Generalized Poincaré Plots Analysis of Cardiac Interbeat Intervals in Heart Failure

Mirjana M. Platiša[1][a], Nikola N. Radovanović[2][b], Aleksandar Kalauzi[3][c] and Siniša Pavlović[2][d]
[1]University of Belgrade, Faculty of Medicine, Institute of Biophysics, 11129 Belgrade, Serbia
[2]University of Belgrade, University Clinical Center of Serbia, Pacemaker Center, 11000 Belgrade, Serbia
[3]University of Belgrade, Institute for Multidisciplinary Research, Department for Life Sciences, 11000 Belgrade, Serbia

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Abstract: In this work we applied generalized Poincaré plots (gPp) analysis of interbeat intervals in patients with heart failure. More, we compared gPp with its nearest analogy methods based on existing extended Poincaré plots techniques. Obtained results showed advantages of gPp method over usually used distanced (lagged) Poincaré plots analysis. Only gPp has the potential of three-dimensional visualization of results with quantification of new multiscaling parameters. It is comparable with other methods only in two-dimensional planes where all methods showed a strong negative correlation between patterns of Pearson correlation coefficients and patterns of the *SD1*/*SD2* ratio over the whole range of Pp orders (lags). These results could be used as the basis for further research in new standardization of multiscaling methods in heart rhythm analysis where it is important to follow the pattern of regulatory mechanisms dynamics which is related to the duration of *RR* intervals.

1 INTRODUCTION

Analysis of heart rate variability (HRV) is used to extract important information about the interaction between the cardiovascular system and the nervous system. Usually, linear and nonlinear methods of HRV analysis which revealed the structure and properties of interbeat interval series are applied with several main issues. In medicine, dominantly, through the application as diagnosis of autonomic dysfunction in various disease and prognostic information contained in HRV as a reflection of the activity of the autonomic nervous system and mechanical heart function. Additionally, other multidisciplinary goals were to develop new methods which may better describe dynamics of the cardiovascular system and help to reveal and understand some important information about regulatory mechanisms and their changes in different functions of the autonomic nervous.

The standardized Poincaré plot (Pp) is a representation of a time series into a phase space with delay or lag of one point i.e. in the case of HRV analysis each *RR* interval is plotted as a function of the previous *RR* interval. First of all, it presents useful visual information and it is a part of standardized methods of HRV analysis. There is also a quantitative analysis of the Poincaré scattergram by *SD1* – variance of *RR* intervals in a short scale, *SD2* – variance in a long term scale and their ratio *SD1*/*SD2*. Moreover, the full potential of this approach is searched through the extension of Pp analysis by autocovariance concept at higher lags (Lerma et al, 2003, Thakre and Smith, 2006). Standardized Poincaré plot analysis is one method of HRV analysis derived from nonlinear dynamics analysis. However, some indices derived from this approach are strong correlates to the linear HRV measures derived from spectral analysis (Contreras et al, 2007).

Recently we proposed a new, generalized Pp analysis method and applied it to ECG recordings of

[a] https://orcid.org/0000-0002-0915-2823
[b] https://orcid.org/0000-0002-6545-2230
[c] https://orcid.org/0000-0003-4833-0757
[d] https://orcid.org/0000-0002-1395-4407

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patients with permanent atrial fibrillation (Platiša et al, 2016), and to ECG recordings of three different physiological conditions in young healthy trained and untrained subjects (Platiša et al, 2019b). Contrary to other lagged (distanced) Poincare plots methods, this unique method instead *RR* interval used R peak in ECG recordings as a referent point for further analysis. This approach allows us to follow *RR* intervals and their duration on both sides of chosen R peak and calculate correlations between symmetrical distanced duration of *RR* intervals and moreover asymmetrically distanced durations of *RR* intervals. There were a lot of results obtained with this gPp analysis and only part of them indicate possible interpretation which could be associated with well known physiological mechanisms, primarily directly related to the parasympathetic cardiac control.

The aim of this study is twofold. The first one was to apply gPp method to ECG recordings of heart failure patients and the second one to compare this method with the most approximate variants of extended Poincare plots analyses.

2 METHOD

2.1 Subjects

We included 63 patients with symptomatic heart failure (HF) and reduced left ventricular ejection fraction (LVEF < 35%) who had an indication for an implantable cardioverter-defibrillator or cardiac resynchronization therapy device implantation. Patients were divided into two groups depending on whether they were in sinus rhythm (HFSin) or with permanent atrial fibrillation (HFAF). In the HFSin group, we analyzed 30 heart failure patients (5 women) aged 57.9 ± 7.5 years; while in the (HFAF) 33 heart failure patients (3 women) aged 68.0 ± 7.6 years. The control group consists of 30 healthy middle-aged subjects (15 women) aged 46.3 ± 8.2 years, all were nonsmokers without any history of disease. All participants were instructed to avoid physical activity starting the day prior to measurement and to not eat or drink on the day of the examination.

2.2 Experimental Data

Measurements were done in the Pacemaker Centre of the University Clinical Centre Serbia and in the Laboratory for Biosignals, Institute of Biophysics, Faculty of Medicine. Ethics Committee of the Faculty of Medicine, University of Belgrade approved this study. All subjects gave written informed consent in accordance with the Declaration of Helsinki. Experiments were done in the morning between 8:00 and 11:00 a.m.

ECG recordings were obtained from subjects in the supine position and with spontaneous breathing, 20 minutes in duration (without moving and verbal communication). The ECG was acquired with sampling frequency of 1 kHz by Biopac MP100 system with AcqKnowledge 3.9.1. software (BIOPAC System, Inc., Santa Barbara, CA, USA).

We analysed RR intervals extracted from 20 minutes of supine relaxing ECG recordings. Sequences of approximately 1200 *RR* intervals extracted from ECG data were obtained using OriginPro 8.6 (OriginLab Corporation, USA).

2.3 Standardized Poincaré Plot

A typical HRV Poincaré plot represents scatter graph as the function $(RR)_{i+1} = f((RR)_i)$. The two standard parameters *SD1* and *SD2*, called the Poincaré plot descriptors, describe the distribution of points around two diagonals. It is accepted that *SD1* describes instant heartbeat intervals variability and quantifies short-term HRV, while *SD2* quantifies long-term HRV (Platiša et al, 2019a).

2.4 Generalized Poincaré Plot Analysis

Our recently proposed method is generalized form of Poincaré plot analysis where we track dependence and correlation between the duration of *j* preceding and *k* next *RR* intervals by varying *j* and *k* around chosen R peak in ECG (Platiša et al, 2016, Platiša et al, 2019b).

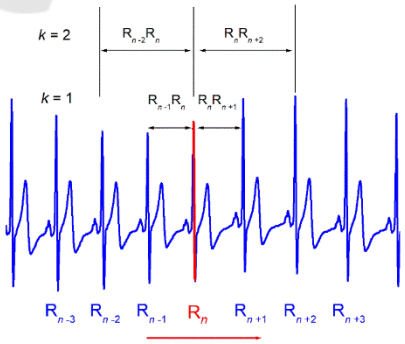

Figure 1: Simplified example of chosen sliding R peak in ECG recording and the duration of *k* preceding and *k* next RR interval.

Both quantities were calculated by simply adding the durations of the corresponding intervals around a

chosen R wave which was moving along the ECG signal (Figure 1). For an ECG signal with a total number of N *RR* intervals, only $N-j-k$ points could be drawn. For results obtained with specific values of j and k, i.e. for a pair of number of intervals, *(j,k)*, we propose the term "order of the gPp". In cases when symmetric ($j = k$) gPp were calculated, for previous k and following k intervals in duration, integral dynamics of interbeat intervals appeared as specific trajectories in relaxed healthy subjects (Platiša et al., 2016, Platiša et al., 2019b).

Moreover, in cases when asymmetric ($j \neq k$) gPp were calculated the relationship between previous j and following k summed intervals give as additional information about dynamics of cardiac control mechanisms. In this work we quantified relationship between summed durations of j previous and k following consecutive *RR* intervals by Pearson correlation coefficients of matrices for $j, k = 1, \ldots, 50$ intervals, which we briefly denoted as $r(j, k)$. In order to quantify asymmetry of matrices, we introduce a normalized asymmetry index (*NAI*), which for a $m \times n$ type matrix is defined as

$$NAI = \frac{1}{m \times n} \frac{1}{r} \sum_{j=1}^{m} \sum_{k=j+1}^{n} \left(r(k,j) - r(j,k) \right) \quad (1)$$

where *r(j,k)* represents matrix element, while

$$\bar{r} = \frac{1}{m \times n} \sum_{j=1}^{m} \sum_{k=1}^{n} \left| r(j,k) \right| \quad (2)$$

Another interesting property of these Pearson's matrices was the appearance and positions of local maxima, since each local maximum of correlation could potentially signify a temporal range in which a neurocardiac regulatory mechanism is operating.

All analyses were performed using our original programs developed within MATLAB (MathWorks Inc., Natick, MA01760-2098, United States).

2.5 Distanced Generalized Poincaré Plots Analysis

In order to compare our gPp method with the published methods of extended Poincaré plot analysis we used two approaches. The first one is the nearest analogy to gPp which we called distanced generalized Poincaré plots (dgPp) method. In this method we examined relations between individual *RR* intervals, the k preceding and the k following *RR* interval around chosen R peak in ECG. During calculation we noticed one important limitation of this approach. When we increase distance (Pp order) by one, *RR* intervals are distanced away for two intervals. Hence, only even *RR* intervals are analysed, and odd *RR* intervals are omitted.

2.6 Distanced Poincaré Plots Analysis

This approach actually represents lagged (extended) standardized Poinacre plot analysis which can be found in published literature. Instead of arbitrary chosen R peak in ECG signal, in this approach we started calculation with fixed, the first *RR* interval in time series of RR intervals. For $k = 1$, we track two neighbor *RR* intervals in the whole series, for $k = 2$ we track *RR* intervals distanced by one *RR* interval, etc.

2.7 Statistics

Mann-Whitney U test was used to compare indexes of asymmetry between the group of healthy subjects and two groups of HF patients. The data of *NAI* are given as mean values ± standard errors. Statistical analyses were performed using the software package SPSS Statistics (version 17.0, SPSS Inc, USA). A value of $p < 0.05$ was considered significant.

3 RESULTS

3.1 Generalized Poincaré Plots Analysis in Heart Failure

In order to present the major difference between standardized Pp and generalized Pps analysis we show in Figure 2 examples of standardized Poincaré plot and generalized Poincaré plots of k order in one healthy control subject and two heart failure patients

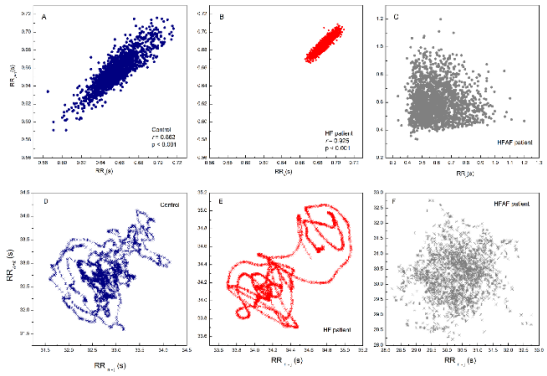

Figure 2: Examples of standardized Pp (top) and gPp for $k = 50$ (bottom) of *RR* intervals for one control subject (blue) and two subjects with heart failure (with sinus rhythm in red and with atrial fibrillation in grey).

(one with sinus rhythm and one with atrial fibrillation). In the gPp analysis we denote by k the order of gPp which means successive sums of RR intervals, in this paper up to 50.

The presence of hanks in gPp method is one of the first advantages of this approach. Considering these with our previous findings, we can conclude that hanks indicate complex dynamical processes in autonomic cardiac control dominantly related to transition pathways of parasympathetic cardiac control. It is interesting that hanks are also present in heart failure patient with sinus rhythm although variability of this time series is reduced compared with Pp (variability of time series) in healthy control subject (Figure 2). This finding and finding in heart failure subject with atrial fibrillation patient where autonomic cardiac control via sinus node ceased to exist suggested that non-existence of hanks indicated absence of parasympathetic cardiac control and that their existence was not related to heart rate variability.

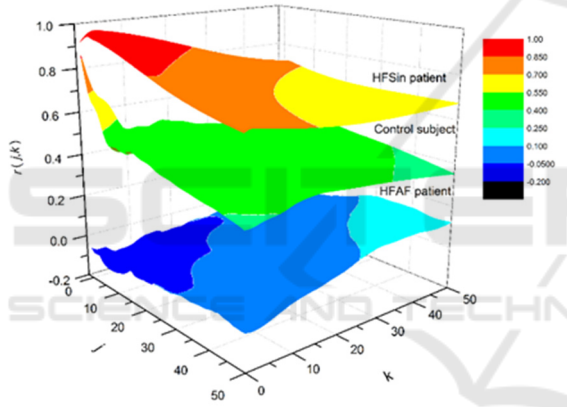

Figure 3: Examples of matrices of Pearson correlation coefficients for (j, $k \leq 50$) in a one control subject and two heart failure patients.

Further, we calculated matrix of Pearson correlation coefficients for (j, k = 50) and present representative examples in Figure 3. The area of correlation coefficients between summed RR intervals for heart failure patient with sinus rhythm was positioned on the top, above the area of correlation coefficients for healthy subject and the area of correlation coefficients which belongs to heart failure patient with atrial fibrillation.

This position which had mild decrease with the highest order of Pp indicated strongly correlated summed *RR* intervals up to the 50th order of Pp. On the other hand, in control subject summed *RR* intervals were strongly correlated only in the small range of few first orders of Pp, while in HFAF patient Pearson correlation coefficients were reduced over

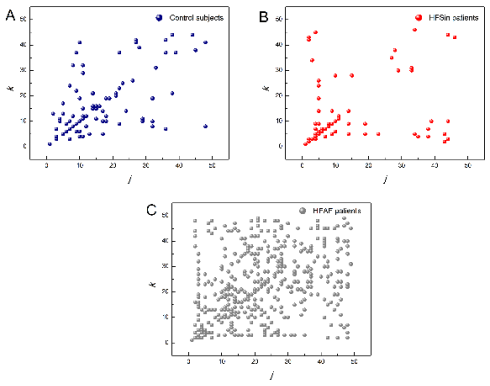

Figure 4: Pooled local maxima of Pearson's correlation coefficients matrices projected on the (j, k) plane in the group of control subjects (A), in the group of HFSin patients (B) and in the group of HFAF patients (C).

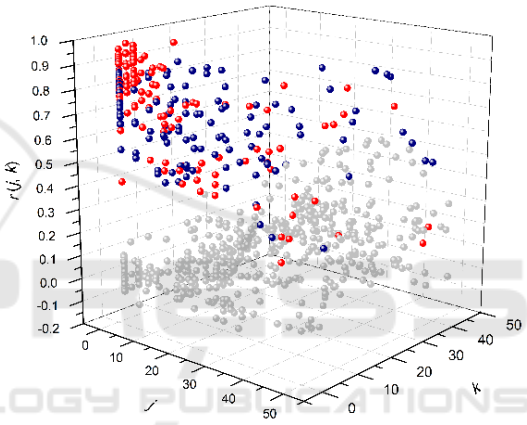

Figure 5: Distribution of pooled maxima of Pearson's correlation coefficients matrices in the group of healthy subjects (blue), in the group of HFSin patients (red) and in the group of HFAF patients (grey) plotted in 3D.

the all area. Pooled local maxima of Pearson correlation matrix in each group were determined and they are presented in Figure 4 and Figure 5. More, we determined normalized index of asymmetry (*NAI*) and compared their mean values between the groups.

There were statistically significant difference only between the group of control and the HFSin group (Figure 6).

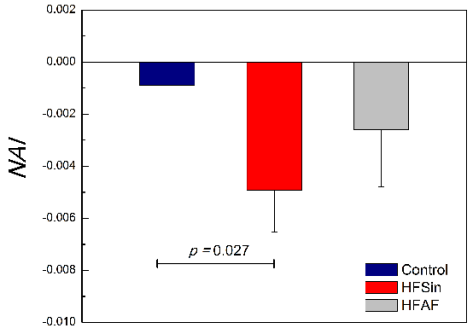

Figure 6: Normalized asymmetry index (*NAI*). Data are presented as mean with standard errors.

3.2 Comparisons of gPp with Other Methods

Unfortunately, nature of the other approaches in Pp analysis is limited and results were not comparable in three-dimensional space. Hence, we continued further analysis in 2D plots only for symmetric ($j = k$) diagonals elements of Pearson correlation coefficients matrices and the *SD1*/*SD2* ratio for all gPp orders (k = 1 ,…, 50).

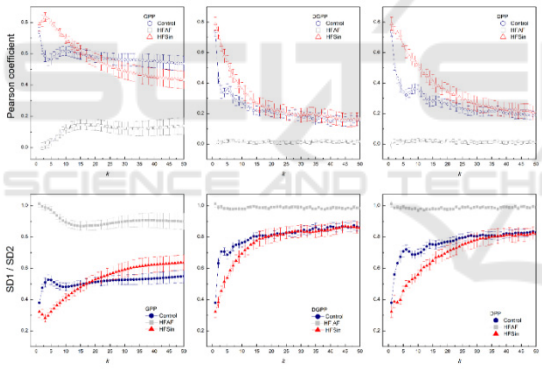

Figure 7: Figure shows dependencies of averaged Pearson correlation coefficient and averaged the ratio *SD1*/*SD2* parameters for all three approaches in the group of control healthy subjects and the HFSin and the HFAF group.

In results obatined from all methods we found strong negative correlation between patterns of the ratio *SD1*/*SD2* and patterns of the Pearson correlation coefficients over the whole range of Pp orders (Figure 7).

4 DISCUSSION

In this paper, we describe results of applied recently proposed gPp analysis of *RR* intervals in heart failure patients and control subjects. Consistent with findings in our previous studies, we showed that gPp analysis can also differentiate heart failure patients with sinus rhythm and with atrial fibrillation. It is well known that reduced heart rate variability is one of the major properties of sinus rhythm in heart failure patients. Besides this property, approved with standardized Poincare plot, we showed that the existence of hanks was not influenced by reduced HRV in the group of HFSin patients. In our previous papers we found that activities of parasympathetic cardiovascular control were described by hanks (Platiša et al, 2016, Platiša et al, 2019b).

Further, we obtained, from gPp Pearson coefficient matrix, strong correlations between summed *RR* intervals in HFSin patients over all orders ($k = j = 50$), while in healthy subjects strong correlations are present only for few first orders of summed *RR* intervals. Beside estimated strength of correlations i.e. Pearson correlation coefficients we determined local maxima of Pearson correlation coefficients and calculated normalized index of asymmetry (*NAI*). Positions of local maxima in the HFSin patients group were more distanced from the central diagonal while in healthy subjects they are close to this diagonal and there is much more number of maxima on the diagonal. In the group of HFAF patients, we had almost random distribution of local maxima with very low values of Pearson correlation coefficients. Similar result we obtained in our previously published paper (Platiša et al, 2016) where we analyzed data from patients with permanent atrial fibrillation but without heart failure. It is obviously that impact of heart failure in cases with atrial fibrillation on the gPp analysis results is very low or almost neglectable.

At this moment, we didn't recognize any particular physiological mechanisms related to the maxima on areas of Pearson correlation coefficients. They may be related to time scales over which physiological mechanisms operate via the duration of summed *RR* intervals. As additional information, we captured the integral information from positions of pooled maxima in each group of subjects and quantified it by *NAI*. In both groups of heart failure patients *NAI* is more negative than in the control group but there is a statistically significant difference only between the HFSin group and the control group.

Furthermore, we show that independently of Poincaré plot analysis approach, over all orders of Pp (or of lags), a strong relationship between the pattern of Pearson coefficients and the pattern of the *SD1*/*SD2* ratio exited (like an inverted picture in the mirror).

Averaged Pearson correlation coefficients calculated by gPp just for diametrical, symmetric cases ($j = k$), changed with gPp orders and they were lowest for the HFAF group. It is very interesting that changes of Pearson correlation coefficients with k were noticeable up to the 13th order of gPp analysis in all analyzed groups. Similarly, inverted changes can be seen in dependence of the *SD1*/*SD2* ratio on the gPp order k. In the control group there is the maxima for $k = 1$ and minimal correlations approximately around 3th or 4th order, while in HFSin group maxima is at $k = 3$, and the value of coefficients between the group are different up to 10th gPp order. These maxima and minima positions probably revealed times at which operated dominant regulatory cardiac control mechanisms.

In dgPp analysis, a real analogy technique to the gPp, we obtained different dependencies of Pearson coefficients on the k in analyzed groups. As expected, Pearson coefficients in the HFAF group were close to zero and the *SD1*/*SD2* ratio around 1. In the HFSin group, Pearson coefficients monotonically decreased with k, while in control subjects there were two maxima in dependence of Pearson coefficients of k (at $k = 1$ and at $k \approx 5$). In simple lagged Pp analysis, which we called dPp, we obtained similar dependencies of Pearson coefficients and the *SD1*/*SD2* on lag k as in dgPp, but they were stretched because in calculation entered all *RR* intervals.

5 CONCLUSIONS

In summary, we showed advantages of generalized Pp analysis which takes referent R peak in ECG recording instead of referent *RR* interval in analysis of heart rhythm. This approach for symmetrical cases ($j = k$) revealed interesting patterns of integrated cardiac control which were not related to the absolute value of heart rate variability, well-known measure of autonomic cardiac control. In the extended part of gPp analysis, when asymmetrically cases ($j \neq k$) were involved, areas of Pearson correlation coefficients matrices were obtained whose physiological background needs to be discovered in further work.

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