Fractal Behaviour of Heart Rate Variability Reflects Severity in Stroke Patients

Gianni D’ADDIO, Graziamaria CORBI, Agostino ACCARDO, Giovanna RUSSO, Nicola FERRARA, M. Cristina MAZZOLENI, Tanja PRINCI

a S. Maugeri Foundation, Telese – Pavia, Italy
b Department Health Sciences, University of Molise, Campobasso, Italy
c Department E.E.I., University of Trieste, Italy
d Department Life Sciences, University of Trieste, Italy

Abstract. Non-linear parameters obtained from heart rate variability (HRV) analysis have recently been recognized to provide valuable information for physiological interpretation of heart rate fluctuation. Among the numerous non-linear parameters related to the fractal behaviour of the HRV signal, two classes have gained wide interest in the last years: the beta exponent based on the 1/f-like relationship, starting from the spectral power, and that based on fractal dimension. In order to evaluate the relationship between lesion’s severity and fractal behaviour, 20 first-ever stroke subjects and 10 healthy subjects were studied. Patients were divided in two groups according to single or multiple medium cerebral artery lesions. All subjects underwent 24-hour Holter recording analysed by fractal and 1/f-like techniques. Differently from methods usually used in literature to evaluate the fractal dimension (FD), in this work the FD was extracted by using the Higuchi’s algorithm that permits to calculate the parameter directly from the HRV sequences in the time domain. Results show that fractal analysis contains relevant information related to different HRV dynamics that permits to separate normal subjects from stroke patients. FD is also able to distinguish between normal and stroke subjects with different lesion’s severity.

Keywords. HRV, beta exponent, fractal dimension, Higuchi’s algorithm, stroke

1. Introduction

Stroke has been shown to cause changes in autonomic function, increase the incidence of cardiac arrhythmias, cause myocardial damage and raise plasma catecholamine levels. It has been hypothesized that these abnormalities are mediated by the central nervous system as a result of the cerebrovascular event. The mechanisms responsible for this phenomenon, however, have not been fully elucidated yet [1, 2].

The analysis of heart rate variability (HRV) is a well-recognized tool in the investigation of the autonomic control of the heart [3]. Limited data, however, are available on the use of HRV in the assessment of the autonomic imbalance in patients after a prior stroke [4], and only traditional time linear methods have been considered [5,6]. Among non-linear methods proposed so far to measure the fractal behaviour of the HRV signal, that based on the beta exponent of the 1/f-like relationship, starting

1 Corresponding Author: Tanja Princi – Department Life Sciences, University of Trieste, Italy; E-mail: tprinci@units.it.
from the spectral power [7–10], and that based on the fractal dimension (FD), have
gained wide interest in the last years [11–13]. The latter has traditionally been
approached following the chaos-theory, with the aim of modelling the attractor
extracted from HRV sequences [14], and the FD parameter has usually been estimated
from the slope of the 1/f relationship [15]. However, the FD can also be directly
extracted from HRV sequences by means of many methods [16, 17]. In this work we
followed this approach, using the FD estimated by the Higuchi algorithm [16]. This
method allows better fractal estimation, eliminating the errors due to the indirect
estimation of FD from the spectral power. The aim of this study was to assess whether
the Higuchi’s FD is capable of discriminating stroke patients from normal subjects and,
within stroke patients, those with a single lesion from those with a multiple lesion.
Results were compared with those obtained from the classical beta exponent.

2. Materials and Methods

2.1. Subjects

We studied 14 male patients consecutively admitted to Neurology Rehabilitation
Division of “Salvatore Maugeri” Foundation, Institute of “Telese Terme” (Table 1).
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.
Exclusion criteria were: presence of congestive heart failure (NYHA functional class
IV), renal, hepatic or pulmonary failure, cerebral neoplasm, severe cranial trauma,
psychosis, FIM score <40 or >60 or atrial fibrillation. Patients were divided in two
groups of 7 subjects according to a computer tomography finding of medium cerebral
artery single (SL) or multiple (ML) lesion. The control group (N) consisted of 7 healthy
subjects.

Table 1. Mean age±SD of the three groups considered in the study and beat correction summary (total
number of analysed beats, total number of corrections and proportion of correction)

<table>
<thead>
<tr>
<th>Population</th>
<th>Age ± SD</th>
<th># Beats</th>
<th># corrections</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (N)</td>
<td>45±5</td>
<td>102,115</td>
<td>2,234</td>
<td>2.1</td>
</tr>
<tr>
<td>Single Lesion (SL)</td>
<td>67±9</td>
<td>93,072</td>
<td>6,715</td>
<td>7.2</td>
</tr>
<tr>
<td>Multiple Lesion (ML)</td>
<td>63±5</td>
<td>93,202</td>
<td>8,857</td>
<td>8.7</td>
</tr>
</tbody>
</table>

2.2. Holter Analysis

The study population underwent 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. 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 through to 5:00
AM) and half of the daytime (from 7:30 AM through to 11:30 AM) [18]. Before
analysis, identified RR time series were preprocessed according to the following
criteria: 1) RR intervals associated with single or multiple ectopic beats or artifacts
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 artifacts (Table 1).

2.3. Fractal Dimension Analysis

Fractal dimension was calculated by using the Higuchi’s algorithm [16]. 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

\[ \text{Xm}_k: X(m), X(m+k), X(m+2k), ... , X(m+\text{int}((N-m)/k)*k) \]

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.

2.4. Beta Exponent Analysis

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 of the linear fit in the very low frequency band (<0.05 Hz) of the log(power) on log(frequency) relationship [18].

2.5. 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.

3. Results

Descriptive statistics for the FD and beta exponent parameters in the three study groups are reported in Table 2. The global null hypothesis of no difference between groups

<table>
<thead>
<tr>
<th></th>
<th>FD</th>
<th>Beta exponent</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1.435 ± 0.069</td>
<td>0.959 ± 0.067</td>
</tr>
<tr>
<td>SL</td>
<td>1.801 ± 0.089</td>
<td>1.015 ± 0.123</td>
</tr>
<tr>
<td>ML</td>
<td>1.855 ± 0.101</td>
<td>1.167 ± 0.132</td>
</tr>
</tbody>
</table>

Table 2. Mean±SD of Higuchi’s fractal dimension (FD) and beta exponent calculated on the three study groups. N: normal subjects; SL: single lesion patients; ML: multiple lesion patients
was highly significant for both HRV indexes ($p=0.003$). Results from Tukey post-hoc analysis are given in Table 3. 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.

Table 3. Significance levels from post hoc tests by the Tukey honest significant difference method

<table>
<thead>
<tr>
<th></th>
<th>FD</th>
<th>Beta exponent</th>
</tr>
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<tbody>
<tr>
<td>N vs. SL</td>
<td>0.0002</td>
<td>0.63</td>
</tr>
<tr>
<td>N vs. ML</td>
<td>0.0002</td>
<td>0.009</td>
</tr>
<tr>
<td>SL vs. ML</td>
<td>0.52</td>
<td>0.058</td>
</tr>
</tbody>
</table>

This finding is clearly illustrated by the scatterplot of Figure 1. 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 for the difference between normal subjects and patients with a single lesion.

Figure 1. Higuchi’s fractal dimension (FD) values in the three studied groups. N: normal subjects; SL: single lesion patients; ML: multiple lesion patients

4. Discussion and Conclusion

These preliminary results indicate that fractal indexes reflect the impairment of the autonomic nervous system in patients after single stroke. 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 does not detect any difference between single and multiple lesions. The beta exponent, on the contrary, 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 super-imposable results. Scarce are the studies in stroke patients that, using linear and spectral indexes of HRV, found association between cerebrovascular damages and impaired autonomic regulation [1, 2, 19, 20, 21], while it has not yet completely investigated if nonlinear analysis of HRV might provide more valuable information for the physiological interpretation of heart rate fluctuations and for the
risk assessment in these patients. A major limitation of this study is the small sample size of the studied groups. Therefore our findings should be interpreted as purely exploratory. Nevertheless, they clearly suggest that fractal analysis contains relevant information related to different heart rate variability dynamics of stroke subjects, prompting this approach for future risk assessment studies of these patients.

References