Fractal Behaviour of Heart Rate Variability Reflects Abnormal Respiration Patterns in OSAS Patients

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Abstract

Although heart rate variability (HRV) decreasing has been usually described in obstructive sleep apnea syndrome (OSAS), some studies have recently questioned the validity of spectral HRV analysis in presence of respiratory and arrhythmic disorders. Fractal analysis of HRV is an emerging nonlinear technique overcoming these limitations and allowing short term HRV assessment during hypo/apnea phases. The aim of this study is to analyse the Fractal features in sleep apnea in order to find as these characteristics could change during abnormal respiration patterns in OSAS. We studied 30 polysomnographic recordings of severe OSAS (AHI≥30) pts. (age 55±9) and 10 PR of normal subjects (age 46±4). Hypo/apnea phases and related beat-to-beat time series have been detected and classified by automated algorithms and manually verified by expert technicians. Fractal analysis was performed by the Higuchi algorithm (FD). Results showed that while FD does not significantly differ between Normals (1.61±0.09) and normal breath epochs in OSAS, it significantly (p<0.005) tends to a less fractal structure from normal breath (1.60±0.15) to hypopneas (1.52±0.13), obstructive (1.50±0.12) and mixed apneas (1.48±0.11) epochs, with a significant Dunn's multiple comparisons post test only between normal breath vs. obstructive and mixed apneas.

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a highly prevalent disease in the population, affecting 1–4% of adults, mostly aging within 30 to 60 years old and just in 19% over 60 [1]. It is characterized by repeated episodes of upper airway obstruction during sleep, leading to significant hypoxia. Polysomnographic studies are usually used to diagnose OSAS. Measurements of nasal and oral breath flow, recordings of snoring and oxygen saturation as well as of thoracic and abdominal movements permit to score OSAS severity counting the number of apneas and hypopneas per hour during sleep, defined as apneas/hypopneas index (AHI) which has been associated to worse prognosis and mortality [2], mainly due to an increased rate of cardiovascular morbidity.

Different pathological respiratory events, classified as obstructive, central or mixed apneas, involve different and specific autonomic system responses characterized by complex cardio-respiratory interactions not fully investigated, although changes of the cardiac autonomic regulation are considered to be involved in the development of cardiovascular disease in patients with OSAS [3].

Although sympatho-vagal balance is usually assessed by measuring heart rate variability [4-9], some studies have questioned the validity of these methods in the presence of sleep disordered breathing [10] mainly both for non-stationarity due to nonlinear heart period modulation caused by highly dynamic pathological respiratory patterns and for the elevated incidence of cardiac arrhythmias, including ventricular premature complexes and sequences of tachycardia-brachycardia.

Fractal analysis is an emerging nonlinear technique that proved to be a valid analytical tool in the study of HRV in pathological conditions involving autonomic impairments [11-12]. In particular, the Fractal Dimension (FD) index showed interesting clinical value for HRV assessment with functional an neurohormonal correlations [13, 14]. In this work we estimated FD by means of the Higuchi method [15] that, working directly in the time domain on HRV sequences, is able to overcome the linear analysis limitations allowing short term HRV assessment during hypo/apnea phases. In this paper we examine the Fractal features in sleep apnea with the aim to find out whether and to which extend Fractal HRV reflects abnormal respiration patterns in OSAS.

2. Materials and methods

2.1. Study population

We studied 10 polysomnographic recordings (PR) of normal subjects (age 46±4) and 30 PR of severe OSAS (age 67±10; AHI=55±15; Body Mass Index=72±11) pts.

Patients with PR including at least 30 episodes of hypopnea, 30 of obstructive and 30 of mixed apneas lasting >20 seconds been selected from a wider OSAS PR database of the Pneumological Rehabilitation Unit of Maugeri Foundation of Telese Terme (BN, Italy) with the following exclusion criteria: treatment with betablocking agents, history of cardiac disease or presence of central apneas in PR recordings, left ventricular dysfunction (ejection fraction < 50%), diabetes mellitus, and periodic breathing pattern.

2.2. Polysomnographic monitoring

Additionally to traditional polysomnographics signals of breath flow, snoring, thoracic and abdominal movements and pulse oximetry, all subject underwent to an Holter ECG monitoring between 11 p.m. and 6 a.m, contemporary available by means of Somntè (Compumedics) polysomnograhic system. The ECG was sampled at 256 Hz while the breath flow was sampled at 10 Hz.

Hypopneas epochs have been defined as reduction in oronasal flow of more than 30 - 50% for at least 10 seconds associated with oxygen desaturation of O2 equal to or higher than the 3-4%. Obstructive apneas epochs have been defined as an airflow amplitude reduction of at least the 80% for more than 10 s and a fall of at least the 4% in oxygen saturation accompanied by the presence of thoracic and abdominal movements. Central apneas epochs have been defined as obstructive apneas but without the presence of thoracic and abdominal movements. And mixed apneas epochs have been defined as epochs beginning as central and continuing as obstructive apneas

Respiratory events and AHI of all recordings has been automatically calculated by the system with an algorithm for respiratory pattern recognition and manually verified by an expert technician. Each heart beat has been labeled as normal, VPC or aberrant according to recognition by the system with an algorithm for ECG Holter analysis and after an investigator's verification.

2.3. Fractal analysis of HRV

All ECG data has been imported from Somntè database and post-processed for HRV analysis by a customized Matlab software toolbox developed by the authors. Before to calculate the Fractal Dimension all HRV series were resampled at 2 Hz in order to obtain a constant sampling time. As previously described in details by authors [16-19], the fractal analysis was performed as follow. Let $x(1), x(2), \ldots, x(N)$ be the time series under investigation. Let construct k new time series as follows:

$$x_k^m = \left\{ x(m), x(m+k), x(m+2k), \ldots, x\left(m + \left\lfloor \frac{N-m}{k} \right\rfloor k\right) \right\}$$

where $m = 1,2,\ldots,k$ represents the initial time and k, ranging from 1 to 6, is the time delay.
The symbol $\lfloor a \rfloor$ denotes the integer part of a. For each x_k^m constructed series, the length $L_m(k)$ is calculated as:

$$L_m(k) = \left[\left(\sum_{i=1}^{\left\lfloor \frac{N-m}{k} \right\rfloor} \left| x(m+ik) - x(m+(i-1)k) \right| \right) \cdot \frac{N-1}{\left\lfloor \frac{N-m}{k} \right\rfloor k} \right] \cdot \frac{1}{k}$$

where the term

$$\frac{N-1}{\left\lfloor \frac{N-m}{k} \right\rfloor k}$$

is a normalization factor. The length $L(k)$ is computed for all-time series having the same time delay k as the average of the k lengths $L_m(k)$ for $m = 1,2,\ldots,k$. If $L(k)$ is proportional to k^{-FD}, the time series x_k^m is fractal with dimension FD. Thus, if $L(k)$ is plotted against $1/k$ on a double logarithmic scale, the slope of the straight line fitting the data represents a good estimate of the FD value (Figure 1). The FD values were separately computed in Normal subjects and over epochs of normal breath (NB), hypopneas (HY), obstructive (OS) and mixed (MX) apneas of OSAS patients. Since each kind of epoch was too short for a reliable analysis (Figure 2), successive tracts of the same typology were juxtaposed and segments of 256 points (equivalent to 128 s) were considered.

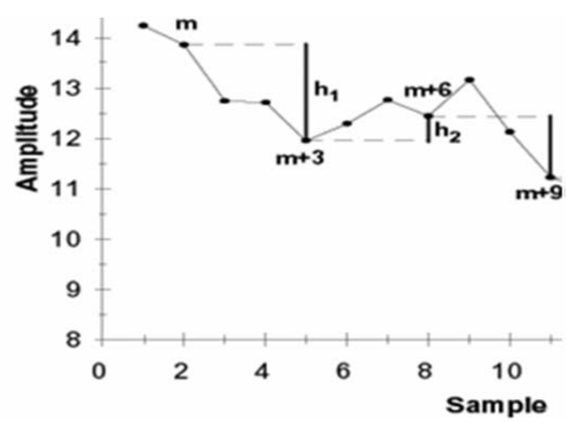

Figure 1. Example of an hi sequence determination on a curve for the length calculation.

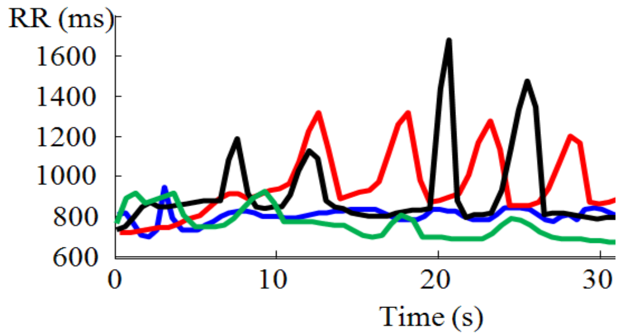

Figure 2. Example of RR trends in the four kind of respiration considered, in an OSAS patient: NB (blue), HY (green), OS (red and MX (black).

2.4. Statistical analysis

Statistical analyses were performed by GraphPad Prism 5.0 software package (GraphPad Software, San Diego California USA). Due to the skewed distributions of all variables (D'Agostino & Pearson omnibus normality test p <0.05), t-test between FD values in Normals and OSAS NB epochs has been performed by Mann Whitney test.

Correlation analysis between FD values in NB, HY, OS and MX apneas epochs of OSAS patients has been performed by Spearman correlation coefficients. Analysis of variance between epochs of NB, HY, OS and MX apneas of OSAS patients has been performed by paired Friedman test followed by Dunn's Multiple Comparison Test between each couple of respiratory pattern (p=0.05).

Descriptive statistics (Table 2) and data plot (Figure 4) have therefore been expressed in medians and percentiles.

3. Results and discussion

A summary of the studied respiratory events and related ECG data in the OSAS group is shown in Table 1. Results of FD analysis in Normals and in NB, HY, OS and MX apneas epochs of OSAS patients are shown in Table 2.

Statistical analysis showed that FD values does not significantly (Mann Whitney test p=0.96) differ between Normal subjects and Normal Breathing epochs in OSAS pts. Spearman correlation analysis (Table 3) showed very strong and significant correlations between FD analysis in NB, HY, OS and MX apneas epochs of OSAS patients, clearly describing a coherent tendency of a FD decreasing from NB to MX epochs for all OSAS studied patients.

Such results is very significantly confirmed by paired Friedman test. Particularly Dunn's multiple comparisons post-test found a very significant difference of NB vs. MX, a significant difference vs. OS and a borderline difference vs. HY (Table 4).

Table 1. Summary of respiratory and related ECG data

	HY	OS	MX
Mean of respiratory events per pts.	86	221	38
Mean respiratory events length (s)	29	30	30
Mean sinus beats number per pts.	3874	4024	1132
Mean beats per minute per pts.	72	70	70

Table 2. FD analysis in Normals and in NB, HY, OS and MX apneas epochs of OSAS patients

	25th perc	median	75th perc
Normal subjects	1.52	1.58	1.65
NB epochs of OSAS pts.	1.51	1.56	1.65
HY epochs of OSAS pts.	1.39	1.51	1.61
OS epochs of OSAS pts.	1.42	1.44	1.61
MXepochs of OSAS pts.	1.35	1.49	1.57

Table 3. Spearman correlation matrix r values between FD analysis in NB, HY, OS and MX apneas epochs of OSAS patients. ** for p< 0.01, * for p< 0.05 .

	NB	HY	OS	MX
NB		0,96**	0,89*	0,96**
HY	0,96**		0,96**	0,93**
OS	0,89*	0,96**		0,86*
MX	0,96**	0,93**	0,86*	

Table 4. ANOVA of FD in NB, HY, OS and MX apneas epochs of OSAS patients

Friedman test	p = 0,0041**	
Dunn's Multiple Comp. Test	rank sum	Significance
NB vs. HY	12,00	ns
NB vs. OS	14,00	*
NB vs. MX	16,00	**
HY vs. OS	2,000	ns
HY vs. MX	4,000	ns
OS vs. MX	2,000	ns

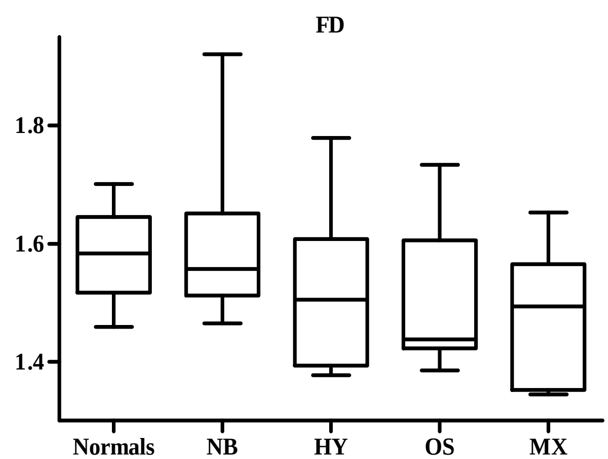

Figure 3. Box&Whiskers plot of FD values of Normals and in NB, HY, OS and MX epochs of OSAS pts. (lines from the bottom upwards respectively at 10th, 25th, median, 75th and 90th percentile of the distributions).

4. Conclusion

The study shows that F-behaviour of HRV reflects abnormal respiration patterns in OSAS patients, highlighting the following three novel findings. The first is that FD analysis has been proved as an appropriate technique for a short term autonomic balance evaluation during highly dynamic pathological respiratory patterns. FD analysis of HRV is able to discriminate normal breathing epochs from abnormal ones, candidating this parameter as a further useful tool for advanced algorithms for automated respiratory pattern recognition and in-time home-care monitoring based on swarm intelligence [20]. The second is that FD values during normal breathing epochs of OSAS patients are not different to those of normal subjects. Therefore the sympathetic nervous system increasing activity in OSAS is not related to normal breathing periods as mainly to the loss of variability just during abnormal respiration patterns. The third is that heart rate clearly tends to assume a less fractal and more regular structure from NB to HY and from HY to full apnea phases and that, although not with statistical significance in our data, this trend seems to be partially recovered from OS to MX apneas epochs with the partial absence of thoracic and abdominal movements. Fractal analysis of the heart rate appears as a useful tool in further studies needed for a better understanding of the complex and still not fully understood pathophysiological mechanisms at the base of the autonomic alterations leading to cardiovascular disease in OSAS patients.

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