Perturbation in Parasympathetic Nervous System Activity Affects Temporal Structure of Poincaré Plot

Chandan Karmakar, Ahsan Khandoker, Marimuthu Palaniswami

Dept. of Electrical & Electronic Engineering, The University of Melbourne, Parkville, Australia

Abstract

A novel descriptor (Complex Correlation Measure (CCM)) for measuring the variability in the temporal structure of Poincaré plot has been developed to characterize or distinguish between Poincaré plots with similar shapes. This study was designed to assess the changes in temporal structure of the Poincaré plot using CCM during atropine infusion, 70^0 head-up tilt and scopolamine administration. The aim of this study was to asses the changes in temporal structure of the Poincaré plot using CCM during atropine infusion (parasympathetic blockade) and transdermal scopolamine patch administration (enhanced parasympathetic activity) phases. The change in CCM values during these autonomic perturbation phases revealed the physiological relevance of the new descriptor. The concordant reduction and enhancement in CCM values with parasympathetic activity indicates that the temporal variability of Poincaré plot is modulated by the parasympathetic activity which correlates with changes in CCM values.

1. Introduction

Heart rate variability (HRV) is one of the powerful non-invasive method for analyzing the function of the autonomic nervous system. It is useful to understand the interplay between the sympathetic and parasympathetic autonomic nervous system [1]. HRV is thought to reflect the heart's adaptability to the changing physiological conditions. Assessment of HRV provides quantitative information about the modulation of heart rate (HR) by sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). Interactions of SNS and PNS using HRV signal have been well studied and their importance established with a number of cardiac diseases including myocardial infarction [2], patients with congestive heart failure [3], patients at risk of sudden cardiac death [4, 5] and patients with hypertension [6, 7].

Poincaré plot is a visual presentation of time series signal to recognize the hidden patterns. It is also a quantitative technique in the sense that it has various parameters (ex: short-term variability ($SD1$) and long-term variability ($SD2$)) to quantify the information from the plot. The Poincaré plot of HRV signal is constructed by plotting consecutive points of RR interval time series (i.e., lag-1 plot). It is a representation of HRV signal on phase space or Cartesian plane [8], which is commonly used to asses the dynamics of the HRV [9–12] signal. Poincaré plot has been used to describe the sympathetic and parasympathetic modulation of heart rate [13, 14]. The popular technique used to quantify the Poincaré plot is fitting an ellipse to the shape of the Poincaré plot and measure the dispersion along the minor and major axis of the ellipse, termed as $SD1$ and $SD2$ respectively [9]. Later, the description of $SD1$ and $SD2$ in terms of linear statistics, given by Brennan et. al. [15], showed that the standard descriptors guide the visual inspection of the distribution. In case of HRV, it reveals a useful visual pattern of the RR interval data by representing both short and long term variations of the signal [9, 15].

In our previous study [16], we have developed a novel measure, complex correlation measure (CCM), to quantify the temporal variation of the Poincaré plot. In that study, it was shown that CCM is more sensitive to changes in temporal structure of the signal than $SD1$ and $SD2$. In [16], it was reported that it is possible to have two Poincearé plots with similar $SD1$ and $SD2$ having varied temporal structure. In such scenario, CCM can be used to successfully distinguish two Poincaré plots. CCM was also shown as a measurement from a series of lagged Poincaré plots (multiple lag correlation) which can potentially provide more information about the behavior of Poincaré plot than the conventional lag-1 plot measurements ($SD1$ and $SD2$). Moreover, CCM has shown to be better generalization capability over different pathology than $SD1$ and $SD2$, and it was reported as a novel parameter to characterize the variability in the temporal structure of the Poincaré plot.

In this study, we demonstrate the physiological significance of the novel measure CCM by analyzing the effects of perturbations of autonomic function on Poincaré plot descriptors ($SD1$ and $SD2$) in young healthy subjects caused by the 70^0 head-up tilt test, atropine infusion and

transdermal scopolamine patch.

2. Methods

2.1. Subjects and study design

In this study, five subjects with normal sinus rhythm, did not smoke, had no cardiovascular abnormalities and were not taking any medications were studied. Subjects were aged between 20 and 40 years (30.2±7.2 year). The sequence of phases was maintained strictly as follows [13]:

Baseline study:All baseline studies were conducted in subjects in the post-absorptive state after resting for 10 minutes in the supine position.

Seventy degree head-up tilt:Data were collected after subjects were tilted 70^0 on a motorized table.

Atropine infusion:Atropine sulphate (1.2mg) was added to 50ml of 5 intravenous dextrose and infused at a rate of 0.12mg/min for 5 minutes and then at a rate of 0.24mg/min until completion of this phase of study.

Transdermal scopolamine:A low-dose transdermal scopolamine patch (hyoscine 1.5mg) was applied overnight to an undamaged hair free area of skin behind the ear.

Details of the study design and data collection were published in [13].

2.2. Complex correlation measure (CCM)

CCM evaluates point-to-point variation of the signal plotted in a Poincaré plot. Moreover, as will be seen later, CCM is a function of multiple lag correlation of the signal. CCM is computed in a windowed manner which embeds the temporal information of the signal. A moving window of three consecutive points from the Poincaré plot are considered and the area of the triangle formed by these three points are computed. This area measures the temporal variation of the points in the window. If Poincaré plot is composed of N points then the temporal variation of the plot, termed as CCM, is composed of all overlapping three point windows and can be calculated as:

$$CCM(m) = \frac{1}{C_n(N-2)} \sum_{i=1}^{N-2} \|A(i)\| \qquad (1)$$

where m represents lag of Poincaré plot, $A(i)$ represents area of the triangle (formed with i^{th}, $(i+1)^{th}$ and $(i+2)^{th}$ points of Poincaré plot) and C_n is the normalizing constant which is defined as, $C_n = \pi * SD1 * SD2$, represents the area of the fitted ellipse over Poincaré plot. The length of major and minor axis of the ellipse are $2SD1$, $2SD2$, where $SD1$, $SD2$ are the dispersion perpendicular to the line of identity (minor axis) and along the line of identity (major axis) respectively.

After few steps of derivation from equations 1, the conventional *lag-1* Poincaré plot $CCM(1)$ can be represented as:

$$CCM(1) = F\left[\gamma_{RR}(-1), \gamma_{RR}(0), \gamma_{RR}(2), \gamma_{RR}(3)\right] \quad (2)$$

Where $\gamma_{RR}(m)$ represents the autocorrelation at lag m. This supports our hypothesis that CCM is measured using multiple lag correlation of the signal rather than single lag. The detail derivation of CCM is reported in [16].

2.3. Sensitivity to changes in temporal structure

Literally the sensitivity is defined as the rate of change of the value due to the change in temporal structure of the signal. The sensitivity of CCM was analyzed in order to define how it was affected by increasing amount of change in temporal structure. By increasing the number of surrogating points we have increased the probability of the amount of change in temporal structure of time-series signal. At each step number of surrogated points is increased by 50. We calculated $SD1$, $SD2$ and CCM of a RR interval signal by increasing number of surrogating points at a time. For a selected number of surrogating points, we have shuffled the points for 30 times and calculated all descriptors each time after shuffling. Finally the surrogated values of descriptors were taken as a mean of the calculated values. Now the sensitivity of descriptors $\Delta SD1_j$, $\Delta SD2_j$ and ΔCCM_j was calculated using equations 3-5:

$$\Delta SD1_j = \frac{SD1_j - SD1_0}{SD1_0} \times 100\% \qquad (3)$$

$$\Delta SD2_j = \frac{SD2_j - SD2_0}{SD2_0} \times 100\% \qquad (4)$$

$$\Delta CCM_j = \frac{CCM_j - CCM_0}{CCM_0} \times 100\% \qquad (5)$$

where $SD1_0$, $SD2_0$ and CCM_0 were the parameters measured for the original data set without surrogation and j represents the window number whose data was surrogated. Moreover, $SD1_j$, $SD2_j$ and CCM_j represent the $SD1$, $SD2$ and CCM values respectively after surrogation of j^{th} step.

3. Results

The errorbars of log-scaled $SD1$, $SD2$ and CCM values for four groups of subjects are shown in figure 1. The atropine administration resulted into reduction in mean value of $SD1$ (SD of ΔRR) all subjects which was also reported in [13]. The similar effect was also found for $SD2$ and CCM. The use of scopolamine patch increased both the width and height of the Poincaré plot which resulted into increase in mean values of CCM as well as $SD1$,

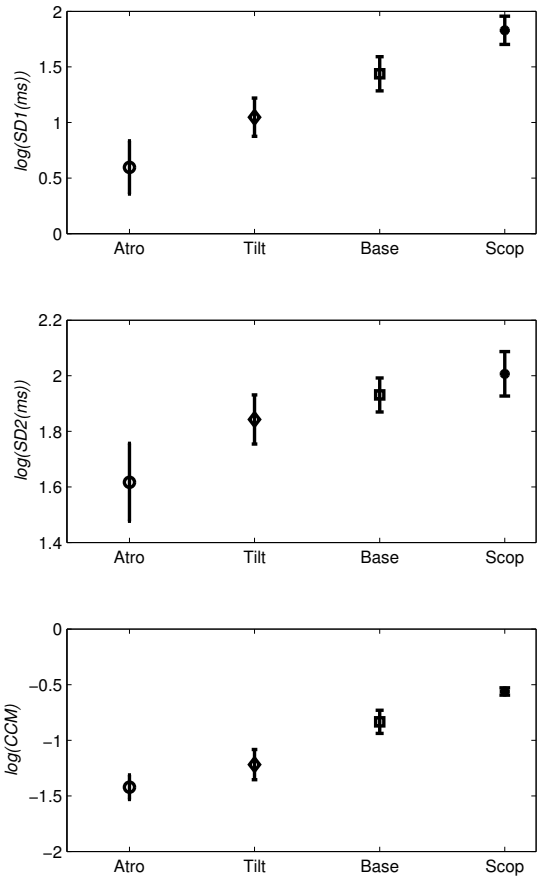

Figure 1. Errorbar (n=5) of $log(SD1)$, $log(SD2)$ and $log(CCM)$ for Atropine, 70^0 head-up tilt, baseline and scopolamine phase. All values were calculated for short segment ($\sim$ 20 minutes) RR interval time series signal.

$SD2$. All subjects have shown a marked reduction in $SD1$, $SD2$ and CCM values in 70^0 head-up tilt phase compared to the baseline.

Figure 2 represented the change of descriptors $SD1$, $SD2$ and CCM with increasing number of shuffled RR intervals. From figure 2 it is apparent that the both $SD1$ and CCM value increases with increasing number of surrogation point with few exceptions. Whereas, value of $SD2$ decreases with increasing number of surrogation point. The rate of change for $SD1$ and $SD2$ is much lesser compared to CCM and the difference in rate of change also increases with increasing number of surrogation points.

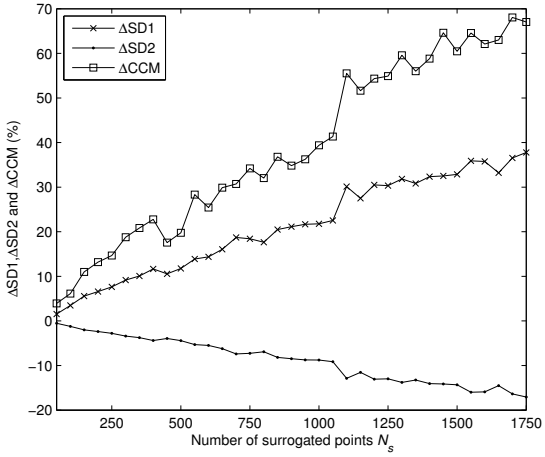

Figure 2. Sensitivity of $SD1$, $SD2$ and CCM with number of shuffled points N_s. At each step the number of shuffled points increased by 50. Each time the signal has been shuffled for 30 times and its mean has been taken to calculated the sensitivity.

4. Discussion and conclusions

The low-dose transdermal scopolamine patch (hyoscine 1.5mg) may decrease heart rate by a paradoxical vagomimetic effect [17]. Delivery by transdermal patch substantially increases both baseline and reflexly augmented levels of cardiac parasympathetic activity over 24 hours in normal subjects [18, 19]. Both time-domain HRV (Mean, SD) and frequency domain HRV (high frequency power) increased to a greater extent during administration of low-dose scopolamine, which indicates the increase in parasympathetic activity [17]. The increase in parasympathetic activity decreases the heart rate and increases the RR interval as well as instantaneous variance in the RR, as measured by SD1 of Poincaré plot. The increased value of SD1 correlates with increase high frequency power and supported by the previous study reported by Kamen et. al. [13]. In this study, the variability in the temporal structure of the Poincaré plot (measured as CCM) was also found to be increased with increase in parasympathetic activity during administration of low-dose scopolamine (Figure 1). The increase in CCM value indicates that it reflects the change in parasympathetic activity harmoniously.

In this study, we have found that CCM correlates with the parasympathetic activity similar to $SD1$ [13]. In [16], we have shown that CCM is sensitive to change in temporal structure of the signal irrespective of temporal position of the signal. In line with the previous finding [16], in this study the relation of CCM with increasing number of shuffled RR intervals has been studied. From figure 2 it is obvious that rate of change with number of shuffled RR

intervals were highest for CCM at any point than $SD1$ and $SD2$. Therefore, we can conclude that CCM is much more sensitive than $SD1$ and $SD2$ with respect to change in temporal structure or the change in autocorrelation of the signal which was earlier reported in [16]. Moreover, sensitivity of CCM with small number of RR intervals increases its applicability to short length HRV signal analysis.

By using the quantitative Poincaré plot analysis of HRV signal, we observed that atropine infusion, 70^0 head-up tilt and scopolamine administration result in changes in heart rate variability [short term variation ($SD1$) as well as long term variation ($SD2$)] and heart rate dynamics [temporal structure (CCM) values]. Subtle differences in dynamics of HRV signal were detected by CCM in all phases of the study. These observations provide some novel information on the physiological relevance of CCM for Poincaré plot analysis: 1) The variability of temporal structure of Poincaré plot of HRV, quantified using CCM, correlates the parasympathetic activity 2) CCM is highly sensitive to changes in parasympathetic activity (vagal tone) as compared to $SD1$ and $SD2$. Further studies of CCM of HRV signal with changes in sympathetic activity may give the complete physiological explanation of CCM with respect to sympathovagal activity.

References

[1] Akselrod S, Gordon D, Ubel F, Shannon D, Berger A, Cohen R. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. Science 1981;213(4504):220–222.

[2] Carney RM, Blumenthal JA, Stein PK, Watkins L, Catellier D, Berkman LF. Depression, heart rate variability, and acute myocardial infarction. Circulation 2001;104:2024–2028.

[3] Aronson D, Burger AJ. Effect of beta-blockade on heart rate variability in decompensated heart failure. Int J Cardiol 2001;79:31–39.

[4] Corr PB, Pitt B, Natelson BH, J. RD, Shine KI, Skinner JE. Sudden cardiac death neural-chemical interactions. Circulation 1987;76 (Suppl I):208–214.

[5] Makikallio TH, Seppanen T, Airaksinen KE, Koistinen J, Tulppo MP, Peng CK, Goldberger AL, Huikuri HV. Dynamic analysis of heart rate may predict subsequent ventricular tachycardia after myocardial infarction. Am J Cardiol 1997;80:779–783.

[6] Pagani M, Lucini D. Autonomic dysregulation in essential hypertension: insight from heart rate and arterial pressure variability. Auton Neurosci 2001;90:76–82.

[7] Takahashi N, Nakagawa M, Saikawa T, Ooie T, Yufu K, Shigematsu S. Effect of essential hypertension on cardiac autonomic function in type 2 diabetic patients. J Am Coll Cardiol 2001;38:232–237.

[8] Liebovitch LS, Scheurle D. Two lessons from fractals and chaos. Complexity 2000;5:34–43.

[9] Tulppo MP, Makikallio TH, Takala TES, Seppanen T, V. HH. Quantitative beat-to-beat analysis of heart rate dynamics during exercise. Am J Physiol 1996;271:H244–H252.

[10] Tulppo MP, Makikallio TH, Seppanen T, Airaksinen JKE, V. HH. Heart rate dynamics during accentuated sympathovagal interaction. Am J Physiol 1998;247:H810–H816.

[11] Toichi M, Sugiura T, Murai T, Sengoku A. A new method of assessing cardiac autonomic function and its comparison with spectral analysis and coefficient of variation of r-r interval. J Auton Nerv Syst 1997;62:79–84.

[12] Hayano J, Takahashi H, Toriyama T, Mukai S, Okada A, Sakata S, Yamada A, Ohte N, Kawahara H. Prognostic value of heart rate variability during long-term follow-up in chronic haemodialysis patiens with end-stage renal disease. Nephrol Dial Transplant 1999;14:1480–1488.

[13] Kamen PW, Krum H, Tonkin AM. Poincaré plot of heart rate variability allows quantitative display of parasympathetic nervous activity in humans. Clinical Science 1996; 91:201–208.

[14] Brennan M, Palaniswami M, Kamen P. Poicare plot interpretation using a physiological model of hrv based on a network of oscillators. Am J Physiol Heart Circ Physiol 2002; 283:1873–1886.

[15] Brennan M, Palaniswami M, Kamen P. Do existing measures of poincare plot geometry reflect nonlinear features of heart rate variability. IEEE Trans on Biomed Engg 2001; 48:1342–1347.

[16] Karmakar C, Khandoker A, Gubbi J, Palaniswami M. Complex correlation measure: a novel descriptor for poincaré plot. BioMedical Engineering OnLine 2009;8(1):17.

[17] La Rovere MT, Mortara A, Pantaleo P, Maestri R, Cobelli F, Tavazzi L. Scopolamine improves autnomic balance in advanced congestive heart failure. Circulation 1994; 90(2):838–843.

[18] Dibner-Dunlap ME, Eckberg DL, Magid NM, Cintron-Trevino NM. The long-term increase of baseline and reflexly augmented levels of human vagal-cardiac nervous activity induced by scopolamine. Circulation 1985; 71(4):797–804.

[19] Vybrial T, Byrg RJ, Maddens ME, Bhasin SS, Chronin WE, Boden WE, Lehmann MH. Effects of transdermal scopolamine on heart rate variability in normal subjects. Am J Cariol 1990;65:604–608.

Address for correspondence:

Chandan Karmakar

Dept. of EEE, The University of Melboure, Parkville, VIC-3010, Australia

c.karmakar@ee.unimelb.edu.au