Correlation between Fractal Behavior of HRV and Neurohormonal and Functional Indexes in Chronic Heart Failure

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Abstract— **Higher neurohormonal activation levels are known markers of severity and adverse prognosis in heart failure (HF) patients. Classical linear indexes of heart rate variability (HRV) have been shown to be associated with neurohormonal activation. Whether and to what extent non-linear properties of HRV, as expressed by the fractal dimension (FD) index, also reflect neurohormonal activation is not known. Aim of the study was to assess the association between FD, plasma norepinephrine (NPE) levels and functional parameters as compared to classical linear indexes of HRV in HF patients. Ninety-nine stable mild-to-moderate HF patients in sinus rhythm (age: 51±8 years, New York Heart Association class II-III, left ventricular ejection fraction [EF] 24±6%, maximal oxygen consumption [VO2max] during exercise tests 14±4 mL kg-1 min-1) were studied. Each patient underwent to a 24-hour Holter recording and to NPE assay within one week plasma, besides standard clinical and laboratory examinations. The 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. The FD was estimated by the Higuchi method. The association between HRV and neurohormonal and functional indexes was assessed by Spearman correlation coefficient. NPE, LFP, SDNN and FD were respectively (mean ± SD): 363±210 pg/l, 162±171 ms2, 36±15 ms and 1.6±0.1. Both SDNN and LFP showed a moderate but significant negative correlation with NPE levels (r=-0.37 and -0.44 respectively, p<0.0001 for both); FD exhibited a weaker association (r=0.29, p<0.005). Linear indexes were significantly associated with VO2max (r=0.31 and 0.36 respectively, p<0.001), while FD showed a negative correlation of similar magnitude (r=-0.34, p<0.001). Similar relationships were found with EF (r=0.34, 0.35 and -0.42 for SDNN, LFP and FD, respectively, p<0.001 for all). These findings suggest that although the association of linear and fractal dimension HRV indexes with functional parameters is similar, the former, particularly the power in the low frequency band, appears to reflect more closely the level of adrenergic activation of HF patients.**

Keywords— **HRV, fractal dimension, chronic heart failure.**

I. 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 noninvasive assessment technique of the heart autonomic control. Linear indexes of HRV have been shown to be associated with neurohormonal activation [3].

More recently, it has been speculated than nonlinear HRV indexes might provide more valuable information about assessment of autonomic control impairments in cardiac patients. Fractal analysis is an emerging nonlinear technique. Among several methods proposed so far to measure the fractal behavior of the HRV signal, that based on spectral power-law relationship [4,5,6] and that based on iterative direct algorithms from RR time series [7, 8] have gained wide interest in the last years. The first way has traditionally been approached following the chaos-theory, with the aim of modeling the attractor extracted from HRV sequences [6], estimating the fractal dimension (FD) from the slope of the 1/f-like relationship [9]. Alternatively a FD value can be directly estimated from HRV sequences by means of Higuchi algorithm [8]. This method, whose good reproducibility has been already studied in CHF [10], allows better fractal estimation, eliminating the errors due to indirect estimation of FD from the spectral power. Since whether and to what extent non-linear properties of HRV, as expressed by the FD index, also reflect neurohormonal activation is not known, aim of this study was to assess the association between FD, plasma norepinephrine (NPE)

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levels and functional parameters as compared to classical linear indexes of HRV in HF patients.

II. MATERIALS AND METHODS

A. 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 (EF) evaluation, ECG stress test for maximal oxygen consumption (VO_2max) estimation and a blood sample for plasma norepinephrine assay collected within one week from the Holter recording and assessed by a single-isotope radioenzymatic method.

B. 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)[11].

Before analysis, identified RR time series were preprocessed according to the following criteria: 1) RR intervals associated with single or multiple ectopic beats or artefacts were automatically replaced by means of an interpolating algorithm, 2) RR values differing from the preceding one more than a prefixed threshold were replaced in the same way as for artefacts. The RR time series were finally interpolated by piecewise cubic spline and resampled at 2 Hz.

C. Fractal Dimension Analysis

Fractal dimension was calculated by using the Higuchi's algorithm [8]. From a given time series X(1), X(2), ... X(N), the algorithm constructs k new time series; each of them, Xm^k, is defined as

$$Xm^k: X(m), X(m+k), X(m+2*k), ..., X(m+int((N-m)/k)*k)$$

where m=1,2,...,k and k are integers indicating the initial time and the interval time, respectively.

Then the length, $L_m(k)$, of each curve Xm^k is calculated and the length of the original curve for the time interval k, L(k), is estimated as the mean of the k values $L_m(k)$ for m=1, 2, ..., k.

If the L(k) value is proportional to k^{-D}, the curve is fractal-like with the dimension D. Then, if L(k) is plotted against k, for k ranging from 1 to kmax, on a double logarithmic scale, the data should fall on a straight line with a slope equal to -D.

Thus, by means of a least-square linear best-fitting procedure applied to the series of pairs (k, L(k)), obtained by increasing the k value, the angular coefficient of the linear regression of the graph ln(L(k)) vs. ln(1/k), which constitutes the D estimation, is calculated.

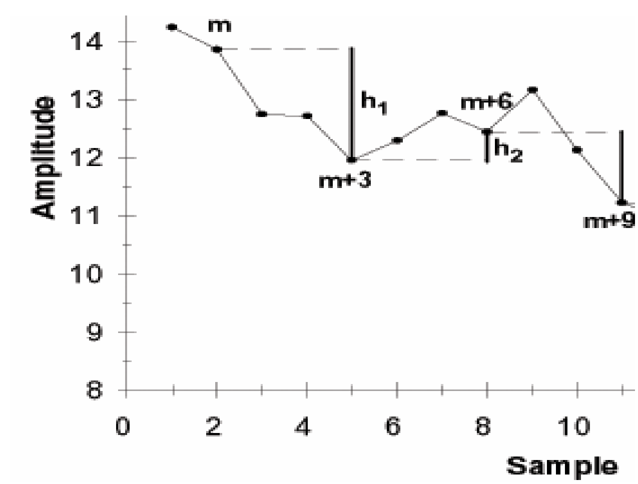

Fig. 1 Example of an hi sequence determination on a curve for the length calculation

D. Linear Analysis

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, as defined in accordance with the ACC/AHA/ESC consensus [12].

E. 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.

III. Results

In Tables 1 neurohormonal levels and functional indexes are reported.

Mean and standard deviation of HRV indexes obtained by linear and fractal analysis are shown in Table 2.

In Table 3 the Spearman correlation analysis between neurohormonal levels and functional indexes with HRV indexes is listed.

Results showed a moderate but significant negative correlation between NPE levels and both SDNN and LFP; FD exhibited a positive weaker association (see also figure 2).

Linear indexes showed a moderate but significant positive association with VO2max; FD showed a negative correlation of similar magnitude (see also figure 3).

FD showed a moderate but significant negative correlation with EF values; SDNN and LFP exhibited positive weaker correlation (see also figure 4).

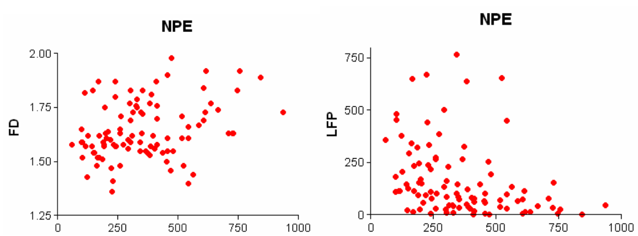

Fig. 2 Correlation between FD and LFP with NPE

Table 1 Mean and standard deviation of neurohormonal levels and functional indexes

NPE [pg/L]	363 ± 210
EF [%]	24 ± 6
VO2max [(mLxkg-1x min-1]	14 ± 4

Table 2 Mean and standard deviation of HRV indexes

FD	1.6 ± 0.1
LFP [ms^2]	162 ± 171
SDNN [ms]	36 ± 15

Table 3 Spearman correlation analysis between neurohormonal levels and functional indexes with HRV indexes: r and p values (in brackets)

	NPE	VO2max	EF
FD	0.29 (.0035)	- 0.34 (.0008)	-0.42 (.0001)
LFP	-0.44 (.0001)	0.36 (.0003)	0.35 (.0004)
SDNN	-0.37 (.0002)	0.31 (.0023)	0.34 (.0009)

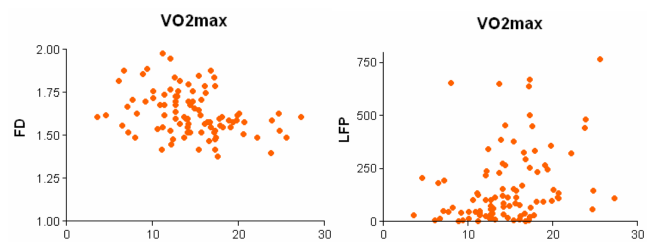

Fig. 3 Correlation between FD and LFP with VO2max

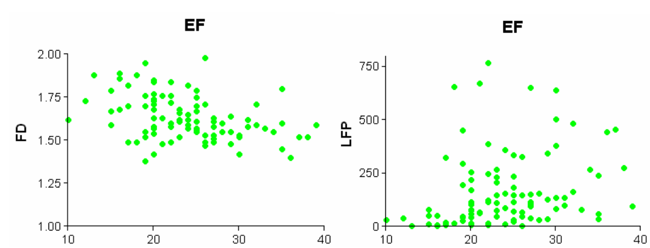

Fig. 4 Correlation between FD and LFP with EF

IV. Conclusions

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. 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.

Some nonlinear methodologies have been also recently proposed to estimate sympathetic and parasympathetic cardiac modulation [14].

Results obtained in this work, suggest that, although the association of linear and fractal dimension HRV indexes with functional parameters is similar, the former, particularly the power in the low frequency band, appears to reflect more closely the level of adrenergic activation in HF patients.

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