Neurohormonal and Functional Correlates of Linear and Poincarè plot Indexes of Heart Rate Variability in Heart Failure Patients

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Abstract

Higher neurohormonal activation levels are known markers of severity in heart failure (HF). Aim of the study was to assess the association of Poincarè plot indexes (PPI) of RR time series with plasma norepinephrine (NPE) levels and functional parameters as compared to classical linear indexes of HRV. Ninety-nine HF patients underwent to a 24-hour Holter recording and a standard clinical and laboratory examinations included plasma NPE assay. The SDNN and the power in the low frequency band were computed. PPI were obtained by automated quantification of the bi-dimensional length, L and tri-dimensional (peak's number Np, radii of the semi-ellipse of inertia Px,Py,Pz morphological characteristics. Both SDNN and LFP showed a moderate but significant negative correlation with NPE levels while a weaker association was found for L, Np and Py. Linear indexes were significantly associated with VO2max and between PPI similar correlation were found for L, Py and Pz. Similar relationships were found with EF for SDNN, LFP, L, Np, Pz, with a negative correlation for Px. These findings suggest that although the association of linear and PPI of HRV with functional parameters is similar, the former, particularly the power in the low frequency band, appear to reflect more closely the level of adrenergic activation of HF patients.

1.   Introduction

Cardiovascular diseases are the first cause of morbidity and mortality in western and industrialized countries. Heart failure (HF) is a disabling and deadly condition which usually worsens over time, involving about 10% of the elderly population and accounting for 1-2% of health-care costs [1].

HF is associated with prominent alterations in the autonomic control of the cardiovascular system and higher neurohormonal activation levels are known markers of severity and adverse prognosis in these patients [2]. Heart rate variability (HRV) is a well-known non-invasive assessment technique of the heart autonomic control. As well as traditional linear indexes of HRV, Poincarè plots (PPlots) analysis of beat-to-beat time series is a well-known method that have been tested in clinical settings in the last years, allowing to detect patterns resulting from non-linear processes that may not be observable by time- and frequency-domain analysis [3,4].

Linear indexes of HRV have been shown to be associated with neurohormonal activation [5] and also has been shown that PPlots analysis of HRV allow quantitative display of parasympathetic nervous activity [6] and that quantitative descriptors of PPlots are better predictors of mortality in cardiac patients than time-domain conventional indexes [7].

Aim of the paper is to assess the association of quantitative descriptors of PPlots with neurohormonal activation levels and functional parameters as compared to classical linear indexes of HRV in heart failure subjects.

2.   Study Group

Ninety-nine stable mild-to-moderate HF patients in sinus rhythm (age: 51±8 years, New York Heart Association class II-III) admitted to the Heart Failure Unit of the Scientific Institute of Montescano were studied. Inclusion criteria were: sinus rhythm, stable clinical condition during the last 2 weeks, absence of pulmonary or neurological disease, or any other disease limiting survival, no recent (within the previous 6 months) myocardial infarction or cardiac surgery.

All patients underwent to a 24-hour Holter recording and standard clinical and laboratory examinations, including 2D echocardiography for left ventricular ejection fraction (LVEF) evaluation, ECG stress test for maximal oxygen consumption (VO2max) estimation and a blood sample for plasma norepinephrine (NPE) assay collected within one week from the Holter recording and assessed by a single-isotope radioenzymatic method.

3.   Holter recordings

Holter recordings were performed using a two-channel recorder and processed using a Synetec System (ElaMedical, S.p.A., Segrate-Milano, Italy) with a sampling rate of 200 Hz. After automatic scanning, an expert analyst carefully edited all the recordings.

In order to be considered eligible for the study, each recording had to have at least 12 hours of analyzable RR intervals in sinus rhythm. Moreover, this period had to include at least half of the nighttime (from 00:00 AM trough to 5:00 AM) and half of the daytime (from 7:30 AM trough to 11:30 AM)[8].

4.   Poincarè plot analysis

The PPlots technique consists on maps constructed by plotting each RR interval against the preceding one. Only normal classified QRS complexes were considered, excluding RR intervals preceding or following not-normal beats and plotting only time-closed RR couples. Usually bi-dimensional (2D) PPlots are just visually classified into three typical comet, torpedo or fan-shaped patterns [3] but with the limitation of a subjective plot's classification. Quantitative 2D PPlots analysis' methods have been proposed in literature, but it has clearly been shown that most of them bring back to existing linear measure of HRV [9] and only non-geometric techniques, such as scanning parameters [10], allow to detect patterns resulting from non-linear processes that cannot be detectable by time- and frequency-domain analysis.

A dedicated software developed by the authors allowed to automatically calculate the main morphological characteristics of bi and three-dimensional (3D) maps obtained plotting the RR couple repetition's number as the third dimension (Fig. 1). Technical details on the procedure have been described elsewhere and excellent reproducibility of obtained indexes has been previously demonstrated [10]. The most meaningful parameters extracted from 2D PPlots are measures of the extension and dispersion of the ellipsoidal cloud of points around the bisecting line, namely the length (L), the area (A), the highest variability extension (HVE), that can be obtained scanning the plot with a vertical line and generating a curve which represent the measure of width of the scatter at different RR intervals, and percentage of length which corresponds the maximum plot wideness (P) (Figure 2). The most interesting parameters extracted from 3D PPlots are measures related to the plot's height, taking into account the RR couples' repetition number, namely the peaks' number (Np), the mean peaks' distance from the bisecting line (Dp), and the length of the three radii of inertia (P_x, P_y, P_z) of the semi-ellipsoidal 3D cloud of points (Figure 2).
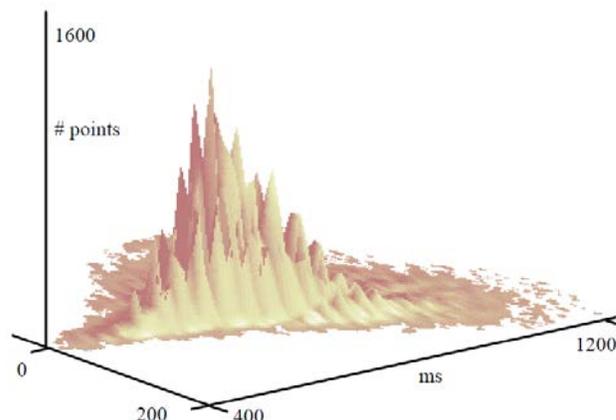

Figure 1. 3D Poincarè plot analysis

5.   Linear analysis

Annotated RR time series were processed according to previously described criteria [11] in order to correct ectopic beats, arrhythmic events and artifacts which are known to alter the estimation of HRV indices [12].

Most important time- and frequency-domain parameters (standard deviation between normal to normal beats – SDNN-, and the power in the low frequency band LFP, 0.04- 0.15 Hz) were computed on consecutive 5-min RR sequences. Five minutes sequences with < 95% of sinus beats and sequences containing large transients or artefacts were discarded. Results computed on all analyzable 5 minutes segments were averaged.

Spectral analysis was performed using the autoregressive approach (Burg algorithm) with spectral decomposition, and was verified using the classical Blackman-Tukey method.
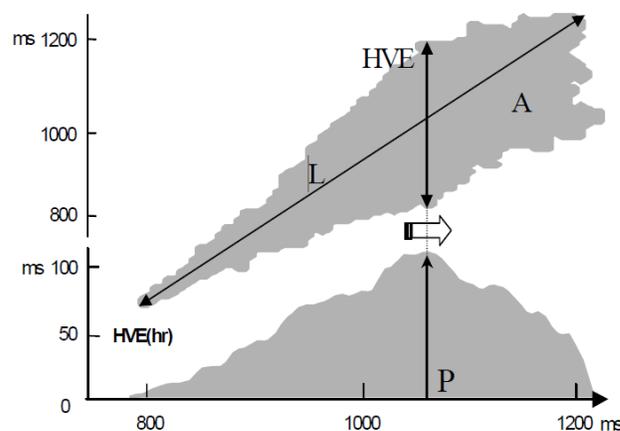

Figure 2. 2D Poincarè plot parameters

6. Statistical analysis

Kolmogorov-Smirnov (KS) test was used to assess the normality of the distribution of all variables studied and, due to the marked skewness in the distribution of some variables, the associations between HRV, neurohormonal and functional indexes were assessed by Spearman correlation coefficient.

7. Results

In Table 1 demographic, clinical and functional characteristics of the studied population are reported. In Table 2 linear and PPlots indexes of HRV in the studied population. In Table 3 the Spearman correlation analysis between neurohormonal and functional VO2max and LVEF levels with HRV indexes is listed.

Both SDNN and LFP showed a moderate but significant negative correlation with NPE levels (r=-0.37 and -0.44 respectively, p<0.0001); while a weaker negative association was found for L, Np and Pz ranging from r=-0.33 to -0.25, p<0.0001).

Linear indexes were significantly moderately associated with VO2max (r=0.31 and 0.36 respectively, p<0.001) but over all a slightly higher significant positive correlation has been exhibited by Py (r= 0.37 with p<0.001).

Almost all indexes showed moderate but significant positive correlation with LVEF, also if the higher values have been exhibited by L and Px, (r= 0.36 and -0.38 respectively with p<0.0001).

8. Discussion

The assessment of autonomic control of the cardiovascular function is crucial to understand the pathophysiology of heart failure. For this purpose, several techniques have been proposed so far, yet this still represents a challenging task.
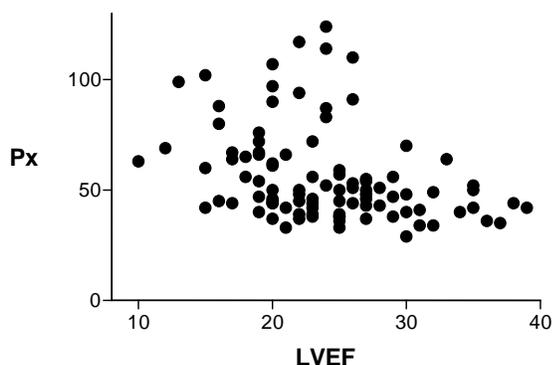
Table 1. Demographic, clinical and functional characteristics of the studied population (N=99). All data expressed as mean ± standard deviation.

Age (years)	51 ± 8
Male (%)	84
NYHA class II.II (%)	88
NPE (pg/L)	363 ± 210
V02max (mL/kg·min)	14 ± 4
LVEF (%)	24 ± 6

Table 2. Linear and PPlots indexes of HRV in the studied population. All data expressed as mean ± standard deviation.

SDNN (ms)	36 ± 15
LFP (ms^2)	162 ± 171
L (ms)	577 ± 190
Np	28 ± 19
Px (ms)	56 ± 21
Py (ms)	113 ± 29
Pz (ms)	102 ± 43

Table 3. Spearman correlation analysis, r value and *** for p<0.001; ** for 0.001<p<0.01; * for 0.01<p<0.05

	correlation vs NPE	correlation vs VO2max	correlation vs LVEF
SDNN (ms)	-0.37***	0.31***	0.35***
LFP (ms^2)	-0.44***	0.36***	0.34***
L (ms)	-0.33***	0.33**	0.36***
Np	-0.29**	ns	0.33**
Px (ms)	0.28**	-0.26*	-0.38***
Py (ms)	-0.25*	0.37***	0.24*
Pz (ms)	-0.31**	0.32**	0.34***

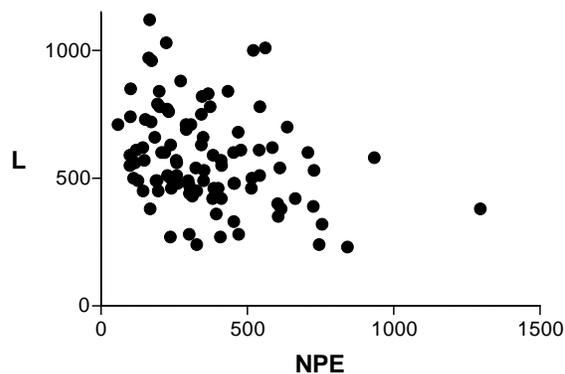Figure 3. Scatterplot of Px as a function of LVEF

Figure 4. Scatterplot of L as a function of NPE

The measurement of plasma catecholamines levels provides a practical way to assess sympathetic activity and has been widely used, despite its limitation of being a "systemic" instead of organ specific measurements of sympathetic activation. The use of more specific measurements, such as cardiac norepinephrine spillover, is limited to small studies due to the invasiveness and complexity of these techniques [13]. Since heart rate variability is under the control of the autonomic nervous system, many efforts have been devoted to the development of methods based on the analysis of spontaneous fluctuations in heart rate to assess both sympathetic and parasympathetic branches of the autonomic nervous system.

Similarly, left ventricular ejection fraction evaluated by 2D echocardiography and maximal oxygen consumption under ECG stress test are very used and well-known clinical markers of severity and adverse prognosis in heart failure patients.

Results obtained in this work suggest the following findings. First, the general data framework of the correlations of all HRV studied indexes is coherent with the considered neurohormonal and functional clinical parameters. An heart failure worsening described by higher NPE levels and lower VO2max and LVEF values is associated to a decreasing of linear HRV indexes and to a general PPlots contraction.

Second, while the power in the low frequency band, appears to reflect more closely the level of adrenergic activation in HF patients, some PPlots quantitative indexes, namely L and the length of the radii of inertia of 3D maps, seem to be better associated to functional clinical parameters, expecially with the LVEF.

These results can help assigning a clinical interpretation to mathematical indexes describing PPlots, suggesting further studies addressed to propose novel PPlots descriptors more closely related to clinical markers of severity and adverse prognosis in heart failure patients.

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