Autonomic Control of Heart Period and QT Interval Variability during the Aging Process

Camila Bianca Falasco Pantoni[1,2], Alberto Porta[3,4], Juliana Cristina Milan-Mattos[1,2], Vinícius Minatel[2], Patricia Rehder-Santos[2], Sílvia C.G. Moura-Tonello[2], Mariana O. Gois[2], Anielle C.M. Takahashi[2], Beatrice Cairo[3], Vlasta Bari[3,4], Aparecida M. Catai[2]

[1] Department of Gerontology, Laboratory of Multidisciplinary Assessment and Care in Gerontology, Federal University of São Carlos; [2] Department of Physical Therapy, Cardiovascular Physical Therapy Laboratory, São Carlos, SP, Brazil; [3]Department of Biomedical Sciences for Health, University of Milan, Milan, Italy; [4]Department of Cardiothoracic, Vascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy

Abstract

Aging is associated with autonomic nervous system (ANS) impairment. Heart period variability (HPV) analysis suggested a decrease of the parasympathetic modulation and an increase of the sympathetic one with age. In addition, the variability of the time interval between Q-wave onset and T-wave end (QTV) has been used to evaluate the sympathetic modulation directed to ventricles. The aim of this study is to evaluate the age-related changes in QTV and compare them with those of HPV. We studied 111 male subjects divided into five groups according to the age ranges: 20-29; 30-39; 40-49; 50-59; 60-69. We assessed the ANS modulation directed to the sinus node and to the ventricles at rest in supine position (REST) and during active standing (STAND) via time and frequency domain HPV and QTV indexes. Lower values of σ^2_{HP} and HFa_{HP}, and higher values of σ^2_{QT} and LFa_{QT} at REST were observed specially in the last two decades compared to the youngest one. STAND reduced further the HP values and increased further these QT values. Our findings showed that both HPV and QTV are age-dependent, with the most significant QTV alterations occurring in the late bins of age. Spectral analyses of HPV and QTV suggest a reduced vagal and increased sympathetic modulations with age.

1. Introduction

Aging process is associated with modifications of electrical and mechanical properties of the cardiac muscle. Moreover, there is an autonomic nervous system (ANS) impairment [1]. Heart period variability (HPV) has been widely used in many different conditions in healthy and pathological subjects [2-4], to typify cardiac activity and ANS state. In aging studies, HPV analysis suggested a decrease of the parasympathetic modulation and an increase of the sympathetic one with age [5, 6]. The variability of the time interval between Q-wave onset and T-wave end (QT) also provides important insight on sympathetic cardiac control [7]. The amount of QT variability (QTV) has been used as a risk predictor for sudden cardiac death and higher values of QTV have been related to a more pronounced sympathetic modulation directed to ventricles [8-10]. Thus, QTV has shown its clinical importance as a non-invasive assessment of the cardiac sympathetic [11]. Data of QT interval and QTV on different experimental conditions and/or cohorts of subjects are present [7-14]: however, scanty data are present in literature on the dependence of QTV on age. Therefore, this study aims to evaluate the age-related changes in QTV and compares them with those in HPV.

2. Materials and methods

2.1. Study population

We studied 111 male subjects divided into five groups according to the age ranges: 20-29; 30-39; 40-49; 50-59; 60-69. All subjects were apparently healthy, based on anamnesis, clinical and physical examinations, laboratory tests, standard electrocardiogram (ECG) at rest and during a cardiopulmonary exercise test. Subjects with clinical evidence of any disease, users of illicit drugs, smokers and habitual drinkers were excluded from the study. None of the subjects included in the study was taking medicine that influenced the cardiovascular system.

2.2. Experimental protocol

The study was conducted at the Laboratory of Cardiovascular Physiotherapy, Department of Physiotherapy of the Federal University of São Carlos, São Carlos, Brazil. The study was approved by the local human

research ethics committee (No. 1.293.582) and was performed according to the principles of the Declaration of Helsinki, and all subjects signed an informed consent form before participation. All subjects were evaluated in the afternoon, following the recommendations of the standardization checklist of procedures [15], and they were familiarized with the equipment and the experimental procedures before the initiation of the protocol. After that, the subjects were maintained at supine resting for 10 min. The signals were, then, acquired for 15 min at rest in supine position (REST) and 15 min during active standing (STAND). The subjects breathed spontaneously without talking. The ECG was acquired from modified lead I via a bioamplificator (BioAmp FE132, ADInstruments, Sydney, AUS) with a sampling rate of 1000 Hz.

2.3. Series extraction and analysis

ECG recordings were pre-processed according to [16] to limit broadband noise and cancel baseline wandering. The temporal distance between two consecutive R-wave peaks was considered as a heart period (HP). The R-wave peak was detected with a derivative threshold algorithm, and the T-wave end was located according to a threshold on the absolute first derivative set as a fraction (i.e., 30%) of the absolute maximal first derivative value computed on the T-wave downslope [16]. The temporal distance between R-wave peak and T-wave end was considered an approximation of QT interval and all R-wave peak detections were carefully checked, as previously described [7]. Sequences of 256 consecutive HP and QT measures were considered. After the computation of the RR and QT means (μ_{HP} and μ_{QT}), the HP and QT series were linearly detrended and then, the HP and QT variances (σ^2_{HP} and σ^2_{QT}) were calculated [7, 16]. Spectral analysis was performed using a parametric approach, considering the autoregressive (AR) model [5], which describes the beat-to-beat series in the time domain as a linear combination of *p* past samples weighted by constant coefficients plus a zero mean random white noise. The Levinson-Durbin recursion algorithm was used to estimate the coefficients of the AR model and the white noise variance directly from the data. The parameter *p* was chosen according to the Akaike figure of merit. Power spectral density was computed from the AR coefficients and the white noise variance. The power spectral density was decomposed into spectral components. The power of the HP series in high frequency (HF, from 0.15 to 0.5 Hz) band, expressed in absolute units, indicated as HFa_{HP}, and the power of the QT series in the low frequency (LF, from 0.04 to 0.15 Hz) band, expressed in absolute units and denoted as LFa_{QT}, were calculated and taken as representative, respectively of the vagal modulation directed to the sinus node and of the sympathetic modulation directed to the ventricles [5, 7, 9].

2.4. Statistical Analysis

Normality in the distribution of data was assessed by the Kolmogorov-Smirnov test. One-way analysis of variance (Tukey test for multiple comparisons) or Kruskal-Wallis one-way analysis of variance on ranks (Dunn´s method for multiple comparisons) was applied to check the significance of differences among the groups. Analyses were carried out using a SigmaPlot 11.0, Systat, Chicago, IL, USA. Statistical significance was set at $p<0.05$.

3. Results

3.1. Characteristics of the studied subjects

The anthropometric characteristics of the 111 studied subjects showed that the height was significantly lower in the 60–69 group compared to 20–29 and 30-39. The weight and body mass index did not differ between groups.

3.2. Results of the HRV and QTV analyses

Results obtained from the analysis of HPV and QTV are reported in Table 1. Concerning HPV data, the μ_{HP} did not differ among groups. As expected, the σ^2_{HP} was significantly lower in 50-59 and 60-69 compared to 20-29 and in 60-69 compared to 30-39 and 40-49. The HFa_{HP} was lower in 50-59 and 60-69 compared to 20-29 and 30-39 groups, and in 60-69 compared to 40-49. In the QTV analysis, the μ_{QT} was significantly longer in 60-69 compared to 20-29. The σ^2_{QT} was higher in 40-49, 50-59, and 60-69 compared to 20-29, and LFa_{QT} was significantly higher in 50-59 and 60-69 compared to 20-29.

Table 1. HPV and QTV parameters at REST.

	REST				
Age	**20-29** (n=23)	**30-39** (n=23)	**40-49** (n=28)	**50-59** (n=18)	**60-69** (n=19)
μ_{HP} [ms]	911 (854-1037)	998 (913-1069)	966 (847-1080)	910 (875-1036)	899 (867-1030)
σ^2_{HP} [ms^2]	2448 (1919-4165)	2797 (1189-4918)	1694 (1084-2625)	949 (590-2142)*	810 (479-1115)$^{*\#\&}$
HFa_{HP} [ms^2]	983 (356-1657)	722 (292-1539)	370 (189-654)	224 (56-426)$^{*\#}$	111 (75-213)$^{*\#\&}$
μ_{QT} [ms]	336 (318-351)	352 (334-376)	351 (341-361)	342 (326-357)	355 (345-376)*
σ^2_{QT} [ms^2]	6.0 (4.6-8.5)	8.0 (6.0-11.7)	12.4 (6.3-18.8)*	12.5 (7.3-22.1)*	12.0 (8.3-27.4)*
LFa_{QT} [ms^2]	1.3 (0.9-2.0)	1.8 (1.0-3.1)	2.2 (1.2-3.8)	2.7 (1.4-4.9)*	3.0 (1.2-6.4)*

Data expressed as median (1st-3rd quartile). The symbols *, #, & indicate $p<0.05$ vs 20-29, vs 30-39, and vs 40-49.

Table 2 shows the results of the analysis of HPV and QTV during STAND. The μ_{HP} was longer in the 60-69 group compared to 20-29, and the σ^2_{HP} was lower in the 50-59 and 60-69 compared to 20-29 and 30-39 groups. The HFa_{HP} was lower in 50-59 compared to 20-29 and 30-39 and lower in 60-69 compared to 30-39. Importantly, the μ_{QT} was significantly longer in the 40-49 group, compared to 20-29 and in the 60-69 group, compared to 20-29 and

30-39. Both σ^2_{QT} and LFa_{QT} were higher in the 40-49 compared to 20-29.

Table 2- HPV and QTV parameters during STAND.

	STAND				
Age	**20-29** (n=23)	**30-39** (n=23)	**40-49** (n=28)	**50-59** (n=18)	**60-69** (n=19)
μ_{HP} [ms]	725 (665-780)	794 (729-855)	810 (709-944)	778 (728-876)	817 (738-979)*
σ^2_{HP} [ms^2]	2242 (1421-2614)	2071 (1384-3567)	1030 (710-2214)	927 (476-1770)*#	546 (303-1095)*#
HFa_{HP} [ms^2]	218 (102-426)	236 (92-478)	98 (39-240)	51 (32-92)*#	66 (31-162)#
μ_{QT} [ms]	306 (285-320)	317 (305-336)	324 (310-346)*	318 (308-338)	343 (329-363)*#
σ^2_{QT} [ms^2]	12.9 (8.9-18.1)	16.4 (12.9-22.1)	27.5 (18.3-38.4)*	27.6 (8.2-47.2)	21.3 (13.1-48.0)
LFa_{QT} [ms^2]	2.5 (1.6-4.5)	3.1 (2.5-5.5)	5.4 (3.6-10.5)*	4.8 (1.0-6.3)	3.8 (2.2-10.0)

Data expressed as median (1st-3rd quartile). The symbols *, #, & indicate $p<0.05$ vs 20-29, vs 30-39, and vs 40-49.

4. Discussion

The present study extends our knowledge about cardiac control both directed to the sinus node and ventricles in healthy subjects. As already described in the literature, the cardiac control directed to the sinus node, evaluated here by HPV, is modified according to age, with a reduction of vagal autonomic modulation in the older groups. As a main novel finding, the aging process is associated with alteration of cardiac control directed to the ventricles, as demonstrated by QTV modifications, with the most significant QTV alterations occurring in the late bins of the age.

The assessment of cardiac autonomic function by HPV focuses on the autonomic influence on sinus node [2], and the data on the QTV provide information about the autonomic control at the level of the ventricles [7], allowing the stratification risk of ventricular arrhythmias by the evaluation of ventricular abnormalities [8]. In this context, the evaluation of QTV is an additional tool to evaluate cardiac autonomic function, compared with the well-known trend of HPV. Moreover, time and frequency domain indexes derived from QTV were able to identify a possible alteration of cardiac autonomic control directed to the ventricles, which started about 40 years old with the most significant alterations occurring in the late bins of studied age.

At REST condition, the 50-59 and 60-69 groups presented with lower values of σ^2_{HP}, compared to the youngest ones, and these findings suggest that the magnitude of the HP changes became smaller with the advancing age, as already described before [1-3, 6]. Moreover, we observed, at REST, lower values of HFa_{HP} band in the groups 50-59 and 60-69, compared to younger people, showing a reduction of vagal contribution to the HPV. At STAND, the same pattern was observed. Our results are in accordance with those that showed significant variations of HPV with the aging process [1-3, 6] that have already been described to affect cardiac autonomic function, towards a decrease of parasympathetic and an increase of sympathetic modulation [2, 3].

The QTV has been used as a tool to measure cardiac control [10, 11]. Different from the well-known trend of HPV, the QTV indexes provide information about autonomic control directed to the ventricles [7]. In this context, the identification of age-related alteration of QTV might be important for risk stratification and prognosis of ventricular arrhythmias. In the present study we showed that QTV in healthy subjects also depends on age. At REST, our data showed that the subjects over 40 years old presented modifications of QTV, with the overall magnitude of σ^2_{QT} higher in the older groups, compared to the youngest men and LFa_{QT} was greater in the 50-59 and 60-69 group, compared to 20-29. AT STAND, we confirm that QTV also depends on age.

It is known that the QT interval duration is dependent on HP [17, 18], and some studies have already showed the relationship between QTV and HPV, due to the dependence of ventricular repolarization duration on HP [9, 11, 17, 18]. Although this dependence, the ventricular repolarization duration depends on factors independent of the HP, like the ANS modulation and the aging itself [9, 11, 18], the concomitant assessment of HPV and QTV markers, namely the HFa_{HP} and LFa_{QT} powers, provided a possibility to monitor vagal and sympathetic modulation on the sinus node and ventricles during the aging process [2, 7, 11, 17]. Our study showed that an additional analysis grounded on the assessment of QTV, may be important and showed earlier alterations of sympathetic cardiac autonomic modulation impairment with aging. Additional analyses that might provide further insight might be based on the computation of transfer function between HPV and QTV, on the assessment of the QTV-HRV coupling and on the fraction of QTV unrelated to HRV [9, 10, 18]. Even the application of tools assessing complexity of cardiac control might add new indexes exploring the evolution of ANS influences on age [19-21].

5. Conclusion

Our findings showed that both HPV and QTV are age dependent, with the most significant QTV alterations occurring in the late bins of age. Spectral analyses of HPV and QTV suggest a reduced vagal and increased sympathetic modulations with age. These results are relevant for assessing the impact of senescence on cardiac function and for designing specific countermeasures favouring healthy aging.

Acknowledgments

The authors acknowledge I. A. Verzola Aniceto for the clinical evaluations and the volunteers of our study. This study was funded by FAPESP (#2010/52070-4) and

CAPES, (CAPES-CSF-PVE: 23038.007721/2013-41), Brazil. The funding source was not involved in the study design, collection and analysis of the data, or article preparation.

References

[1] S. M. Pikkujämsä *et al.*, "Cardiac interbeat interval dynamics from childhood to senescence: comparison of conventional and new measures based on fractals and chaos theory," *Circulation*, vol. 100, no. 4, art. no. 4, July 1999, doi: 10.1161/01.cir.100.4.393

[2] A. Voss, R. Schroeder, A. Heitmann, A. Peters, and S. Perz, "Short-Term Heart Rate Variability—Influence of Gender and Age in Healthy Subjects," *PLoS ONE*, vol. 10, no. 3, art. no e0118308, 2015, doi: 10.1371/journal.pone.0118308

[3] A. M. Catai *et al.*, "Effects of aerobic exercise training on heart rate variability during wakefulness and sleep and cardiorespiratory responses of young and middle-aged healthy men," *Braz. J. Med. Biol. Res.*, vol. 35, no. 6, art. no. 6, 2002.

[4] C. B. F. Pantoni *et al.*, "Recovery of linear and nonlinear heart rate dynamics after coronary artery bypass grafting surgery," *Clin Physiol Funct Imaging*, vol. 34, no. 6, pp. 449–456, 2014, doi: 10.1111/cpf.12115

[5] 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," *Circulation*, vol. 93, no. 5, 1043–1065,1996

[6] N. M. Perseguini *et al.*, "Cardiac autonomic modulation, C-reactive protein or telomere length: Which of these variables has greater importance to aging?," *Int J Cardiol*, vol. 178, pp. 79–81, 2015, doi: 10.1016/j.ijcard.2014.10.123

[7] A. Porta *et al.*, "Autonomic Control of Heart Rate and of QT Interval Variability Influences Arrhythmic Risk in Long QT Syndrome Type 1," *J Am Coll Cardiol*, vol. 65, no. 4, pp. 367–374, 2015, doi: 10.1016/j.jacc.2014.11.015

[8] W. L. Atiga *et al.*, "Beat-to-beat repolarization lability identifies patients at risk for sudden cardiac death," *J Cardiovasc Electrophysiol*, vol. 9, no. 9, pp. 899–908, 1998, doi: 10.1111/j.1540-8167.1998.tb00130.x

[9] A. Porta, E. Tobaldini, T. Gnecchi-Ruscone, N. Montano, "RT variability unrelated to heart period and respiration progressively increases during graded head-up tilt," *Am J Physiol Heart Circul Physiol*, vol. 298, pp. H1406–H1414, 2010, doi: 10.1152/ajpheart.01206.2009

[10] 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, doi: 10.1016/j.jelectrocard.2011.08.002

[11] 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, no. 6, pp. 925–944, 2016, doi: 10.1093/europace/euv405

[12] R. E. Carpenter *et al.*, "Changes in heart rate variability and QT variability during the first trimester of pregnancy," *Physiol Meas*, vol. 36, no. 3, pp. 531–545, 2015, doi: 10.1088/0967-3334/36/3/531

[13] J. F. Valencia *et al.*, "Symbolic dynamics to discriminate healthy and ischaemic dilated cardiomyopathy populations: an application to the variability of heart period and QT interval," *Philos Trans A Math Phys Eng Sci*, vol. 373, no. 2034, art. no. 20140092, 2015, doi: 10.1098/rsta.2014.0092

[14] Baumert, B. Czippelova, A. Porta, and M. Javorka, "Decoupling of QT interval variability from heart rate variability with ageing," *Physiol Meas*, vol. 34, no. 11, pp. 1435–1448, 2013, doi: 10.1088/0967-3334/34/11/1435

[15] A. M. Catai, C. M. Pastre, M. F. de Godoy, E. da Silva, A. C. de M. Takahashi, and L. C. M. Vanderlei, "Heart rate variability: are you using it properly? Standardisation checklist of procedures," *Brazilian Journal of Physical Therapy*, vol. 24, no. 2, art. no. 2, 2020, doi: 10.1016/j.bjpt.2019.02.006

[16] A. Porta *et al.*, "Performance assessment of standard algorithms for dynamic R-T interval measurement: comparison between R-Tapex and R-Tend approach," *Med Biol Eng Comput*, vol. 36, no. 1, pp. 35–42, 1998, doi: 10.1007/BF02522855

[17] M. Malik, "Beat-to-beat QT variability and cardiac autonomic regulation," *Am J Physiol Heart Circ Physiol*, vol. 295, no. 3, pp. H923–H925, 2008, doi: 10.1152/ajpheart.00709.2008

[18] A. Porta *et al.*, "Quantifying electrocardiogram RT-RR variability interactions," *Med Biol Eng Comput*, vol. 36, pp. 27–34, 1998, doi: 10.1007/BF02522854

[19] 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, doi: 10.3390/e16126686

[20] A. Porta *et al.*, "Effect of age on complexity and causality of the cardiovascular control: comparison between model-based and model-free approaches," *PLoS ONE*, vol. 9, art. no. e89463, 2014, doi: 10.1371/journal.pone.0089463

[21] 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, doi: 10.1371/journal.pone.0093808

Address for correspondence:
Aparecida M. Catai, PT and Ph.D.
Cardiovascular Physical Therapy Laboratory/ Department of Physical Therapy/Federal University of São Carlos, UFSCar. Via Washington Luís, km 235, 13565-905- São Carlos, SP, Brazil.
Email: mcatai@ufscar.br