Symbolic Analysis and Amplitude Symbolic Analysis Provide Complementary Information on Cardiac Control

Alberto Porta[1,2], Paolo Castiglioni[3,4], Beatrice Cairo[1], Vlasta Bari[1,2], Beatrice De Maria[5], Luc Quintin[6]

[1]Department of Biomedical Sciences for Health, University of Milan, Milan, Italy
[2]Department of Cardiothoracic, Vascular Anesthesia and Intensive Care, IRCCS Policlinico San Donato, San Donato Milanese, Milan, Italy
[3]Department of Biotechnology and Life Sciences, University of Insubria, Varese, Italy
[4]IRCCS Fondazione don Carlo Gnocchi, Milan, Italy
[5]IRCCS Istituti Clinici Scientifici Maugeri, Milan, Italy
[6]Hopital d'Instruction des Armées Desgenettes, University of Lyon, Lyon, France

Abstract

Symbolic analysis (SA) is usually applied for the assessment of cardiac control from spontaneous variability of heart period (HP). However, SA does not account for the amplitude of HP changes because patterns featuring small and large variations are included in the same class. The aim of this study is to propose an amplitude SA (ASA) approach accounting for pattern amplitudes. The adopted SA method was grounded on a uniform 6-bin quantization, on the construction of length-3 patterns and on their grouping into four families according to the number and sign of the variations between adjacent symbols. The percentages of patterns belonging to a given class were computed. ASA assessed the variance of the pattern over the original HPs and averaged it within each class. SA and ASA were applied during a pharmacological challenge inducing central sympathetic inhibition and vagal enhancement in 8 healthy male volunteers (age range: 25-46 yrs). We found that both SA and ASA suggest a shift toward vagal activation with a greater presence of patterns featuring fast changes and larger variations. Remarkably, SA and ASA indexes computed over the same class were found to be uncorrelated, thus suggesting that they can capture different features of the HP dynamics and complementary aspects of the cardiac control.

1. Introduction

Methods based on symbolic analysis (SA) were utilized to assess cardiac control from spontaneous fluctuations of heart period (HP) [1,2]. Their exploitation is justified by the ability of SA approaches to decompose the HP dynamics into a sequence of patterns of simple interpretation. For example, patterns featuring a small variety of symbols indicate a reduced sinus node responsiveness, a more predictable HP dynamics and a low complexity of the cardiac control, while patterns composed by a larger number of symbols suggest a greater promptness to changes, richness of HP dynamics and a more complex cardiac regulation. Easiness of interpretation, direct link with complexity of the cardiac control and fastness of decomposition procedure contributed to the success of this class of methods for HP variability analysis [3,4].

Regardless of the class of SA approaches, being roughly classified into amplitude-based (AB) and variation-based (VA) methods [5], the major limitation of SA is the missing inclusion of information about the amplitude of the HP fluctuations. Indeed, in AB approaches the HP series is normalized between the minimum and the maximum before coding the original value with a symbol [6-10], while VB approaches are mainly based on the sign of variations and use the information relevant to the magnitude of variations only to limit the impact of noise [10-15].

The aim of this study is to extend a traditional SA method [1,2] by accounting for the amplitude of variations among adjacent components composing the patterns. The approach, referred to as amplitude SA (ASA), was compared to traditional SA during a pharmacological challenge protocol [16] to assess complementary information.

2. Methods

2.1. SA

 ISSN: 2325-887X DOI: 10.22489/CinC.2025.008

We followed the symbolic approach described in [6,7]. Briefly, the series $y=\{y_i,\ i=1,\ldots,N\}$, where i is the progressive beat counter and N is the series length, was coarse-grained by subdividing the min-max range of y into ξ bins of equal amplitude. Each value y_i was substituted with the integer value y^{ξ}_i, labelling the bin y_i belonged to. Consecutive m integer y^{ξ}_i, values were grouped to form a pattern $\boldsymbol{y}^{\xi}_{m,i} = [y^{\xi}_i \ y^{\xi}_{i+1} \ \ldots \ y^{\xi}_{i+m-1}]$ of length m. According to previous recommendations, N was set to 256 to focus short-term regulatory mechanisms, ξ and m were set to 6 and 3 respectively [6]. Each pattern $\boldsymbol{y}^{\xi=6}_{m=3,i}$ was classified into four classes according to the number and sign of variations between adjacent components: i) no variation (0V) featuring m=3 equal symbols; ii) one variation (1V) presenting two consecutive equal symbols, while the third one was different; iii) two like variations (2LV) featuring two non-zero variations of the same sign between adjacent symbols; iv) two unlike variations (2UV) presenting two non-zero variations of opposite sign between adjacent symbols. Since any pattern $\boldsymbol{y}^{\xi=6}_{m=3,i}$ fell into one, and only one, category, the sum of the number of 0V, 1V, 2LV and 2UV patterns was $N–m+1$. The percentage of 0V, 1V, 2LV and 2UV patterns, indicated as 0V%, 1V%, 2LV% and 2UV%, was computed.

2.2. ASA

ASA approach acted on the pattern $\boldsymbol{y}^{\xi=6}_{m=3,i}$ attributed to the 0V, 1V, 2LV and 2UV classes but it came back to the original HPs composing the pattern $\boldsymbol{y}_{m=3,i}$ and assessed their variance within $\boldsymbol{y}_{m=3,i}$. The variance was averaged within each class, expressed in ms^2 and labelled as a0V, a1V, a2LV, and a2UV.

3. Experimental protocol and series extraction

3.1. Experimental protocol

The experimental protocol was an arm of the pharmacological procedure designed to induce modifications of sympatho-vagal control [16]. All the subjects gave their written informed consent. The protocol adhered to the principles of the Declaration of Helsinki. The human research and ethical review board of the Hospices Civils de Lyon approved the protocol. Briefly, we studied 8 healthy male volunteers aged from 25 to 46 years. Electrocardiogram (ECG) and noninvasive finger blood pressure (Finapress 2300, Ohmeda, Englewood, Colorado, USA) were recorded. Each experiment consisted of 15-20 minutes of recording at baseline (B) while resting in supine position followed by 15-20 minutes of recording taken 120 minutes after oral administration of 6 μg·kg^{-1} of clonidine hydrochloride (CL). CL blocked the sympathetic outflow to heart and vasculature, while centrally increasing the cardiac parasympathetic activity [17].

3.2. HP variability extraction

HP was measured as the temporal distance between two consecutive R-wave peaks detected on the ECG. HP was extracted on a beat-to-beat basis and corrected in the case of erroneous and missing detections. The series were linearly detrended. Sequences of 256 consecutive measurements were randomly selected inside each experimental condition. The mean and the variance of HP were indicated as μ_{HP} and σ^2_{HP} respectively. They are expressed in ms and ms^2 respectively.

3.3. Statistical analysis

Paired t-test, or Wilcoxon signed rank test when appropriate, was applied to check the impact of CL. After pooling together all markers regardless of the experimental condition, linear regression analyses between SA and ASA indexes computed over the same class were performed. We computed Pearson product moment correlation coefficient r and type I error probability p. Statistical analysis was performed with a commercial statistical software (Sigmaplot v.14.0, Systat Software, San Jose, CA, USA). A $p<0.05$ was always deemed as significant.

4. Results

After CL μ_{HP} lengthened significantly, while σ^2_{HP} remained unvaried.

The vertical error bar graphs of Fig.1 show 0V% (Fig.1a), 1V% (Fig.1b), 2LV% (Fig.1c), and 2UV% (Fig.1d) as a function of the experimental condition (*i.e.*, B and CL). 2LV% decreased, and 2UV% increased after CL, while 0V% and 1V% did not vary.

Figure 2 has the same structure as Fig.1, but it shows a0V (Fig.2a), a1V (Fig.2b), a2LV (Fig.2c), and a2UV (Fig.2d). Both a1V and a2UV increased after CL, while a0V and a2LV remained constant.

A significant correlation was detected between 1V% and a1V (r=−0.745 and p=9.26×10^{-4}) and between 2UV% and a2UV (r=0.661 and p=5.34×10^{-3}), while 2LV% and a2LV were uncorrelated (r=−0.144, p=5.95×10^{-1}) as well as 0V% and a0V (r=−0.403, p=1.22×10^{-1}).

5. Discussion

5.1. SA vs ASA approach

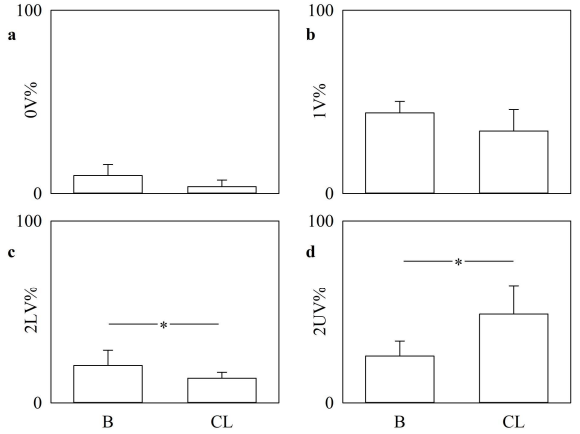

Figure 1. The vertical error bar graphs show 0V% (a), 1V% (b), 2LV% (c), and 2UV% (d) at B and after CL. Data are reported as mean + standard deviation. The symbol * indicates $p<0.05$.

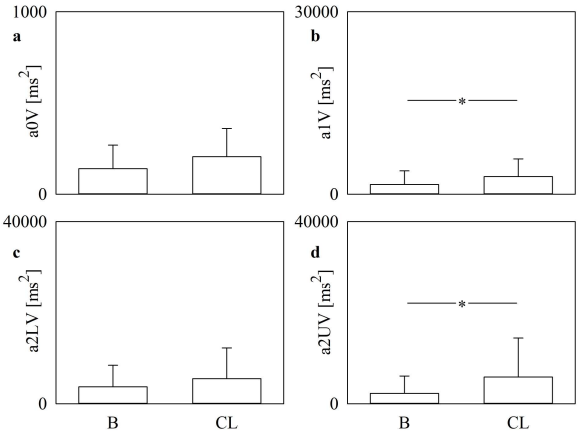

Figure 2. The vertical error bar graphs show a0V (a), a1V (b), a2LV (c), and a2UV (d) at B and after CL. Data are reported as mean + standard deviation. The symbol * indicates $p<0.05$.

SA is based on the decomposition and classification of patterns present in HP variability series with the aim of enhancing features linked to autonomic control and its complexity [3,4]. Being a nonlinear method, SA has the possibility to overcome limitations of more traditional time domain indexes such as the variance. In addition, SA is not based on the strict definition of frequency bands like spectral analysis [18], thus preventing categorizations based on arbitrary definitions of inferior and superior frequency limits. The characteristics support the hypothesis that SA might be more powerful than time and frequency domain methods in describing nonlinear interactions across different time scales and phenomena that cannot be explained according to the usual paradigm of reciprocal interactions between vagal and sympathetic modulations [19,20], such as those observed during strenuous exercise and exercise recovery [21].

The major limitation of the SA technique is that SA accounts exclusively for the likelihood of the pattern class regardless of the amplitude of the changes of the HP values composing the pattern belonging to the considered class. Conversely, ASA method was explicitly designed to provide the magnitude of HP changes within the pattern that was averaged over all the patterns belonging to a given class. The concomitant use of SA and ASA approaches allows one to complement the information on the rate of the class with that of the relevance of the class in contributing to the variability of HP series.

5.2. Impact of CL

CL induced an increase of μ_{HP}, even though the magnitude of HP variability was not affected. Remarkably, SA and ASA were more powerful than the time domain approach in describing the impact of CL on HP variability. Indeed, SA and ASA indicated that both the rate and the amplitude of the fastest class, namely 2UV, significantly increased. This result agrees with the notion that CL induces an inhibition of sympathetic control and an activation of the vagal one [16,17]. It is worth noting that the combined use of SA and ASA suggested a shift toward the high frequency oscillations given that 2LV% significantly decreased after CL, while 2UV% and a2UV significantly augmented.

5.3. SA and ASA provide complementary information

When the level of association between SA and ASA indexes relevant to the same class was computed, we found that markers might be uncorrelated, thus indicating that classes of SA and ASA markers might provide complementary information. While the uncorrelation between 0V% and a0V might be expected because of the low likelihood of 0V class in our experimental protocol combined to the small variability of HP values forming the patters belonging to the 0V family, uncorrelation between 2LV% and a2LV suggests that there is no direct relationship between the rate of a pattern class and the magnitude of HP variability computed within a pattern averaged over the all components of the class.

6. Conclusions

The study proposes the concomitant use of SA and ASA for a deeper characterization of the autonomic control from the analysis of spontaneous HP fluctuations. The combination of methods assures the concomitant evaluation of the rate of pattern families and amplitude of HP changes within patterns belonging to the same class. We recommend the combined use of SA and ASA for the characterization of autonomic function, especially in situations featuring modifications of cardiac control

complexity such as during aging and sleep [22,23].

Acknowledgments

This work was supported by the University of Milan via Piano di Sostegno alla Ricerca 2023, linea 2.

References

[1] S. Guzzetti et al., "Symbolic dynamics of heart rate variability: a probe to investigate cardiac autonomic modulation," *Circulation*, vol. 112, no. 4. pp. 465-470, 2005, doi: 10.1161/circulationaha.104.518449

[2] A. Porta et al., "Assessment of cardiac autonomic modulation during graded head-up tilt by symbolic analysis of heart rate variability," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 293, no. 1, H702–H708, 2007, doi: 10.1152/ajpheart.00006.2007

[3] A. Porta, M. Baumert, D. Cysarz, and N. Wessel, "Enhancing dynamical signatures of complex systems through symbolic computation," *Phil. Trans. R Soc. A Math. Phys. Eng. Sci.*, vol. 373, art. no. 20140099, 2015, doi: 10.1098/rsta.2014.0099

[4] D. Cysarz, A. Porta, N. Montano, P. Van Leeuwen, and J. Kurths, "Quantifying heart rate dynamics using different approaches of symbolic dynamics," *Eur. Phys. J. Spec. Top.*, vol. 222, no. 2, pp. 487–500, 2013, doi: 10.1140/epjst/e2013-01854-7

[5] A. Porta et al., "Comparison of symbolization strategies for complexity assessment of spontaneous variability in individuals with signs of cardiovascular control impairment," *Biomed. Signal Process. Control*, vol. 62, art. no. 102128, 2020, doi: 10.1016/j.bspc.2020.102128

[6] A. Porta et al., "Entropy, entropy rate and pattern classification as tools to typify complexity in short heart period variability series," *IEEE Trans. Biomed. Eng.*, vol. 48, pp. 1282–1291, 2001, doi: 10.1109/10.959324

[7] A. Porta et al., "Conditional symbolic analysis detects non linear influences of respiration on cardiovascular control in humans," *Phil. Trans. R. Soc. A Math, Phys Eng Sci.*, vol. 373, art. no. 20140096, 2015, doi: 10.1098/rsta.2014.0096

[8] D. Cysarz, F. Edelhauser, M. Javorka, N. Montano, and A. Porta, "On the relevance of symbolizing heart rate variability by means of a percentile-based coarse graining approach," *Physiol. Meas.*, vol. 39, art. no. 105010, 2018, doi: 10.1088/1361-6579/aae302

[9] A. Voss et al., "The application of methods of non-linear dynamics for the improved and predictive recognition of patients threatened by sudden cardiac death," Cardiovasc. Res. vol. 31, no. 3, pp. 419–433, 1996.

[10] N. Wessel et al., "Short-term forecasting of life-threatening cardiac arrhythmias based on symbolic dynamics and finite-time growth rates," *Phys. Rev. E*, vol. 61, no. 1, pp. 733–739, 2000. doi: 10.1103/physreve.61.733

[11] D. Cysarz, H. Bettermann, and P. Van Leeuwen, "Entropies of short binary sequences in heart period dynamics," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 278, no. 6, pp. H2163–H2172, 2000, doi: 10.1152/ajpheart.2000.278.6.H2163

[12] D. Cysarz, P. Van Leeuwen, F. Edelhauser, N. Montano, and A. Porta, "Binary symbolic dynamics classifies heart rate variability patterns linked to autonomic modulations," *Comput. Biol. Med.*, vol. 42, no. 3, pp. 313–318, 2012, doi: 10.1016/j.compbiomed.2011.04.013

[13] M. Baumert et al., "Joint symbolic dynamics analysis of beat-to-beat interactions of heart rate and systolic blood pressure in normal pregnancy," *Med. Biol. Eng. Comput.*, vol. 40, no. 2, pp. 241–245, 2002, doi: 10.1007/BF02348131

[14] M. Baumert, K. Javorka, and M.M. Kabir, "Joint symbolic dynamics for the assessment of cardiovascular and cardiorespiratory interactions," *Phil. Trans. R. Soc. A Math, Phys Eng Sci.*, vol. 373, art. no. 20140097, 2015, doi: 10.1098/rsta.2014.0097

[15] M.M. Kabir et al., "Quantification of cardiorespiratory interactions based on joint symbolic dynamics," *Ann. Biomed. Eng.*, vol. 39, no. 10, pp. 2604–2614, 2011, doi: 10.1007/s10439-011-0332-3

[16] J. Parlow, J.-P. Viale, G. Annat, R.L. Hughson. and L. Quintin, "Spontaneous cardiac baroreflex in humans: comparison with drug-induced responses," *Hypertension*, vol. 25, no. 5, pp. 1058–1068, 1995, doi: 10.1161/01.hyp.25.5.1058

[17] E. Toader, A. Cividjian, N. Rentero, R.M. McAllen, and L. Quintin, "Cardioinhibitory actions of clonidine assessed by cardiac vagal motoneuron recordings," *J. Hypertens.*, vol. 26. no. 6, pp. 1169–1180, 2008, doi: 10.1097/HJH.0b013e3282fd10e0

[18] B. Pomeranz et al., "Assessment of autonomic function in humans by heart rate spectral analysis," *Am. J. Physiol. Heart Circ. Physiol.*, vol. 248. Pp. H151–H153, 1985, doi: 10.1152/ajpheart.1985.248.1.H151

[19] M Kollai, and K Koizumi, "Reciprocal and non-reciprocal action of the vagal and sympathetic nerves innervating the heart," *J. Auton. Nerv. Syst.*, vol. 1, no. 1, pp. 33–52, 1979, doi: 10.1016/0165-1838(79)90004-3

[20] J.F.R. Paton, P. Boscan, A.E. Pickering, and E Nalivaiko, "The yin and yang of cardiac autonomic control: vago-sympathetic interactions revisited," *Brain Res. Rev.*, vol. 49, no. 3, pp. 555–565, 2005, doi: 10.1016/j.brainresrev.2005.02.005

[21] J.L. Storniolo, B. Cairo, A. Porta, and P. Cavallari, "Symbolic analysis of the heart rate variability during the plateau phase following maximal sprint exercise," *Front. Physiol.*, vol. 12, art. no. 632883, 2021, doi: 10.3389/fphys.2021.632883

[22] A.C.M. Takahashi et al., "Aging reduces complexity of heart rate variability assessed by conditional entropy and symbolic analysis," *Intern. Emerg. Med.*, vol. 7, no. 3, pp. 229–235, 2012, doi: 10.1007/s11739-011-0512-z

[23] A. Porta et al., "An integrated approach based on uniform quantization for the evaluation of complexity of short-term heart period variability: application to 24h Holter recordings in healthy and heart failure humans," *Chaos*, vol. 17, art. no. 015117, 2007, doi: 10.1063/1.2404630

Address for correspondence:

Prof. Alberto Porta, PhD
Università degli Studi di Milano
Dipartimento di Scienze Biomediche per la Salute
IRCCS Policlinico San Donato
Piazza E. Malan 2, 20097, San Donato Milanese, Milan, Italy
Tel: +39 02 52774382; email: alberto.porta@unimi.it