



Extended Central Tendency Measure and difference plot for heart rate variability analysis

Rascius-Endrigho A.U. Belfort^a, Sara P.C. Treccossi^b, João L.F. Silva^a, Valdir G. Pillat^a, Celso B.N. Freitas^c, Laurita dos Santos^{d,*}

^a Universidade do Vale do Paraíba, São José dos Campos, SP, Brazil

^b Western Paraná University Hospital – Unioeste, Cascavel, PR, Brazil

^c Telefonaktiebolaget L. M. Ericsson, São José dos Campos, SP, Brazil

^d Scientific and Technological Institute, Universidade Brasil – Campus Itaquera, Rua Carolina Fonseca 584, Itaquera, São Paulo, SP, Brazil

ARTICLE INFO

Article history:

Received 12 March 2019

Revised 21 August 2019

Accepted 29 September 2019

Keywords:

Extended Central Tendency Measure

Heart Rate Variability

RR intervals time series

Impairment of autonomic nervous system

ABSTRACT

Heart rate variability (HRV) is a non-invasive alternative to analyze the role of the autonomic nervous system (ANS) on heart functioning. Many tools have been developed to analyze collected cardiac data. Among them, the Central Tendency Measure (CTM) is a quantitative method for variability analysis of RR intervals. The values of the CTM must be between 0 and 1 (inclusive) for different radius, which follows the intrinsic characteristics of each time series. Using the conventional CTM, the successive differences of the time series may be calculated, and it can classify and differentiate the disturbances in the ANS involving HRV. This method was extended (e-CTM) to analyze the differences between RR interval time series. In this extension, a new parameter is added, which allows analysis of long time intervals, instead of successive and adjacent RR intervals. The ability of the e-CTM to differentiate the groups of the RR interval time series was verified with 145 RR interval time series divided into three groups: subjects with congestive heart failure, healthy subjects, and nurses during one hour of their workday. Results evidence that the new parameter added differentiates the group with pathology (and subsequent impairment of ANS) and group under stress at work (temporary impairment of ANS). These results suggest that the e-CTM is capable of detection long-term variations in the HRV according to the ANS impairment.

© 2019 IPEM. Published by Elsevier Ltd. All rights reserved.

1. Introduction

The autonomic nervous system (ANS) participates incisively in the homeostasis of the human body functioning including the heart. Such action passes through structures that send information: baroreceptors, chemoreceptors, atrial and ventricular receptors, respiratory system alterations, renin-angiotensin-aldosterone system, and thermoregulatory systems [1].

Heart rate variability (HRV) is a non-invasive alternative to analyze autonomic heart action [2]. HRV is based on the time difference between consecutive heartbeats, that is, intervals between R-R waves, also known as RR interval time series, where the R wave represents ventricular depolarization [3]. The variation among RR intervals is an individual phenomenon that may vary according to certain features, such as age, gender, and circadian time. An

individual can present different HRV at different times or situations during his/her life.

While sports practice can raise HRV, rising vagal response in a group of teenagers [4], some pathologies, such as diabetes type 2 [5] and Chagas disease [3], lead to reduction of HRV. HRV is the result of the competitive stimulation between parasympathetic and sympathetic of ANS, given a non-linear behavior to the signal [6,7]. Cardiac rhythm in adults may show almost periodic oscillations, due to its variability similar to complex deterministic nonlinear systems modulated by ANS [8]. To analyze differences in HRV patterns, some nonlinear methods are used, including First Return Map [9], Detrended Fluctuation Analysis [10], Recurrence Quantification Analysis [11–14], Approximate and Sample Entropy [15–20], and Central Tendency Measure [21,22].

Central Tendency Measure (CTM) is a quantitative measurement of the times series, where the successive differences in the RR intervals are displayed graphically in the second-order difference plot. This representation of the time series shows the nonlinear aspects of the successive RR intervals and for a sequence of the intervals [22]. The CTM can be used to classify and differentiate

* Corresponding author.

E-mail addresses: laurita.santos@universidadebrasil.edu.br, lauritas9@gmail.com (L. dos Santos).

disturbances involving, for example, congestive heart failure from healthy individuals [23,24], group of individuals with different health conditions and ages [22], healthy from diabetic individuals [25,26], diagnosis of coronary artery disease [27], individuals with epilepsy [28], different neurological pathologies as changes in intracranial pressure in the hydrocephalus patients, and electromyographic signals from opening and closing of the eyes [29,30]. For different analysis using the RR intervals in long term conditions, instead of immediately adjacent intervals, the CTM method is extended.

This work will introduce the Extended Central Tendency Measure (e-CTM), which verifies the difference between successive RR intervals and in distinct time rhythms. A new parameter (P) is added to the conventional method, which can verifying the ability of ANS to vary the elapsed time of the non-adjacent RR intervals. In total, 145 RR interval time series are used: 29 from adults with congestive heart failure [31], 54 from healthy adults [23], and 62 from nurses during their hospital routine (divided into two groups: first hour and fifth hour of their workday).

The main proposal of this work is to assess the e-CTM and different plots of RR interval time series analysis considering long-term conditions. To evaluate the new parameter added in the e-CTM, the intragroup and intergroup comparisons are provided varying the P for the dataset used.

2. Material and methods

2.1. Databases of time series

In this work, RR interval time series were used from two different datasets: 83 time series from Physionet [23,32–35] (G1) and 62 RR interval time series from a private dataset (G2). The G1 data were obtained by Holter monitor for 24 h, while the G2 data were obtained by Polar® (RS800 and V800) monitor for 1 h. The G2 dataset was approved by Brazilian ethic committee under number 1.345.333. This study follows all ethical principles according to the research regulative norms and directives involving human beings, resolution 466/2012 of the Brazilian National Health Council [36].

Analysis of these two datasets was divided into four groups: 29 RR interval time series from adults with congestive heart failure between 34 and 79 years old (group G1.1), 54 RR interval time series from healthy adults between 30 and 76 years old (group G1.2), 31 RR interval time series from nurses (without diagnosed pathology) between 23 and 43 years old during the first hour of their workday (group G2.1), and 31 RR interval time series from nurses during the fifth to sixth hour (group G2.2) of their workday. The subjects in G2 work in critical sectors (Intensive Care Unit – ICU neonatal, pediatrics, and adult).

All RR interval time series were filtered using an adaptive filter described in [37]. The adaptive filter removes the RR interval less than 350 ms and greater than 1200 ms (not physiological sinus rhythm for the humans) and replaces the point that is more than 20% different than its adjacent points. Recently, a practical interface (T-RR Filter) was elaborated to facilitate the filtering process of the considerable amount of data.

2.2. Extended Central Tendency Measure (e-CTM)

Central Tendency Measure (CTM) quantifies the variability of successive RR intervals [38]. The graphic representation of second-order differences helps analysis of biological systems, hemodynamics, and HRV [21,22,28]. The e-CTM is related to the constant balance of sympathetic and the parasympathetic nervous system. According to [21], the second-order plot represented by $(RR_{i+1} - RR_i)$ in the x-axis and $(RR_{i+2} - RR_{i+1})$ in the y-axis where each RR_i is the

value of the difference between two RR intervals. The CTM was calculated by defining a radius r according to the type of time series analyzed.

For e-CTM, a new parameter (P) was included in the conventional equation. The P parameter obtains the difference of two RR intervals (adjacent or not). This feature allows analysis of the HRV along time (long-term variability). The e-CTM is calculated as

$$e-CTM(r, P) = \frac{\sum_{i=1}^{N-(2P)} \delta(d_i)}{N - (2P)}$$

$$\delta(d_i) = \begin{cases} 1 & \text{if } [(RR_{i+2P} - RR_{i+P})^2 + (RR_{i+P} - RR_i)^2]^{1/2} \\ 0 & \text{otherwise} \end{cases}$$

and P is the new parameter varying from 1 to 5 (inclusive) that reflects the long-term variability, r is the radius given in ms, $N - (2P)$ is the number of differences calculated from time series in the graph.

According to our previous work [22], it is possible to illustrate the discrimination ability of CTM and the second-order difference graph from time series elaborated with different variations between time points. The time series with points spread on the graph (for a specific r) indicates greater variability, while the e-CTM (r, P) value is lower. When $P=1$, the e-CTM is conventional, and when this value (2–5) is incremented, the long-term variability of the RR intervals is expressed. The e-CTM algorithm was developed in Matlab® and Python languages to compare the performance of the calculation for long and short time series.

2.3. Statistical analysis

Statistical descriptive analysis was used to obtain e-CTM (r, P) distribution of values. For intragroup and intergroup comparisons of different e-CTM (r, P), variance analysis ANOVA and Tukey post-test (for Gaussian distribution) or Kruskal–Wallis and Dunn post-test (for non-Gaussian distribution) were used. To compare data pairs, the t -student or Mann–Whitney tests (non-Gaussian distribution) were employed. Significance level of $p > 0.05$ and 95% confidence interval were adopted.

3. Results

3.1. e-CTM analysis for long time series

Fig. 1 illustrates non-filtered and filtered examples of RR interval time series. Fig. 1(a) and (c) include artifacts, which are not related to sinus rhythm. After filtering, (Fig. 1(b) and (d)), no visible artifacts are displayed. The filtered RR interval time series were obtained by T-RR Filter.

Fig. 2 displays the computing time comparison between the .py and .m scripts considering long and short time series. The logical programming was equal for both scripts and all parameters P (1–5) used. The CTM (r, P) values were obtained from the same conditions and computer. For computing time of the long time series, the .py script required more execution time than .m script considering some time series (Fig. 2(a) and (b)). However, for computing time of the short time series, the .py script was faster for all time series analyzed compared to .m script (Fig. 2(c) and (d)). The computational complexity of the CTM and the e-CTM were similar to $O(n)$ linear.

Fig. 3 is the scatterplot obtained with different parameter P from $P=1-5$. The r values used to evidence the scattering were $r=\{1, 2, \dots, 20\}$ with step of 1 ms, and $r=\{30, 40, \dots, 150\}$ with step of 10 ms. When the $r=150$ ms for group G1.1, the e-CTM (r, P) reached the maximum value 1 for all values of the P

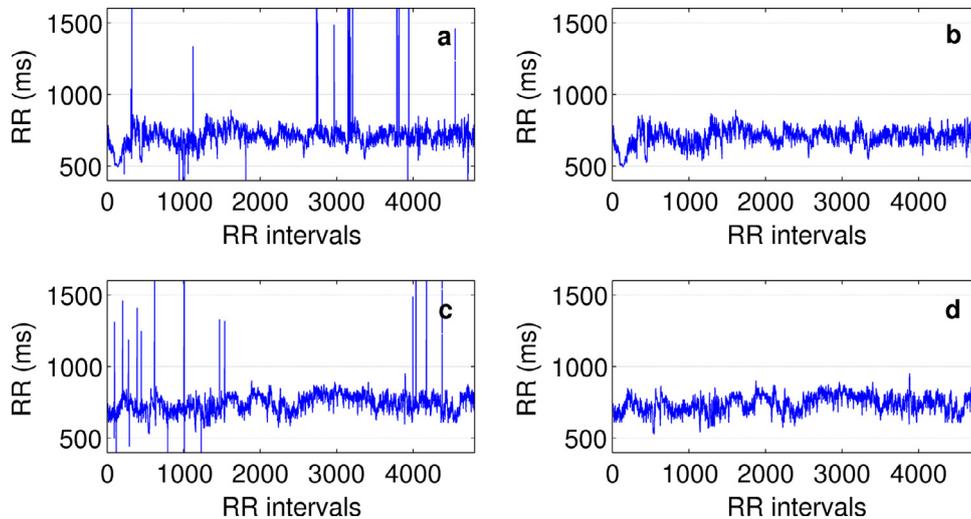


Fig. 1. Examples of RR interval time series before and after adaptive filtering: (a) non-filtered time series of adult with congestive heart failure, (b) filtered time series of adult with congestive heart failure, (c) non-filtered time series of healthy adult, and (d) filtered time series of healthy adult.

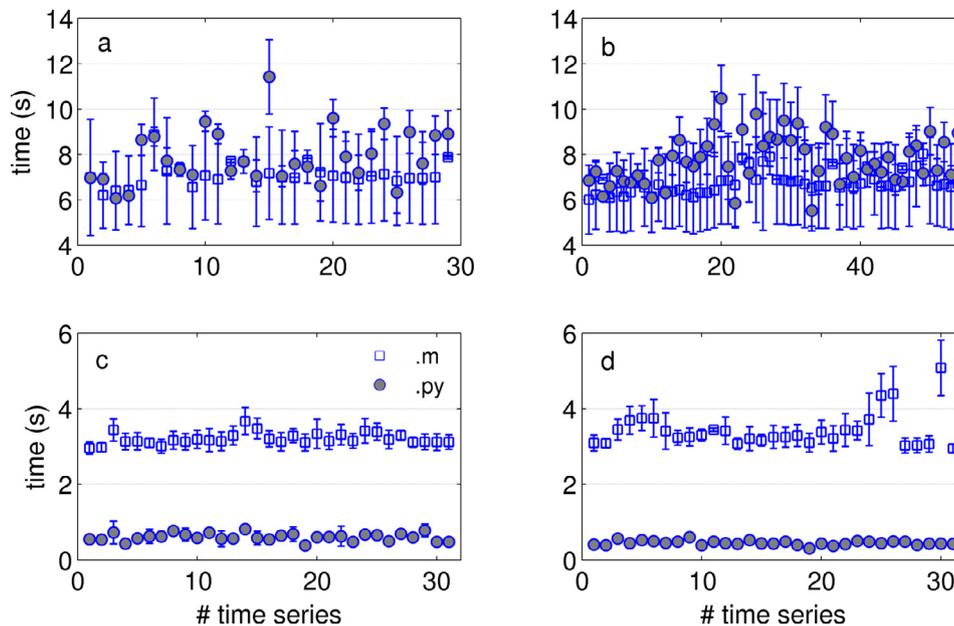


Fig. 2. Average and standard deviation of the computing time for RR intervals time series of the e-CTM calculation and difference plot considering `.py` and `.m` scripts. (a) Congestive heart failure (G1.1), (b) healthy adult (G1.2), (c) adults during the first hour of their workday (G2.1), (d) adults during the fifth hour of their workday (G2.1).

parameter. However, the scatter plot for G1.2 (Fig. 4) was visually different according to the P variation, particularly for $P=3, 4,$ and 5 .

The average and standard deviation of the e-CTM (r, P) for group G1.1 are in Fig. 5. The saturation of e-CTM (r, P) = 1 was $r=100$ ms. The e-CTM (100, 1) was the first to present saturation. Values for e-CTM (r, P) had no significant statistical differences.

Same as the previous group, Fig. 6 shows the e-CTM (r, P) values for healthy individuals (G1.2). When $P=1$, the e-CTM (r, P) reached saturation for $r=120$ ms. For $P=3, 4,$ and 5 , the e-CTM did not have saturation until $r=150$ ms. Statistical comparison (ANOVA) between e-CTM (r, P) values varying parameter P identified statistically significance differences ($p < 0.05$) between e-CTM ($r, 1$) and e-CTM ($r, 2$); e-CTM ($r, 1$) and e-CTM ($r, 3$); e-CTM ($r, 1$) and e-CTM ($r, 4$); e-CTM ($r, 1$) and e-CTM ($r, 5$); e-CTM ($r, 2$) and e-CTM ($r, 3$); e-CTM ($r, 2$) and e-CTM ($r, 4$); e-CTM ($r, 2$) and e-CTM ($r, 5$).

3.2. Comparison between groups G1.1 and G1.2 – Physionet data

Comparative statistical analysis was conducted between individuals in G1.1 and G1.2 for each value of e-CTM (r, P). The comparisons between e-CTM ($r, P=1$), from $r=1$ ms ($p < 0.0001$) to 70 ms ($p=0.0277$) found statistically significant differences. For the comparisons between two groups for e-CTM ($r, P=2$), e-CTM ($r, P=3$), e-CTM ($r, P=4$), and e-CTM ($r, P=5$), all radius from $r=1$ ms ($p < 0.0001$) to $r=150$ ms ($p=0.0031$) had statistically significant differences. Comparisons between these groups proved that the increment of parameter P can detect differences beyond those obtained when $P=1$.

3.3. e-CTM analysis for short time series

Fig. 7 shows the difference plots for G2.1 obtained from variation of parameter P (from 1 up to 5). The points are more spread

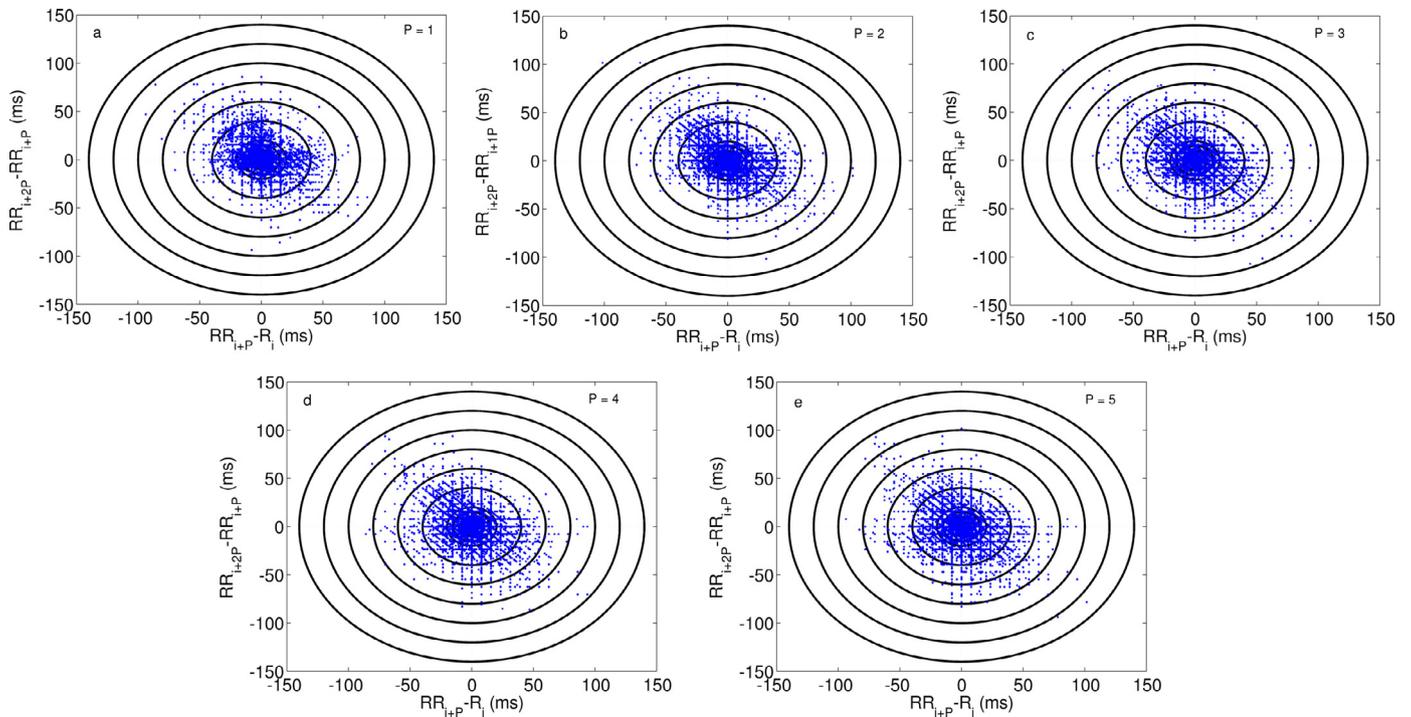


Fig. 3. Scatterplot for the same individual from group G1.1 varying the parameter P . (a) $P=1$, (b) $P=2$, (c) $P=3$, (d) $P=4$, and (e) $P=5$.

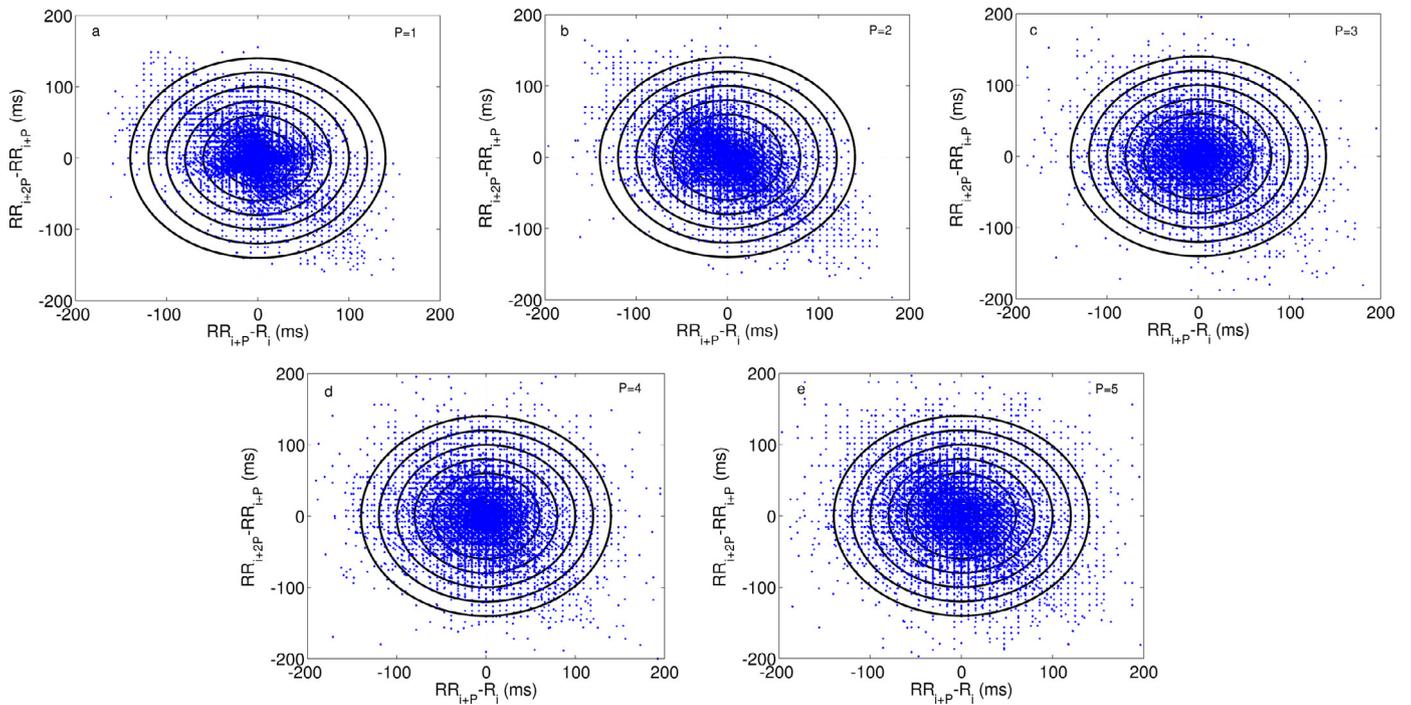


Fig. 4. Scatterplot for the same individual of group G1.2 varying the parameter P . (a) $P=1$, (b) $P=2$, (c) $P=3$, (d) $P=4$, and (e) $P=5$.

according to the increment in parameter P . This behavior suggests that the parameter P can reflect the situation of ANS along time, instead of the immediate situations.

For comparison of the e-CTM (r, P) values of the all P variations considering $r=1$ ms to 150 ms, the results were significantly different ($p < 0.05$) for e-CTM ($r, 1$) and e-CTM ($r, 3$); e-CTM ($r, 1$) and e-CTM ($r, 4$); e-CTM ($r, 1$) and e-CTM ($r, 5$) for

all r values (Fig. 8). There was statistical difference between e-CTM ($r, 1$) and e-CTM ($r, 2$) when r varies from 1 ms to 50 ms; e-CTM ($r, 2$) and e-CTM ($r, 4$) for $r=2$ ms, 30 ms, 40 ms, 50 ms, 140 ms, and 150 ms. These results reinforce that the variation of P parameter could also obtain more information regarding HRV in G2.1 and G2.2, both composed of individuals without apparent pathology.

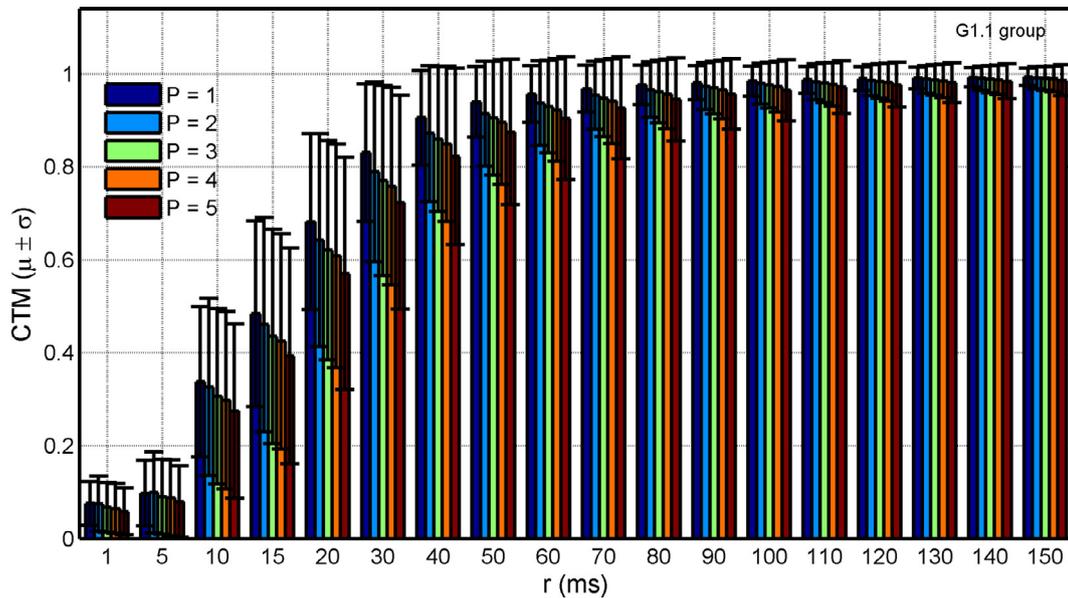


Fig. 5. e-CTM(r, P) values (varying $P=1$ to $P=5$) for different radius values for group G1.1 (adults with congestive heart failure). The saturation (e-CTM(r, P)=1) was $r=100$ ms.

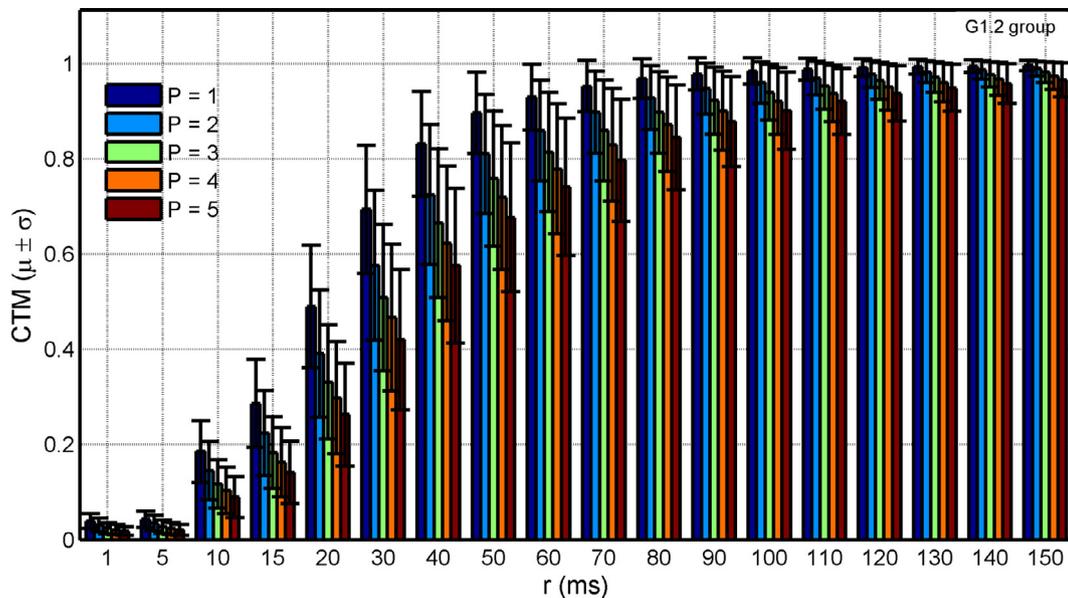


Fig. 6. e-CTM(r, P) values ($P=1$ to $P=5$) for different r values for G1.2 (healthy adults). The saturation of e-CTM(r, P)=1 was $r=120$ ms.

Fig. 9 shows e-CTM values for G2.2. These results were more discrepant than the results showed previously, mainly in terms of saturation. The e-CTM(r, P) for $P=3, 4$, and 5 did not have the saturation (e-CTM(r, P)=1) at least until $r=150$ ms. Same as the previous group, statistical significance occurred when comparing values of the e-CTM($r, 1$) and e-CTM($r, 3$); e-CTM($r, 1$) and e-CTM($r, 4$); e-CTM($r, 1$) and e-CTM($r, 5$) from $r=1$ ms to $r=150$ ms. The values of the e-CTM($r, 1$) and e-CTM($r, 2$) had statistically significant difference only when $r=30$ ms; e-CTM($r, 2$) and e-CTM($r, 5$). There was statistically significant difference for $r=2$ ms up to $r=150$ ms.

4. Discussion

From the physiological view, individuals with congestive heart failure (G1.1 group) are expected to have reduced HRV, which is

associated with high cardiovascular morbidity and mortality, due to a greater activation of ANS sympathetic branch [39]. Some authors [40–42] suggest a predominance of sympathetic activity over the sinus node, and others [43–45] elucidate that the sympathetic hyperactivity and minor vagal action increase the cardiac frequency. This feature may lead to vasoconstriction of capillaries and veins with a redistribution of flow. To quantify this ability of ANS, the e-CTM and its variation ($P=1-5$) corroborated with decreasing of HRV in this group (G1.1) for short and long terms. The e-CTM measurement of G1.1 found no statistical difference, suggesting the ANS was impaired in this specific group.

A different scenario is presented in G1.2, G2.1, and G2.2, which were patients without apparent pathology. Studies discuss that HRV in a healthy individual is elevated [46,47]. In this work, such information was reinforced by the statistical analysis conducted on

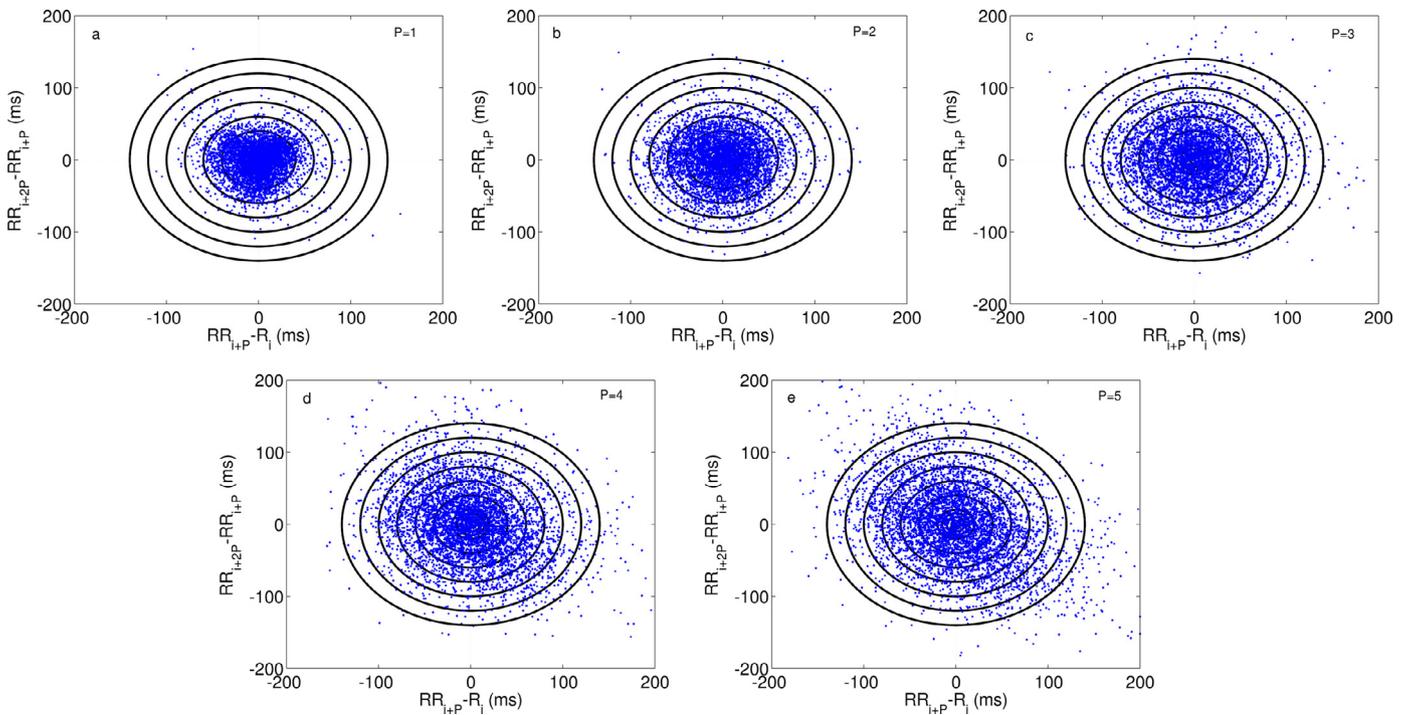


Fig. 7. Scatterplot for the same individual from G2.1 (nurses during first hour at their workday) varying the parameter P . (a) $P=1$, (b) $P=2$, (c) $P=3$, (d) $P=4$, and (e) $P=5$.

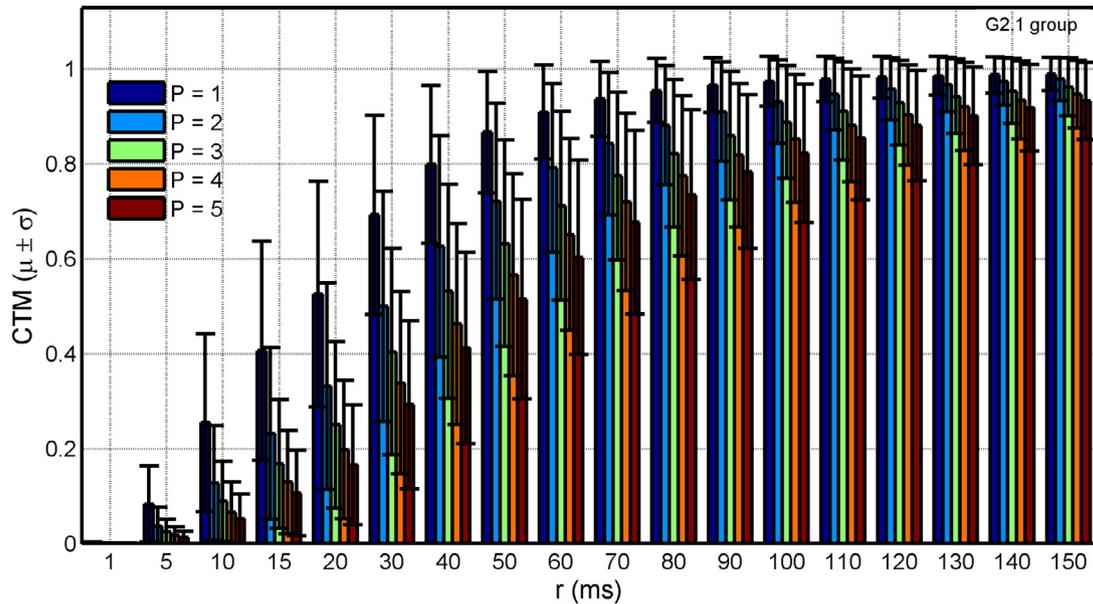


Fig. 8. Average and standard deviation of e-CTM (r, P) values considering different r values for the G2.1.

the three mentioned groups. The results suggest with e-CTM analysis, considering short- to long-term (variation of parameter P from 1 to 5) HRV, a delay in saturation (e-CTM = 1). For total saturation, r value must be increased.

The alteration of the CTM provides the short- and long-term evaluation of the HRV, indicating that HRV behaves differently in cardiovascular conditions. Subjects with low variability and impairment of ANS displayed saturation (e-CTM = 1) for small r values in the short or long term. Consequently, it requires a fewer number of

radiuses to encompass all different RR intervals. For the analysis of G2, G2.1 (first hour of the workday) saturated (e-CTM = 1) before G2.2 (fifth hour of the workday). This result verifies that stress factor and cortisol liberation reduced the HRV [48]. In terms of performance of the algorithm, both scripts could be used to highlight the computing time of the .py script for analysis of short time series. The advantage of this script is that Python is an open high-level programming language and does not require many computational resources

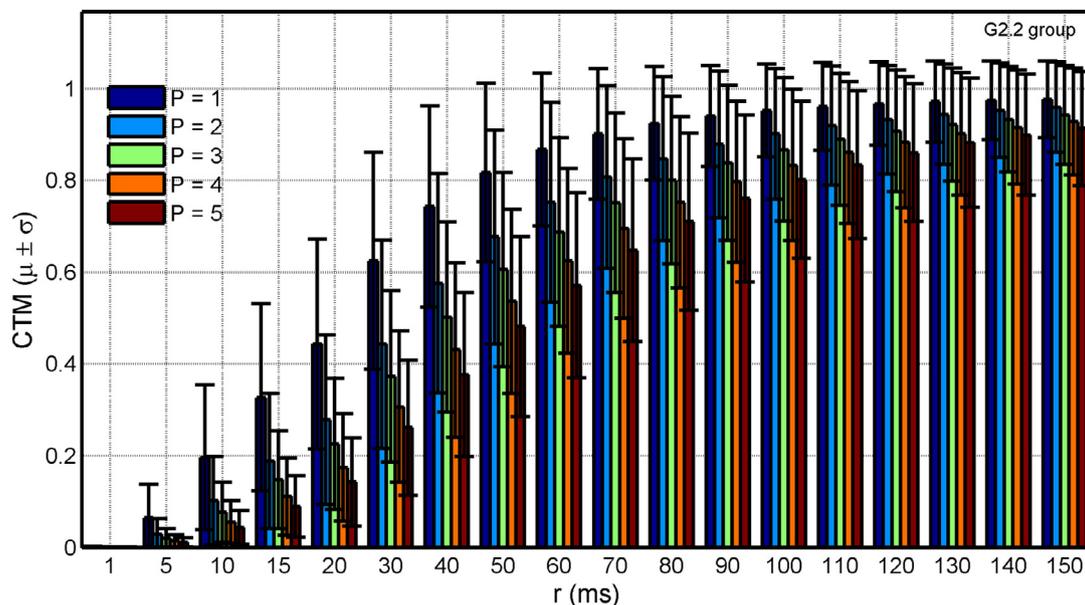


Fig. 9. e-CTM values for r values for the G2.2. When $P=1$, the e-CTM reaches value 1 for $r=60$ ms, when $P=2$ for $r=140$ ms, and for the other P variations e-CTM was not reached value 1 until $r=150$ ms.

5. Conclusion

E-CTM is a prominent tool for short- and long-term analysis of HRV. More specifically, we provided experimental evidence that our metric can distinguish between permanent alteration on ANS (congestive heart failure, for example) and temporary stress factor (during a workday). For the first situation, there was no difference among the e-CTM (r, P) values including the variation of parameter P . However, there was a difference between the e-CTM (r, P) values varying the parameter P for the temporarily stress factor group. This result suggests that the environment had a considerable influence on the ANS, which was detected by adding the P parameter in the extended Central Tendency Measure. The e-CTM is a useful tool to detect more information in terms of long-term variability of HRV. Considering clinical use, this methodology may be applied outside the sample database. For the future research, e-CTM is a potential tool for real-time analysis considering groups with different ANS impairments.

Declaration of Competing Interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

Acknowledgment

The authors thank the Conselho Nacional de Desenvolvimento Científico e Tecnológico for support. L. dos Santos thanks the Fundação de Amparo à Pesquisa do Estado de São Paulo (Grant no. 2018/03517-8) for financial support.

Ethical approval

The G2 dataset was approved by Brazilian ethic committee under number 1.345.333. This study follows all ethical principles according to the research regulative norms and directives involving human beings, resolution 466/2012 of Brazilian National Health Council.

References

- [1] Mondoni GH, de O, Vanderlei LCM, Saraiva B, Vanderlei FM. Effects of exercise on cardiac autonomic modulation in children: literature update. *Fisioter Em Mov* 2015;28(3):627–36. doi:10.1590/0103-5150.028.003.AR03.
- [2] Hoshi RA, Pastre CM, Vanderlei LCM, Godoy MF. Poincaré plot indexes of heart rate variability: relationships with other nonlinear variables. *Auton Neurosci Basic Clin* 2013. doi:10.1016/j.autneu.2013.05.004.
- [3] Nasario-Junior O, Benchimol-Barbosa PR, Pedrosa RC, Nadal J. Assessment of autonomic function by phase rectification of RR Interval histogram analysis in chagas disease. *Arq Bras Cardiol* 2015. doi:10.5935/abc.20150032.
- [4] Cayres SU, Vanderlei LCM, Rodrigues AM, Silva MJCE, Codogno JS, Barbosa MF, et al. Prática esportiva está relacionada à atividade parassimpática em adolescentes. *Rev Paul Pediatr* 2015. doi:10.1016/j.rpped.2014.09.002.
- [5] Michel-Chávez A, Estañol B, Gien-López JA, Robles-Cabrera A, Huitrardo-Duarte ME, Moreno-Morales R, et al. Heart rate and systolic blood pressure variability on recently diagnosed diabetics | variabilidade da frequência cardíaca e da pressão arterial sistólica em diabéticos com diagnóstico recente. *Arq Bras Cardiol* 2015. doi:10.5935/abc.20150073.
- [6] Acharya UR, Joseph KP, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. *Med Biol Eng Comput* 2006;44(12):1031–51. doi:10.1007/s11517-006-0119-0.
- [7] Task Force of the ESC-NASPE Heart rate variability: standards of measurement, physiological interpretation, and clinical use. *Circulation* 1996. doi:10.1161/01.CIR.93.5.1043.
- [8] Correa PR, Catai AM, Takakura IT, Machado MN, Godoy MF. Heart rate variability and pulmonary infections after myocardial revascularization]. *Arq Bras Cardiol* 2010;95:448–56.
- [9] Roy B, Ghatak S. Nonlinear methods to assess changes in heart rate variability in type 2 diabetic patients. *Arq Bras Cardiol* 2013;101:317–27. doi:10.5935/abc.20130181.
- [10] Chiang J-Y, Huang J-W, Lin L-Y, Chang C-H, Chu F-Y, Lin Y-H, et al. Detrended fluctuation analysis of heart rate dynamics is an important prognostic factor in patients with end-stage renal disease receiving peritoneal dialysis. *PLoS ONE* 2016;11(2):e0147282. doi:10.1371/journal.pone.0147282.
- [11] Eckmann J-P, Kamphorst SO, Ruelle D. Recurrence plots of dynamical systems. *Europhys Lett* 1987;441–5. doi:10.1209/0295-5075/4/9/004.
- [12] Marwan N, Wessel N, Meyerfeldt U, Schirdewan A, Kurths J. Recurrence-plot-based measures of complexity and their application to heart-rate-variability data. *Phys Rev E – Stat Nonlinear Soft Matter Phys* 2002;66(2). doi:10.1103/PhysRevE.66.026702.
- [13] Marwan N, Carmen Romano M, Thiel M, Kurths J. Recurrence plots for the analysis of complex systems. *Phys Rep* 2007;438(5–6):237–329. doi:10.1016/j.physrep.2006.11.001.
- [14] Guo R, Wang Y, Yan J, Yan H. Recurrence quantification analysis on pulse morphological changes in patients with coronary heart disease. *J Tradit Chin Med* 2012;32(4):571–7.
- [15] Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol – Hear Circ Physiol* 2000;278(6):H2039–49.

- [16] Vanderlei LCM, Pastre CM, Hoshi RA, de Carvalho TD, de Godoy MF. Basic notions of heart rate variability and its clinical applicability. *Rev Bras Cir Cardiovasc* 2009.
- [17] Aletti F, Ferrario M, Bertacini Almas De Jesus T, Stirbulov R, Borghi Silva A, Cerutti S, et al. Heart rate variability in children with cyanotic and acyanotic congenital heart disease: analysis by spectral and non linear indices. In: Proceedings of the annual international conference on IEEE Engineering in Medicine and Biology Society EMBS; 2012. <https://doi.org/10.1109/EMBC.2012.6346890>.
- [18] Kunz VC, Borges EN, Coelho RC, Gubolino LA, Martins LEB, Silva E. Linear and nonlinear analysis of heart rate variability in healthy subjects and after acute myocardial infarction in patients. *Braz J Med Biol Res Rev Bras Pesqui Méd Biol/Soc Bras Biofísica* 2012;45(5):450–8 [et Al]. doi:10.1590/s0100-879x2012007500025.
- [19] Neves VR, Takahashi ACM, Do Santos-Hiss MDB, Kiviniemi AM, Tulppo MP, De Moura SCG, et al. Linear and nonlinear analysis of heart rate variability in coronary disease. *Clin Auton Res* 2012;22(4):175–83. doi:10.1007/s10286-012-0160-z.
- [20] Muralikrishnan K, Balasubramanian K, Jawahar Ali SM, Vishwanatha Rao B. Poincare plot of heart rate variability: an approach towards explaining the cardiovascular autonomic function in obesity. *Indian J Physiol Pharmacol* 2013.
- [21] Cohen ME, Hudson DL, Deedwania PC. Applying continuous chaotic modeling to cardiac signal analysis. *IEEE Eng Med Biol Mag* 1996;15(5):97–102. doi:10.1109/51.537065.
- [22] dos Santos L, Barroso JJ, Macau EEN, de Godoy MF. Assessment of heart rate variability by application of central tendency measure. *Med Biol Eng Comput* 2015;53(11):1231–7. doi:10.1007/s11517-015-1390-8.
- [23] Thuraishingham RA. A classification system to detect congestive heart failure using second-order difference plot of RR intervals. *Cardiol Res Pract* 2009;2009:1–7. doi:10.4061/2009/807379.
- [24] Kamath C. A new approach to detect congestive heart failure using teager energy nonlinear scatter plot of r-r interval series. *Med Eng Phys* 2012;34(7):841–8. doi:10.1016/j.medengphy.2011.09.026.
- [25] Pachori RB, Avinash P, Shashank K, Sharma R, Acharya UR. Application of empirical mode decomposition for analysis of normal and diabetic RR-interval signals. *Expert Syst Appl* 2015;42(9):4567–81. doi:10.1016/j.eswa.2015.01.051.
- [26] Pachori RB, Kumar M, Avinash P, Shashank K, Acharya UR. An improved online paradigm for screening of diabetic patients using rr-interval signals. *J Mech Med Biol* 2016;16(01):1640003. doi:10.1142/s0219519416400030.
- [27] Sood S, Kumar M, Pachori RB, Acharya UR. Application of empirical mode decomposition-based features for analysis of normal and cad heart rate signals. *J Mech Med Biol* 2016;16(01):1640002. doi:10.1142/s0219519416400029.
- [28] Pachori RB, Bajaj V. Analysis of normal and epileptic seizure eeg signals using empirical mode decomposition. *Comput Methods Programs Biomed* 2011;104(3):373–81. doi:10.1016/j.cmpb.2011.03.009.
- [29] Thuraishingham RA, Tran Y, Boord P, Craig A. Analysis of eyes open, eye closed eeg signals using second-order difference plot. *Med Biol Eng Comput* 2007;45(12):1243–9. doi:10.1007/s11517-007-0268-9.
- [30] Santamarta D, Abásolo D, Martínez-Madriral M, Hornero R. Characterisation of the intracranial pressure waveform during infusion studies by means of central tendency measure. *Acta Neurochir (Wien)* 2012;154(9):1595–602. doi:10.1007/s00701-012-1441-y.
- [31] Thuraishingham RA. Preprocessing RR interval time series for heart rate variability analysis and estimates of standard deviation of RR intervals. *Comput Methods Programs Biomed* 2006;83(1):78–82. doi:10.1016/j.cmpb.2006.05.002.
- [32] Bigger JTJ, Fleiss JL, Steinman RC, Rolnitzky LM, Schneider WJ, Stein PK. RR variability in healthy, middle-aged persons compared with patients with chronic coronary heart disease or recent acute myocardial infarction. *Circulation* 1995;91(7):1936–43.
- [33] Goldsmith RL, Bigger JT, Bloomfield DM, Krum H, Steinman RC, Sackner-Bernstein J, et al. Long-term carvedilol therapy increases parasympathetic nervous system activity in chronic congestive heart failure. *Am J Cardiol* 1997;80(8):1101–4.
- [34] Stein PK, Ehsani AA, Domitrovich PP, Kleiger RE, Rottman JN. Effect of exercise training on heart rate variability in healthy older adults. *Am Hear J* 1999;138(3):567–76.
- [35] Mietus JE, Peng CK, Henry I, Goldsmith RL, Goldberger AL. The pNNx files: re-examining a widely used heart rate variability measure. *Heart* 2002;88(4):378–80. doi:10.1136/heart.88.4.378.
- [36] Brasil Resolução nº466, de 12 de dezembro de 2012. *Cons Nac Saúde* 2012. doi:10.1017/CBO9781107415324.004.
- [37] dos Santos L, Barroso JJ, Macau EEN, de Godoy MF. Application of an automatic adaptive filter for heart rate variability analysis. *Med Eng Phys* 2013;35(12):1778–85. doi:10.1016/j.medengphy.2013.07.009.
- [38] Jeong J, Gore JC, Peterson BS. A method for determinism in short time series, and its application to stationary eeg. *IEEE Trans Biomed Eng* 2002;49(11):1374–9. doi:10.1109/TBME.2002.804581.
- [39] World Health Organization - Tobacco Free Initiative. Building blocks for tobacco control: a handbook; 2004. doi:10.1111/j.1360-0443.2005.01301.x.
- [40] Musialik-Lydkka A, Sredniawa B, Pasyk S. Heart rate variability in heart failure. *Kardiol Pol* 2003;15(3):230–7.
- [41] Rosen SD, Murphy K, Leff AP, Cunningham V, Wise RJS, Adams L, et al. Is central nervous system processing altered in patients with heart failure? *Eur Heart J* 2004. doi:10.1016/j.ehj.2004.03.025.
- [42] Tulppo M, Huikuri HV. Origin and significance of heart rate variability. *J Am Coll Cardiol* 2004. doi:10.1016/j.jacc.2004.03.034.
- [43] Mortara A, Sleight P, Pinna GD, Maestri R, Prpa A, La Rovere MT, et al. Abnormal awake respiratory patterns are common in chronic heart failure and may prevent evaluation of autonomic tone by measures of heart rate variability. *Circulation* 1997;96(1):246–52. doi:10.1161/01.cir.96.1.246.
- [44] Ponikowski P, Chua TP, Piepoli M, Ondusova D, Webb-Peploe K, Harrington D, et al. Augmented peripheral chemosensitivity as a potential input to baroreflex impairment and autonomic imbalance in chronic heart failure. *Circ* 1997;96(8):2586–94. doi:10.1161/01.CIR.96.8.2586.
- [45] van de Borne P, Montano N, Pagani M, Oren R, Somers VK. Absence of low-frequency variability of sympathetic nerve activity in severe heart failure. *Circulation* 1997;95(6):1449–54. doi:10.1161/01.CIR.95.6.1449.
- [46] Barbosa PRB, Barbosa-Filho J, Cordovil I, Nadal J. The effect of the instantaneous rr interval on the dynamic properties of the heart rate and the ventricular repolarization duration variability. *Computers in Cardiology 2000, Vol 27 (Cat 00CH37163)*. MA: Cambridge; 2000. p. 821–4. doi:10.1109/CIC.2000.898651.
- [47] Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. *Ann Intern Med* 2000;132(7):552. doi:10.7326/0003-4819-132-7-200004040-00007.
- [48] Liew WS, Seera M, Loo CK, Lim E, Kubota N. Classifying stress from heart rate variability using salivary biomarkers as reference. *IEEE Trans Neural Netw Learn Syst* 2016;27(10):2035–46. doi:10.1109/TNNLS.2015.2468721.