 2021.

[7] B. De Maria et al., "Improvement of sympathovagal balance by regular exercise may counteract the ageing process. A study by the analysis of QT variability," *Front. Physiol.*, 2022 (in press).

[8] 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.

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

[10] 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.

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

[12] 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.

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

[14] E. Pueyo et al., "Characterization of QT interval adaptation to RR interval changes and its use as a risk-stratifier of arrhythmic mortality in amiodarone-treated survivors of acute myocardial infarction," *IEEE Trans. Biomed. Eng.*, vol. 51, pp. 1511.1520, 2004.

[15] J. Halamek et al., "Dynamic coupling between heart rate and ventricular repolarization," Biomed Tech, vol. 52, pp. 255-263, 2007.

[16] M. Malik et al., "Importance of QT/RR hysteresis correction in studies of drug-induced QTc interval changes," *J. Pharmacokinet. Pharmacodyn.*, vol. 45, pp. 491-503, 2018.

[17] A. Porta et al., "Performance assessment of standard algorithms for dynamic R-T interval measurement: comparison between R-Tapex and R-T(end) approach," *Med. Biol. Eng. Comput.*, vol. 36, pp. 35-42, 1998.

[18] 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.

[19] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, "Heart rate variability. Standards of measurement, physiological interpretation, and clinical use," *Eur. Heart. J.*, vol. 17, pp. 354–381, 1996.

[20] V. Bari et al., "Transfer Function Gain between Heart Period and QT Variabilities Increased during Sympathetic Activation Induced by Postural Stimuli," Computing in Cardiology (CinC), 2021, doi: 10.23919/CinC53138.2021.9662902.

[21] B. De Maria, V. Bari, B. Cairo, E. Vaini, R. Martins de Abreu, N. M. Perseguini, J. Milan-Mattos, P. Rehder-Santos, V. Minatel, A. M. Catai, L. A. Dalla Vecchia and A. Porta, "Cardiac baroreflex hysteresis is one of the determinants of the heart period variability asymmetry," Am. J. Physiol. Regul. Integr. Comp. Physiol., vol. 317, (4), pp. R539-R551, October 01, 2019

[22] A. M. Catai et al., "Effect of the postural challenge on the dependence of the cardiovascular control complexity on age," *Entropy*, vol. 16, pp. 6686-6704, 2014.

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