Heart Rate Asymmetry in Altered Parasympathetic Nervous System Activity

Chandan Karmakar, Ahsan Khandoker, Marimuthu Palaniswami

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

Abstract

Heart rate asymmetry (HRA) was defined as a visible and quantifiable phenomenon in resting healthy people using Poincaré plot. In our pervious study, HRA has been defined considering geometry of the Poincaré plot to better estimate the HRA in healthy subjects. This study was designed to asses the changes in HRA using Poincaré plot during different phases of perturbation in parasympathetic activity. Parasympathetic perturbations were achieved by Atropine infusion and scopolamine administration phase apart from baseline (normal) phase. The redefined Guzik's index (GIp) was calculated for each subjects in each phase of the experiments. In baseline phase the heart rate variability (HRV) of 7 (out of 8) subjects were found asymmetric which reduced to 5 subjects during atropine infusion. In contrast all 8 subjects were found to be asymmetric during scopolamine administration phase. These findings suggest that screening of HRA changes with change in parasympathetic activity of autonomic nervous system.

1. Introduction

Heart rate variability (HRV) is useful to understand the interplay between the sympathetic and parasympathetic autonomic nervous system, which serves to speed up and slow down the heart rate, respectively [1]. It is dependent predominantly on the extrinsic regulation of the heart rate [2]. 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 are established with a number of cardiac diseases include myocardial infarction [3], patients with congestive heart failure [4], patients at risk of sudden cardiac death [5, 6] and patients with hypertension [7, 8]. Moreover, presence of asymmetry in heart rate of healthy subjects has been studied and reported by several researchers [9–12].

Intuitively, asymmetry refers to the lack of symmetry i.e, the distribution of the signal is imbalanced and/or disproportionate [13]. Heart rate asymmetry was initially described as a visible phenomena, mostly present in healthy subjects, which can be assessed by visual inspection using Poincaré plot [10]. Poincaré plot is a visual presentation of time series signal to recognize the hidden patterns. The Poincaré plot of heart rate variability (HRV) signal is constructed by plotting consecutive points of RR interval time series (i.e., lag-1 plot). In our previous study [9], we have developed a method of quantifying heart rate asymmetry using Poincaré plot. Our definition of asymmetry was correctly defined from geometrical point of view because it considered pattern rather than a single point of the Poincaré plot, perviously reported [14], to categorize a point either as increasing, decreasing or stable and it captured heart rate asymmetry (HRA) of healthy subjects using existing asymmetry indices at higher prevalence than that defined by [14].

The aim of the present study was to determine the effect of changes in parasympathetic activity on HRA in young healthy subjects caused by atropine infusion and transdermal scopolamine administration. These results provide insight into the function of presence of heart rate asymmetry in young healthy subjects in resting condition.

2. Methods

2.1. Subjects and study design

In this study, eight 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 (30.5±7.3 year). The sequence of phases was maintained as follows [15]:

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

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 [15].

2.2. New definition of heart rate asymmetry

Piskorski et. al. [10] has defined the HRA with respect to line of identity ($x = y$) since it has clearer physiological interpretation. That is, in case of RR time series signal - any point above line of identity implies decrease in heart rate and any point bellow line of identity implies increase in heart rate. The HRA was then defined as an unidirectional phenomena, i.e. if the increasing RR intervals (points above line of identity) have larger volume than the decreasing RR intervals (points below line of identity), then it was defined as HRA while the reverse was considered as symmetric. However, the unidirectionality of HRA does not comply with mathematical definition of asymmetry and Porta et. al. [12] has defined asymmetry as a bidirectional phenomena. Hence, any imbalance between increasing RR intervals and decreasing RR intervals,points above and bellow line of identity, indicates the asymmetry in the RR interval time series.

The new definition of HRA considers the pattern of two points of the Poincaré plot and any point P_i positioned above line of identity is considered as part of increasing cloud if the next point P_{i+1} resides above or on line of identity. In contrast, it is considered as part of decreasing cloud if the next point moves to below line of identity. Similarly, any point P_i positioned below line of identity is considered as part of decreasing cloud as long as the next point P_{i+1} does not move to above line of identity. Otherwise, it is considered as part of increasing cloud. However, in case of any point P_i positioned on line of identity is considered as part of neutral cloud only, if the next point P_{i+1} only positioned on the line of identity i.e, both P_i and P_{i+1} represents the same point of the plot. If next point resides above line of identity then it is considered as part of increasing cloud. Finally, the point is considered as part of decreasing cloud while the next point moves to below line of identity. Relational expression of the definition is as follows:

Let the vector **RR** be defined as:

$$\mathbf{RR} \equiv \{RR_1, RR_2, RR_3, \cdots, RR_N\}$$

where RR_i is the i^{th} RR interval and N is the total number of RR intervals. Furthermore, **P**, the set of all Poincaré plot points of *lag 1* is defined as: $\mathbf{P} \equiv \bigcup_{i=1}^{N-1} P_i(RR_i, RR_{i+1})$. For any two points $P_i(RR_i, RR_{i+1})$ and $P_{i+1}(RR_{i+1}, RR_{i+2})$ of the Poincaré plot, which involves three RR intervals $\{RR_i, RR_{i+1}, RR_{i+2}\}$, the status of the point P_i with respect to clouds of points is defined as:

$$\begin{array}{lll} P_i & \in I: & (RR_{i+2} > RR_{i+1} \bigwedge RR_{i+1} > RR_i) \bigvee \\ & & (RR_{i+2} > RR_{i+1} \bigwedge RR_{i+1} \le RR_i) \bigvee \\ & & (RR_{i+2} \ge RR_{i+1} \bigwedge RR_{i+1} < RR_i) \\ & \in D: & (RR_{i+2} < RR_{i+1} \bigwedge RR_{i+1} < RR_i) \bigvee \\ & & (RR_{i+2} < RR_{i+1} \bigwedge RR_{i+1} \ge RR_i) \bigvee \\ & & (RR_{i+2} \le RR_{i+1} \bigwedge RR_{i+1} > RR_i) \\ & \in N: & RR_{i+2} = RR_{i+1} = RR_i \end{array} \quad (1)$$

2.3. HRA Index

In [14], authors have defined the index for measuring the asymmetry of the Poincaré plot. For defining GI, the distance of the plotted points from the line of identity is used. For i^{th} point $P_i(RR_i, RR_{i+1})$ of the plot, the distance can be calculated as

$$D_i = \frac{|\, RR_i - RR_{i+1} \,|}{\sqrt{2}}$$

P_i^+ represents the point above the line of identity ($RR_i < RR_{i+1}$) and the distance D_i is denoted as D_i^+. Whereas, P_i^- is the point below the line of identity, i.e., $RR_i > RR_{i+1}$, and the distance is denoted by D_i^-. Guzik index GI is defined as:

$$GI = \frac{\sum_{i=1}^{C(P_i^+)} (D_i^+)^2}{\sum_{i=1}^{N-1} (D_i)^2} \times 100\% \quad (2)$$

where, $C(P_i^+)$ gives the number of points above the line of identity and N represents number of RR intervals . In the new definition of asymmetry, the line of identity is not used for grouping the plotted points into two different clouds. As a result, it is not possible to calculate the new GI using eq. 2. The set of points $\{P_i^+\}$ used in eq. 2 is equivalent to the increasing cloud defined in the new definition of asymmetry. Hence, using the increasing cloud I, eq. 2 can be redefined using the proposed definition:

$$GI_p = \frac{\sum_{i=1}^{M} (D_i)^2}{\sum_{i=1}^{N-1} (D_i)^2} \times 100\% \quad (3)$$

where the numerator corresponds to the increasing cloud and M is the number of points in cloud I, the denominator corresponds to the total number of points and GI_p is the redefined Guzik's Index. Values of GI_p ranges between 0 and 100, with the index value of symmetry $S = 50$. To reduce the effect of noise on assymetry measurement, we have used the relaxed symmetricity range (R), as 1% of the difference between minimum and maximum index (GI_p) values, which is defined in our previous study [9]. Therefore, if $index \in (S \pm R)$ then the signal is symmetric, otherwise asymmetric.

2.4. Deviation from symmetry $Dist_{sym}$

Deviation of the asymmetry index (GI_p) from symmetric range of the index is defined as $Dist_{sym}$. For i^{th} subject $Dist_{sym}$ is calculated as:

$$Dist_{sym} = |GI_p(i) - GI_p(sym)|$$

Where, $GI_p(sym)$ is the index value for symmetric range and defined as:

$$\begin{array}{lll} GI_p(sym) = 49 & , & GI_p(i) < 49 \\ GI_p(sym) = 51 & , & GI_p(i) > 51 \\ GI_p(sym) = GI_p & , & otherwise \end{array} \quad (4)$$

Finally, $Dist_{sym} = 0$ indicates the absence of HRA whereas $Dist_{sym} > 0$ indicates presence of HRA.

3. Results

Figure 1 shows the HRA index values of all subjects for all three phases of the study. The dotted line represents the range of HRA index value that is considered symmetric. In this study, we have used the HRA index value $49 \leq GI_p \leq 51$ as symmetric as suggested in our previous study [9]. Panel A (Figure 1) shows the HRA index values (GI_p) in atropine infusion phase. As depicted in the figure, the GI_p values of 3 subjects (out of 8) lies inside the symmetric range. On the other hand, GI_p values of 1 subject (out of 8) lies inside the symmetric range in baseline (Panel B) phase. However, all subjects lies outside the symmetric range in scopolamine administration (Panel C) phase. This indicates that the HRA reduces in the subjects during atropine infusion whereas it increases in scopolamine administration.

The effect of parasympathetic activity on HRA also measured as deviation of HRA index (GI_p) values from symmetricity, $Dist_{sym}$, which is shown in Figure 2. In atropine infusion phase 5 subjects (out of 8) were found asymmetric with lowest $mean(Dist_{sym})$ value, as depicted by circle in the errorbar, among all phases. On the other hand, in scopolamine administration phase all 8 subjects (out of 8) were found asymmetric with highest $mean(Dist_{sym})$ value, as depicted using solid dot, among all phases. Whereas, in baseline phase 7 subjects (out of 8) found asymmetric with a $mean(Dist_{sym})$ higher than $mean(Dist_{sym})$ and lower than $mean(Dist_{sym})$.

4. Discussion and conclusions

Asymmetry is related with nonlinear dynamics and time irreversibility, which exhibit the most complex interrelationships [13, 16]. It is reported to be highest for healthy physiological systems under resting conditions [13, 14] and decreases with pathology, thus providing a marker for any loss of normal functionality. However, the exact reason for such asymmetry is largely unknown. In this study, we therefore elucidated the change in heart rate asymmetry with altered parasympathetic activity in healthy subjects which is first of its type to our knowledge.

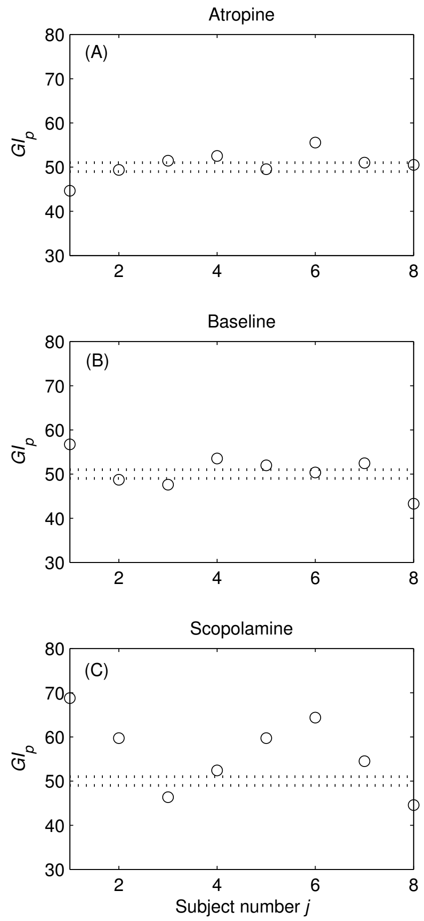

Figure 1. Asymmetry index, GI_p values of HRV signal for all three phases of the study. Dotted line represents the symmetric range i.e, any index values falls in this range indicates that the Poincaré plot of the subject is symmetric. Panels: (A) GI_P values of atropine infusion phase; (B) GI_P values of baseline phase; (C) GI_P values of scopolamine administration phase.

Subjects displayed reduction in the HRA index value (GI_p) during atropine infusion and closed to the symmetric region, measured as the deviation from symmetricity (Figure 2), compared to baseline phase, which indicates that changes in parasympathetic activity affects the presence of HRA as well as deviation of HRA index values (GI_p)

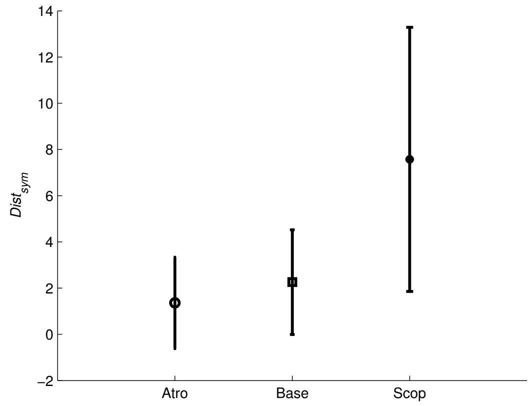

Figure 2. Error bar of $Dist_{sym}$,distance of HRA index (GI_p) from the symmetric range, for atropine infusion, baseline and scopolamine adminstration phase.

from symmetricity. This decrease in parasympathetic activity decreases screened HRA subjects to 5 (out of 8) as compared to 7 (out of 8) in baseline phase. The low-dose transdermal scopolamine patch (hyoscine 1.5mg) may decrease heart rate by a paradoxical vagomimetic effect [17], which is consistent with an increase in parasympathetic nervous system activity [17]. This increase in parasympathetic activity increases screened HRA subjects to 8 (out of 8) as compared to 7 (out of 8) in baseline phase. This concordant decreased and increased HRA screening with parasympathetic activity indicates that HRA reflects the change in parasympathetic activity. In addition, although intersubject variation can be noticed in GI_p values, the HRA index value (GI_p) moves further from the symmetric region (Figure 2) compared to the baseline phase.

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] Acharya UR, Joseph KP, Kannathal N, Lim CM, Suri JS. Heart rate variability: a review. Medical and Biological Engineering and Computing 2006;44(12):1031–1051.

[3] 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.

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

[5] 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.

[6] 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.

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

[8] 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.

[9] Karmakar CK, Khandoker AH, Gubbi J, Palaniswami M. Defining asymmetry in heart rate variability signals using a poincaré plot. Physiological Measurement 2009; 30(11):1227.

[10] Piskorski J, Guzik P. Geometry of the Poincaré plot of RR intervals and its asymmetry in healthy hearts. Physiological Measurement 2007;28:287–300.

[11] Porta A, Guzzetti S, Montano N, Gnecchi-Ruscone T, Malliani A. Time reversibility in short-term heart period variability. Comp Cardiol 2006;33:77–80.

[12] Porta A, Casali KR, Casali AG, Gnecchi-Ruscone T, Tovaldini E, Montano N, Lange S, Geue D, Cysarz D, Leeuwen PV. Temporal asymmetries of short-term heart period variability are linked to autonomic regulation. Am J Physiol Regul Integr Comp Physiol 2008;295:R550–R557.

[13] Costa M, Goldberger AL, Peng CK. Broken asymmetry of the human heartbeat: Loss of time irreversibility in aging and disease. Physical Review Letters 2005;95:198102:1–4.

[14] Guzik P, Piskorski J, Krauze T, Wykretowicz A, Wysocki H. Heart rate asymmetry by Poincaré plots of RR intervals. Biomed Tech 2006;51:530–537.

[15] 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.

[16] Costa M, Goldberger AL, Peng CK. Multiscale entropy analysis of physiological time series. Phys Ref Lett 2002; 89:062102.

[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.

Address for correspondence:

Chandan Karmakar

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

c.karmakar@ee.unimelb.edu.au