Sympathetic Neurohormonal Correlates of Linear and Symbolic Dynamics Heart Rate Variability Indexes in Chronic Heart Failure

R Maestri[1], MT La Rovere[2], A Porta[3], GD Pinna[1]

[1]Department of Biomedical Engineering, S Maugeri Foundation, IRCCS, Montescano, Italy
[2]Department of Cardiology, S Maugeri Foundation, IRCCS, Montescano, Italy
[3]Department of Technologies for Health, Galeazzi Orthopaedic Institute, University of Milan, Italy

Abstract

The aim of this study was to assess whether in chronic heart failure patients (CHF) linear and nonlinear indexes of heart rate variability (HRV) are associated with the plasma level of norepinephrine, a measure of tonic sympathetic nervous activity. In 99 CHF patients with a 24-hour Holter recording and plasma norepinephrine assay, the absolute (LFP) and normalized (LF_nu) power in the low frequency band (LF, 0.04-0.15Hz), the percentage of 3 beats patterns with no variations (0VP) and with two unlike variations (2UVP) were computed.

A significant negative association (Spearman correlation coefficient) was found between LFP and PNE ($r=-0.45$, $p<0.0001$) and between LF_nu and PNE ($r=-0.26$, $p<0.01$), while the association between both 0VP and 2UVP and PNE was largely nonsignificant ($r=-0.07$, $p=0.47$ and $r=0.13$, $p=0.19$).

The finding that symbolic dynamics indexes were not associated with sympathetic neurohormonal activation, suggests that the physiological link of these variables is limited to the modulation of sympathetic outflow to the sinus node.

1. Introduction

Chronic heart failure (CHF) is a major public health problem in western countries, involving about 10 % of the elderly and accounting for 1-2% of health-care expenditure [1]. CHF is associated with prominent alterations in the autonomic control of the cardiovascular system. Neurohormonal activation plays an important role in the pathogenesis and progression of the clinical syndrome and its extent is a marker of severity and adverse prognosis: higher levels of sympathetic activity are associated with a markedly reduced survival in CHF patients [2]. The analysis of heart rate variability (HRV) is considered a noninvasive tool to assess cardiac autonomic regulation. Indeed, classical linear analysis of HRV provides indexes of cardiac autonomic modulation which have been shown to be associated with the degree of sympathoexcitation [3]. However, some features of heart rate dynamics cannot be detected by traditional techniques, and methods based on nonlinear system theory have been developed to investigate these features. Recently, methods based on symbolic dynamics have been found to be suitable to assess changes in cardiac sympathetic modulation induced by experimental and pharmacological conditions characterised by sympathetic activation [4, 5].

The aim of this study was to assess whether in CHF patients classical linear indexes of HRV and symbolic dynamics indexes are associated with the plasma level of norepinephrine, a well established biochemical measure of tonic systemic sympathetic nervous activity.

2. Methods

Study population

We studied a cohort of CHF patients admitted to the Heart Failure Unit of the Scientific Institute of Montescano between 1992 and 1996 for evaluation and treatment of heart failure, usually in conjunction with evaluation for heart transplantation. Inclusion criteria were: sinus rhythm, stable clinical condition during the last 2 weeks, absence of pulmonary or neurological disease, including insulin dependent diabetes or any other disease limiting survival, no recent (within the previous 6 months) myocardial infarction or cardiac surgery, and 24-hour Holter recording analysable for at least half of the nighttime (00:00-05:00 h) and half of the daytime (09:00-19:00 h). All patients underwent standard clinical and laboratory examinations, including 2D echocardiography and routine blood tests within one week from the Holter recording. A subset of 99 patients underwent blood sample collection for plasma norepinephrine assay within one day from Holter recording. Norepinephrine levels

were assessed by a single-isotope radioenzymatic method.

Follow-up information over three years was obtained through periodic controls in the hospital, chart review or telephone interview of the referring physician and relatives.

The local ethics committee approved the study and all patients gave their informed consent.

Holter recordings and preprocessing

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. Annotated RR time series were finally transferred to a personal computer and processed according to previously described criteria [6] in order to correct ectopic beats, arrhythmic events and artifacts which are known to alter the estimation of HRV indices [7].

Computation of selected indexes

Two linear and two symbolic dynamics indexes with an established association with sympathetic cardiac modulation were computed from consecutive 5-min sequences obtained from 24-hour RR interval: the power in the low frequency band (LF, 0.04-0.15Hz), both in absolute units (LFP) and in normalised units (LF_nu), the percentage of patterns lasting 3 beats with no significant variations (0VP) and the percentage of patterns lasting 3 beats with two significant unlike variations (2UVP) [8].

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. The power in the low frequency was computed summing all spectral components with their central frequency within each band, but excluding components < 10% the overall power in the band. The normalized units were obtained calculating the percentage of the LF power with respect to the sum of the LF power and the power of the high frequency band (HF, 0.15-0.45 Hz).

To compute symbolic dynamics indexes, the full range of each sequence was divided into 6 homogeneous levels, transforming each RR interval into a symbol indicating which of the 6 levels the interval belongs to, and identifying in the new series of symbols all possible patterns of length 3. Among these patterns we focused on patterns with no variations (0VP; i.e., all 3 symbols are equal), and patterns with 2 unlike variations (2UVP; i.e., the second symbol was larger or smaller than the others) [4].

Statistical analysis

Due to the marked skewness in the distribution of some variables, descriptive statistics are given as median (lower quartile, upper quartile). The association between each index and plasma norepinephrine (PNE) was assessed by Spearman correlation coefficient. Comparisons between groups were carried out by the Mann-Whitney U test. All hypothesis tests were performed using a significance level of 0.05. All analyses were performed using the SAS/STAT statistical package, release 8.02 (SAS Institute Inc., Cary, NC, USA).

3. Results

Descriptive statistics of clinical and demographic data are reported in Table 1. During the 3 year follow-up (median: 36 months, interquartile range: 24-36), 26 patients died of cardiac death.

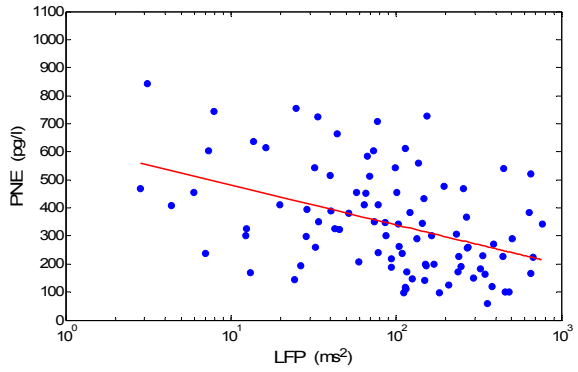
Table 1. Demographic, clinical and functional characteristics of the population studied (N=99).

Age (yrs)	51 (45, 58)
Male (%)	84
NYHA Class II-III (%)	88
LVEF (%)	23 (20, 27)
LFP (ms^2)	103 (40, 237)
LF_nu	0.7 (0.6, 0.8)
0VP (%)	32 (25, 39)
2UVP (%)	21 (17, 24)
PNE (pg/l)	327 (200, 469)

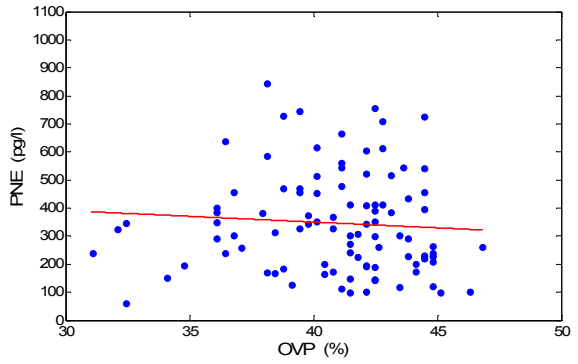
A moderate but significant negative association was found between LFP and PNE ($r=-0.45$, $p<0.0001$) and between LF_nu and PNE ($r=-0.26$, $p<0.01$). On the contrary, the association between both 0VP and 2UVP and PNE was largely nonsignificant ($r=-0.07$, $p=0.47$ and $r=0.13$, $p=0.19$).

PNE was significantly higher in patients who experienced cardiac death (397 (302, 604) pg/l vs 291 (193, 412) pg/l, $p=0.02$). Among HRV indexes, only LF_nu was significantly different between patients who did and did not experienced cardiac death (0.72 (0.63, 0.76) vs 0.66 (0.59, 0.71), $p=0.018$).

The scatterplots of PNE versus LFP and 2UVP are reported in Figure 1a and 1b respectively.



(a)



(b)

Figure 1a: scatterplot of PNE as a function of LFP (semi-logarithmic scale). 1b: PNE as a function of 0VP.

4. Discussion and conclusions

The assessment of autonomic control of the cardiovascular function is crucial to understand the pathophysiology of heart failure. To this purpose, several techniques have been proposed so far, yet this still represents a challenging task. 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 [9]. 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. In particular, the absolute (LFP) and normalised (LF_nu) spectral power of HRV in the low frequency band have been shown to reflect respectively, the mixed sympathetic and parasympathetic outflow to the heart, and the sympathovagal balance [10, 11]. At variance with this approach, some nonlinear indexes based on symbolic analysis of RR sequences have been recently proposed to selectively assess sympathetic and parasympathetic cardiac modulation [4]. In this study we investigated the association between these indexes and plasma level of norepinephrine. LFP and LF_nu were moderately, albeit significantly associated with sympathetic activity, confirming previous findings of an inverse relationship between LF power and the degree of sympatho-exitation as assessed by muscle sympathetic nerve activity [3]. This relationship is the opposite of what is observed in healthy subjects. Our study also confirms the previous observation that patients experiencing cardiac death are characterized by higher level of PNE.

A totally new finding is the lack of association between symbolic dynamics indexes and PNE. This was rather surprising, since in previous studies in healthy subjects these indexes were able to track the gradual shift of cardiac autonomic regulation toward sympathetic predominance during graded head-up tilt, and the association with tilt angles was stronger than spectral indexes [5, 12]. A possible explanation for the observed lack of association could be that symbolic dynamics indexes are physiologically linked only to the modulation of sympathetic outflow to the sinus node, which is only coarsely measured by such a non specific measure as PNE. Another possible explanation is that, since symbolic dynamics indexes are based on pattern recognition and HRV is extremely reduced in heart failure patients with respect to normal subjects, the very low signal to noise ratio of RR time series may affect the accuracy of pattern detection.

It has been proposed that the paradoxical reduction in LF oscillations in heart failure patients who have a well known high resting sympathetic activation might be due to a loss of oscillatory behaviour caused by an overwhelming chronic sympathetic overactivity, and to the effect of impaired baroreflex sensitivity.

References

[1] Bundkirchen A, Schwinger RH. Epidemiology and economic burden of chronic heart failure. Eur Heart J Supplements 2004; 6 (Suppl D): 57-60.

[2] Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984; 311: 819-823.

[3] Kienzle MG, Ferguson DW, Birkett CL, Myers GA, Berg WJ, Mariano DJ. Clinical, hemodynamic and sympathetic

neural correlates of heart rate variability in congestive heart failure. Am J Cardiol 1992; 69 (8): 761-767.
[4] Guzzetti S, Borroni E, Garbelli PE, Ceriani E, Della Bella P, Montano N, Cogliati C, Somers VK, Mallani A, Porta A. Symbolic dynamics of heart rate variability: a probe to investigate cardiac autonomic modulation. Circulation 2005; 112 (4): 465-470.
[5] Porta A, Tobaldini E, Guzzetti S, Furlan R, Montano N, Gnecchi-Ruscone T. Assessment of cardiac autonomic modulation during graded head-up tilt by symbolic analysis of heart rate variability. Am J Physiol Heart Circ Physiol 2007; 293 (1): H702-708.
[6] Maestri R, Pinna GD, Accardo A, Allegrini P, Balocchi R, D'Addio G, Ferrario M, Menicucci D, Porta A, Sassi R, Signorini MG, La Rovere MT, Cerutti S. Nonlinear indices of heart rate variability in chronic heart failure patients: redundancy and comparative clinical value. J Cardiovasc Electrophysiol 2007; 18: 425-433.
[7] Heart rate variability. Standards of measurement, physiological interpretation and clinical use. Task force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996; 93: 1043-1065.
[8] Porta A, Guzzetti S, Montano N, Furlan R, Pagani M, Malliani A, Cerutti S. Entropy, entropy rate, and pattern classification as tools to typify complexity in short heart period variability series. IEEE Trans Biomed Eng 2001; 48 (11): 1282-1291.
[9] Esler M, Kaye D. Measurement of sympathetic nervous system activity in heart failure: the role of norepinephrine kinetics. Heart Failure Reviews 2000; 5: 17-25.
[10] Pomeranz B,, Macaulay RJB, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen RJ, Benson H. Assessment of autonomic function in humans by heart rate spectral analysis. Am J Physiol 1985; 248: 151-153.
[11] Montano N, Gnecchi Ruscone T, Porta A, Lombardi F, Pagani M, Malliani A. Power spectral analysis of heart rate variability to assess the changes in sympathovagal balance diring graded orthostatic tilt. Circulation 1994; 90: 1826-1831.
[12] Cooke WH, Hoag JB, Crossman AA, Kuusela TA, Tahvanainen KUO, Eckberg DL. Human responses to upright tilt: a window on central autonomic integration. J Physiol 1999; 617-628.

Address for correspondence

Roberto Maestri,
Servizio di Bioingegneria,
Fondazione S. Maugeri, IRCCS
Istituto Scientifico di Montescano,
27040 Montescano (PV) - ITALY
Tel. ++39 0385 247277
Fax ++39 0385 61386
E-Mail: roberto.maestri@fsm.it