Effects of Stroke Localization on Nonlinear Indexes of HRV

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Abstract

To evaluate the relationship between lesion's severity and nonlinear indexes of HRV, 20 first-ever stroke subjects and 10 healthy subjects were studied. All patients, divided in two groups according to presence of single or multiple medium cerebral artery lesion, underwent to a 24-hour Holter ECG recording. All RR time series were analyzed by Poincarè Plot, fractal dimension, power-law behaviour, spectral and time-domain techniques.

A direct relationship between increasing lesion's severity and progressive collapsing of PPlots and FD index was observed, while lower significance were found for beta exponent, spectral and time-domain parameters.

These results suggest that PPlots and FD analysis contains relevant information related to different HRV dynamics in normal and stroke subjects with different lesion's severity.

1. Introduction

Cerebrovascular diseases represent one of the main cause of death and disability in western countries. An impaired cardiovascular autonomic regulation has been described in stroke patients (SP) with dysfunction, ~~that~~ often complicating the clinical course of these pathology.

It has been hypothesized that these abnormalities are mediated by the central nervous system as ~~a~~ result of the cerebrovascular event, whereas the mechanism of this phenomenon is not fully understood [1].

The analysis of heart rate variability is a well recognized non-invasive tool to investigate the cardiovascular autonomic control but only limited data are available on the autonomic imbalance assessment of stroke patients by heart rate variability changes after a prior single stroke, using time- and frequency-domain linear methods [2].

Recently non-linear analysis of heart rate variability has been suggested to provide more valuable information for physiological interpretation of heart rate fluctuation and for-risk assessment [3].

Poincarè's plots analysis and measures of the fractal behaviour of beat-to-beat time series are some of the few nonlinear methods tested in clinical settings in the last years.

Poincarè's plots (PPlots) allow to detect patterns resulting from non-linear processes that may not be observable by time- and frequency-domain analysis [4]. Several Poincarè plots analysis' methods have been proposed in literature, but it has clearly been shown that most of them bring back to existing linear measure of heart rate variability [5] and only nongeometric techniques, such as scanning parameters [6], allow to detect patterns resulting from non-linear processes that cannot be measured by time- and frequency-domain analysis.

Among non-linear methods proposed to measure the fractal behaviour of the HRV signal, that based on the beta exponent of the 1/f-like relationship~~,~~ starting from the spectral power [7], and that based on the fractal dimension (FD) have gained wide interest in the last years.

The latter has traditionally been approached following the chaos-theory, with the aim of modelling the attractor extracted from HRV sequences, and the FD parameter has usually been estimated from the slope of the 1/f relationship.

However, the FD can also be directly extracted from HRV sequences using different methods. In this paper we followed an approach based on the use of the FD estimated by Higuchi algorithm [8]. This method allows a better fractal estimation, eliminating the errors due to the indirect estimation of FD from spectral power.

The aim of the present paper was to evaluate the relationship between lesion's severity and nonlinear indexes of HRV in stroke patients, comparing these results with those of traditional time- and frequency-domain linear HRV parameters.

2. Study population

The study population consisted of 20 patients consecutively admitted to Neurology Rehabilitation Division of "Salvatore Maugeri" Foundation. All enrolled subjects were over 45 years old, with a positive past medical history for previous first-ever stroke (ischemic and/or hemorrhagic), presence of neuromotor monolateral deficit at physical examination and FIM score between 40 and 60.

Patients with congestive heart failure (IV NYHA functional class), renal, hepatic or pulmonary failures, cerebral neoplasm, severe cranial trauma, psychosis, FIM score <40 or >60, atrial fibrillation were excluded.

The study population was divided in two groups of 10 patients according to a CT finding of medium cerebral artery single (SL-SP) or multiple (ML-SP) lesion. The control group (N) consisted of 10 healthy subjects (mean-age 42±6 yrs). See table 1. for details.

Table 1: Some variables in the SL and ML groups.

	SL-SP	ML-SP
Age	65.05±15.23	68.38±7.55
BMI	27.84±3.96	26.42±3.77
SBP	138.82±14.95	136.15±21.03
DBP	87.65±9.03	79.23±25.32
Hb	13.12±1.35	13.49±1.87
ADL	4.62±1.94	5.19±1.72
IADL	7.24±2.43	6.75±1.91
Diabetes (%)	2 (9.5)	1 (6.3)
Hypertension (%)	9 (42.9)	6 (37.5)
Ejection fraction	56.49±11.41	56.29±7.94
NYHA class	1.90±0.72	2.19±0.66

Values are mean ± SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; ADL, activity daily living; IADL, instrumental activity daily living.

3. Holter analysis

The study population underwent to a 24-hour Holter ECG recording by a portable three-channel tape recorder, processed by a Marquette 8000 T system with a sampling frequency of 128 Hz.

All recordings were performed while the patients were allowed to standing or sitting next to their beds. Other activities were not allowed.

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 PM).

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 20% (absolute value) were replaced in the same way as for artefacts (Table 2).

Table 2: Beat correction summary (total number of analysed beats, total number of corrections and proportion of correction). of the three groups.

Population	# beats	# corrections	%
Normal (N)	102115	2234	2.1
Single Lesion (SL)	93072	6715	7.2
Multiple Lesion (ML)	93202	8857	8.7

4. Poincarè plot analysis

PPlots technique is based on the analysis of the maps constructed by plotting each RR interval against the preceding one.

Usually bi-dimensional (2D) PPlots are just visually classified into typical patterns [4] and one major limitation of this visual classification is the subjective evaluation of the plots.

To overcome this problem, the automatic quantification of PPlots has been recently proposed by our group and a dedicated software developed by the authors allowed to automatically calculate the main morphological characteristics of bi and three-dimensional (3D) maps. Technical details on the procedure have been described elsewhere and excellent reproducibility of obtained indexes has been previously demonstrated [6].

The most meaningful parameters extracted from 2D PPlots are measures of the dispersion of the ellipsoidal cloud of points around the bisecting line, like the length (L) and the area (A), while the most interesting parameters extracted from 3D PPlots (see figure 1) are measures related to the plot’s height, taking into account the RR couples’ repetition number, like the number of peaks (Np).

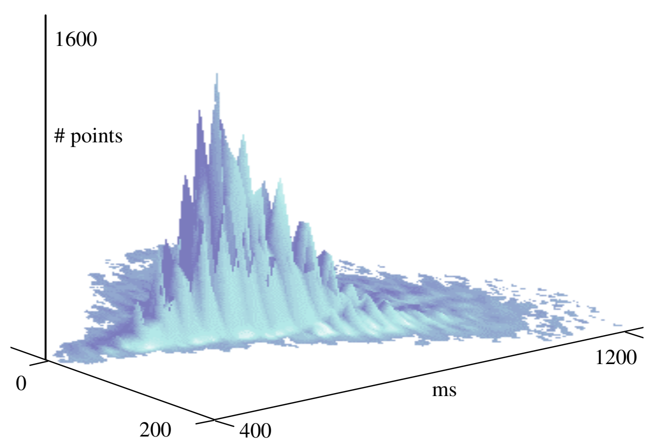

Figure 1: 3D Poincarè plot analysis.

5. 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, Xmk, 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, Lm(k), of each curve Xmk 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 Lm(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.

Power law beta exponent was calculated from the power spectral density function estimated by the Blackman-Tukey method after linear trend removal. The beta index represents the slope (Figure 2) of the linear fit in the very low frequency band (<0.05 Hz) of the log(power) on log(frequency) relationship.

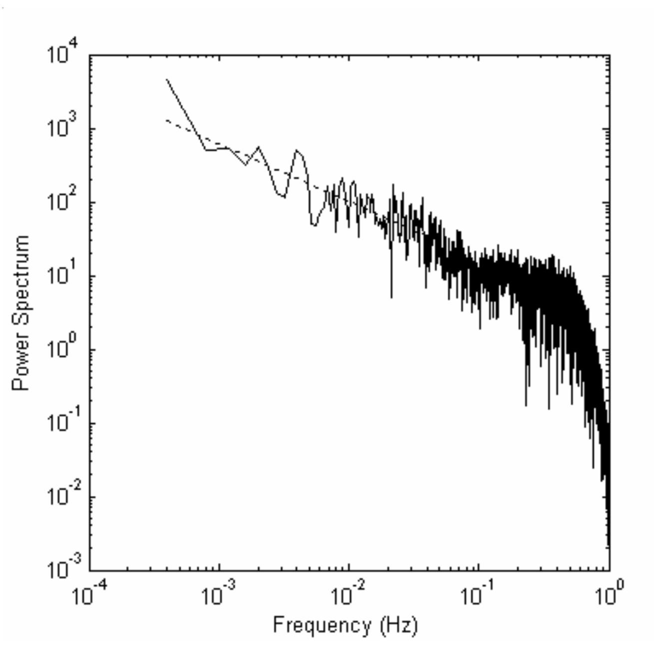

Figure 2: Example of the beta exponent evaluation by means of the slope of the linear best fitting (dashed line) of the power spectrum for frequencies < 0.05Hz.

6. Linear analysis

Spectral analysis was performed by an homemade software [9] on 5 minutes RR sequences extracted from 24-hours holter recordings

Power spectral density was estimated by the Blackman-Tukey method in all accepted segments after linear trend removal. The total power and the power in the low frequency band (LF, 0.04-0.15 Hz) and high frequency band (HF, 0.15-0.45 Hz) were then computed by numerical integration of the spectral density function.

Most important time-domain parameters (SDNN, PNN50, MSSD) were also evaluated for all RR time series.

7. Statistical analysis

The normality of the distribution of HRV variables was assessed by the Shapiro-Wilks test. Between-group comparisons were carried out by the analysis of covariance (ANCOVA), adjusting for age. Post-hoc tests (SL vs. N, ML vs. N, and SL vs. ML), were performed by the Tukey honest significant difference method.

8. Results

Descriptive statistics for studied indexes are reported in table 3.

L, Np and FD, showed the highest significant differences between the three study groups, while lower or no significance levels were found for beta exponent, spectral and time-domain parameters.

We observed a direct relationship between the increasing lesion's severity of SP and a progressive collapsing of both 2D and 3D PPlots, indicating a progressive impairment of cardiac autonomic control and particularly Np was the only index able to discriminate between SL and ML subjects.

Table 3: HRV measurements in Normals and patients with Single and Multiple lesion of medium cerebral artery.

Index	N	SL-SP	ML-SP	p
L	803±108	518±103°°	436±87 **	<0.0001
A	16890±6357	16330±7071	9229±2840 **†	<0.01
Np	44±21	23±9	11±5 **†	<0.0001
FD	1.43±0.07	1.80±0.09°°	1.86±0.10**	<0.0005
Beta	0.96±0.07	1.02±0.12	1.17±0.13*	<0.05
VLF	684±202	1924±1221°°	1355±672	<0.005
LF	988±422	888±516	453±344 *	<0.05
SDNN	53±10	72±20	56±12	ns

Values are mean ± SD. °° SL *vs* N p<0.01; * ML *vs* N p<0.05; ** ML *vs* N p<0.01; †ML *vs* SL p<0.05.

The Higuchi's FD parameter showed almost superimposable mean values in the two pathological groups and a marked, highly significant, increase in the mean value passing from normal to pathological subjects.

Conversely, the beta parameter showed a progressive increasing trend from normal subjects to patients with a single lesion and from the latter to patients with a multiple lesion.

However, statistical significance in post-hoc analysis was reached only by the difference between normal subjects and patients with a multiple lesion, while a clear non significant result was found between normal subjects and patients with a single lesion.

9. Discussion

These preliminary results indicate that PPlot and FD indexes are more sensitive than heart rate variability linear indexes in identification of autonomic nervous system impairment in patients after single stroke event.

Only few studies [10] found strong correlation between stroke and abnormal values of spectral content of HRV as well as a correlation with functional capabilities.

Changes in PPlots indexes seem to be significantly associated with different lesion's severity. Many authors that used PPlots technique just paid their attention to the 2D indexes of the maps.

Depending on the different estimation's methods, this class of parameters can be related to existing linear measures of HRV, hence the intrinsic ability of PPlots to identify non-linear beat-to-beat structure is not completely exploited by bi-dimensional maps alone.

An evidence supporting this consideration can be found in the statistical significance of Np, one of the 3D PPlots indexes that can suggest future improvements in the evaluation of other multi-dimensional PPlots indexes.

The sensitivity of the FD and beta exponent parameters to the severity of the central nervous system damage, however, appears to be different.

Indeed, the Higuchi's index strongly changes passing from normal to pathological subjects but it is not able to detect any difference between single and multiple lesion.

On the contrary, the beta exponent seems rather insensitive to changes in autonomic cardiovascular regulation brought about by a less severe stroke, such as that occurring in single lesion patients, while it clearly detects the changes induced by the more severe multiple lesion damage.

These findings suggest that, although the two algorithms try to measure the same fractal property of HRV, they provide non superimposable results.

A major limitation of this study is the low sample size of the studied groups. Therefore our findings should be interpreted as purely exploratory. Nevertheless, they clearly suggest that PPlots and FD indexes contain relevant information related to different heart rate variability dynamics in stroke subjects, candidating this approach for future risk assessment studies of these patients.

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