Fractal Dynamics of Heart Rate Variability: A Study in Healthy Subjects

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Abstract
The fractal analysis of heart rate variability (HRV) has been associated to the chaos theory. We evaluated the association of the fractal exponents of HRV with the time and frequency domain and geometric indices of HRV for short period. HRV was analyzed with a minimal number of 256 RR intervals in the time (SDNN-standard deviation of normal-to-normal R-R intervals, pNN50-percentage of adjacent RR intervals with a difference of duration greater than 50ms and RMSSD-root-mean square of differences between adjacent normal RR intervals in a time interval) and frequency (LF-low frequency, HF-high frequency and LF/HF ratio) domains. The geometric indexes were also analyzed (RRtri-triangular index, TINN-triangular interpolation of RR intervals and Poincaré plot) as well as short and long-term fractal exponents (alpha-1 and alpha-2) of the detrended fluctuation analysis (DFA). We observed strong correlation of the alpha-1 exponent with RMSSD, pNN50, SDNN/RMSSD, LF (nu), HF (nu), LF/HF ratio, SD1 and SD1/Sd2 ratio. In conclusion, we suggest that the alpha-1 exponent could be applied for HRV analysis with a minimal number of 256 RR intervals.

Key words: Nonlinear dynamics; Autonomic nervous system; Cardiovascular system; detrended fluctuation analysis.

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I. INTRODUCTION

Heart rate variability (HRV) is a conventionally accepted term to describe the fluctuations in the intervals between consecutive heartbeats (RR intervals), which are related to influences of the autonomic nervous system on the sinus node. There are several methods to measure HRV [1, 2]. The use of nonlinear methods that analyze HRV have received great attention, suggesting that mechanisms involved in cardiovascular regulation probably interact between each other in a nonlinear style[3, 4].

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A well-recognized method used for nonlinear analysis is trended fluctuation analysis (DFA). This method quantifies the absence or the presence of fractal correlation properties of the RR intervals[3]. Fractal indices are able to detect slight changes in the RR intervals dynamics better than conventional spectral analyses, including time and frequency domains. Furthermore, changes in fractal correlation properties of long- and short-term dynamics of HRV helps clinical professionals to avoid disease development and identify autonomic impairment[5]. The fractal analysis of HRV includes the short-term fractal exponent (alpha-1) that corresponds to a period of 4 to 11 beats, the long-term fractal exponent (alpha-2) that represents periods longer than 11 beats and the alpha-1/alpha-2 ratio[5].

HRV analysis measures dynamic changes in cardiac autonomic regulation. This method of investigation requires analysis over shorter intervals than the normally used 5–20 min. There are numerous indices that have been proven to be useful in 5–20 min HRV analysis[6]. Nonetheless, it is not clear in the literature if the long-term fractal scaling exponent alpha-2 can be used for 256 RR intervals. In addition, some studies did not find changes in this exponent in pathological conditions[7,8], whereas others reported changes in the alpha-2 exponent derived from the DFA in physiological situations [9]. Thus, in order to provide methodological information regarding those exponents we aimed to investigate the association of the fractal exponents of HRV with the time and frequency domain and geometric indices of HRV for short period (minimal number of 256 RR intervals).

II. METHODS

A. Study Population

We analyzed 53 healthy men aged between 18 and 30 years old (20.27±1.98 years old) selected from our Institution. All volunteers were informed about the procedures and objectives of the study and, after agreeing, have signed a term of informed consent. The Ethics Committee of the Faculty of Sciences of the Universidade Estadual Paulista, Campus de Marilia approved the study procedures by process n º CEP-**2011**-382, following the Resolution 196/96 of the National Health Council 10/10/1996.

B. Exclusion criteria

We did not include subjects under the following conditions: body mass index (BMI) >35 kg/m^2; systolic blood pressure (SBP) >140 mmHg or diastolic blood pressure (DBP) >90 mmHg (at rest); smoking, cardiovascular, neurological or respiratory disorders related and serious postural deviation in the chest such as severe scoliosis, kyphosis or hyperlordosis that could influence the respiratory pattern and treatment with drugs that influence cardiac autonomic regulation, i.e. beta adrenergic, beta-blockers, angiotensin agonists and antagonists.

C. Initial Evaluation

The volunteers were identified by collecting the following information: age, gender, weight, height and body mass index (BMI) before the experimental procedure. Weight was determined by using a digital scale (W 200/5, Welmy, Brazil) with a precision of 0.1kg. Height was determined by using a stadiometer (ES 2020, Sanny, Brazil) with a precision of 0.1 cm and 2.20 m of extension. Body mass index (BMI) was calculated using the following formula: weight (kg)/height (m^2). We also measured systolic and diastolic blood pressure and heart rate.

D. Experimental protocol

We collected the data under controlled temperature (21° C–25° C) and humidity (50%–60%), and volunteers were instructed to avoid consuming alcohol, caffeine and substances that influence the autonomic nervous system for 24 hours before evaluation. Data were collected between 6 p.m. and 9 p.m. All procedures necessary for the data collection were explained to the individuals, and the subjects were instructed to remain at rest and to avoid talking during the data collection.

After the initial evaluation, the heart monitor strap was placed on each subject thorax over the distal third of the sternum. The HR receiver (Polar RS800CX monitor, Polar Electro OY, Kempele, Finland) was placed on the wrist. The subject remained 10 minutes seated at rest with spontaneous breathing.

E. HRV analysis

The R-R intervals recorded by the portable HR monitor (with a sampling rate of 1000 Hz) were downloaded to the Polar Precision Performance program (v. 3.0, Polar Electro, Finland). The software enabled the visualization of HR and the extraction of a cardiac period (R-R interval) file in "txt" format. Following digital filtering complemented with manual filtering for the elimination of premature ectopic beats and artifacts, at least 256 R–R intervals were used for the data analysis. Only series with more than 95% sinus rhythm were included in the study [10]. For calculation of the indices we used the HRV Analysis software (Kubios HRV v.1.1 for Windows, Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland)[11].

F. Time and frequency domain indices of HRV

To analyze HRV in the frequency domain, the low frequency (LF =0.04 to 0.15 Hz) and high frequency (HF = 0.15 to 0.40 Hz) spectral components were used in ms^2 and normalized units (nu), which represents a value relative to each spectral component in relation to the total power minus the very low frequency (VLF) components, and the ratio between these components (LF/HF). The spectral analysis was calculated using the Fast Fourier Transform algorithm[12].

The analysis in time domain was performed by means of SDNN (standard deviation of normal-to-normal R-R intervals), the percentage of adjacent RR intervals with a difference of duration greater than 50ms (pNN50) and RMSSD (root-mean square of differences between adjacent normal RR intervals in a time interval)[13].

G. Geometric indices of HRV

The HRV analysis was performed using the following geometrical methods: RRtri, TINN and Poincaré plot (SD1, SD2 and SD1/SD2 ratio). The RRtri was calculated from the construction of a density histogram of RR intervals, which contains the horizontal axis of all possible RR intervals measured on a discrete scale with 7.8125 ms boxes (1/128 seconds) and on the vertical axis, the frequency with which each occurred. The union of points of the histogram columns forms a triangle-like shape. The RRtri was obtained by dividing the number of RR intervals used to construct the histogram by their modal frequency (i.e., the RR interval that most frequently appeared on RR).

The TINN consists of the measure of the base of a triangle. The method of least squares is used to determine the triangle. The RRtri and the TINN express the overall variability of the RR intervals[14].

Variable	Value
Height (m)	1.75 ±0.09
Weight (kg)	74.06 ±13.53
BMI (kg/m^2)	24.12 ±4.01
HR (bpm)	82.39 ±10.08
Mean RR (ms)	742.72 ±95.7
SAP (mmHg)	114.69 ±9.29
DAP (mmHg)	76.03 ±8.95

Table 1. Baseline diastolic (DAP) and systolic arterial pressure (SAP), heart rate (HR), mean RR interval, weight, height and body mass index (BMI) of the volunteers. Mean+standard-deviation. m: meters; kg: kilograms; bpm: beats per minut; mmHg: millimeters of mercury.

The Poincaré plot is a map of points in Cartesian coordinates that is constructed from the values of the RR intervals. Each point is represented on the x-axis by the previous normal RR interval and on the y-axis by the following RR interval[15].

For the quantitative analysis of the plot, an ellipse was fitted to the points of the chart, with the center determined by the average RR interval. The SD1 indices were calculated to measure the standard deviation of the distances of the points from the diagonal y=x, and SD2 measures the standard deviation of the distances of points from the line y=-x+RRm, where RRm is the average RR interval. The SD1 is an index of the instantaneous recording of the variability of beat-to-beat and represents the parasympathetic activity, whereas the SD2 index represents the long-term HRV and reflects the overall variability. The SD1/SD2 shows the ratio between the short- and long-term variation among the RR intervals[16].

The plot was qualitatively analyzed using HRV analysis software based on the figures formed by its attractor. The expected shapes were described by Tulppo and colleagues as[5]:

1) Figures in which an increase in the dispersion of RR intervals is observed with increased intervals, characteristic of a normal plot.

2) Small figures with beat-to-beat global dispersion without increased long-term dispersion of RR intervals.

H. Fractal analysis of HRV

For the analysis of the fractal properties of the heart rate, detrended fluctuation analysis (DFA) was applied to a time series of the R–R intervals obtained from the participants. The procedure for the calculation of DFA is made up of the following steps:

The R–R series obtained experimentally is integrated using the expression[8]:

$$Y(k) = \sum_{i=1}^{k} [RR(i) - RR_{ave}]$$

in which Y(k) is the k-th term of the integrated series (k = 1, 2,..., N); R–R(i) is the i-th value of the R–R intervals; and $R\text{–}R_{ave}$ is the mean of the R–R intervals of the original series, with N length:

$$RRave = \frac{1}{N} \sum_{i=1}^{N} RR(i)$$

The integrated time series is then divided into intervals with a length of n, (n = 1, 2,..., N). In each of these intervals, the local trend of the series is calculated by a straight line of minimum squares adjusted to the data. The y-coordinate of this straight line was denominated Yn(k). The integrated series was then detrended [Y(k)], subtracting the local tendency Yn(k) in each interval. For a given interval of size n, the size characteristic of the fluctuation for the integrated and detrended series is calculated by:

$$F(n) = \sqrt{\frac{1}{N} \sum_{K=1}^{N} [Y(k) - Yn(k)]^2}$$

This procedure is repeated for all intervals of size *n*, thereby obtaining a relation between the mean of the fluctuations [*F*(*n*)] and the size of the intervals (*n*). A linear relation on a log–log graph indicates a scale exponent law, based on the following formula:

$F(n) \approx n\alpha$

in which α is the scale exponent, which can be calculated by linear regression on a log–log graph (16). The following were calculated: short-term fractal exponent (alpha-1), corresponding to a period of 4 to 11 beats; long-term fractal exponent (alpha-2), corresponding to periods longer than 11 beats; and the alpha-1/alpha-2 ratio[17].

I. Statistical Analysis

Normal Gaussian distribution of the data was verified by the Shapiro-Wilk goodness-of-fit test (z value >1.0). For parametric distributions we applied the Pearson correlation test. For non-parametric distributions we used the Spearman correlation test. We performed correlation of the alpha-1 and alpha-2 exponents with the time and frequency domain and geometric indices of HRV. We considered weak correlation for r < 0.3, moderate correlation for r between 0.31 and 0.49 and strong correlation for r>0.5. Differences were considered significant when the probability of a Type I error was less than 5% ($p < 0.05$). We used the Software Biostat version 5.8.4 for Windows.

III. RESULTS

Data on baseline systolic (SAP) and diastolic arterial pressure (DAP), heart rate (HR) and mean RR interval, age, height, body weight and body mass index (BMI) are presented in Table 1.

As depicted in Table 2 we observed that the alpha-1 exponent was positively and significantly correlated with mean SDNN/RMSSD ratio, LF (nu), LF/HF ratio and SD1/SD2 ratio. We observed negative correlation of the alpha-1 exponent with the RR intervals, RMSSD, pNN50, LF (nu), HF (nu) and SD1.

Index	r	p
Mean RR	-0.58	p<0.0001
Mean HR	-0.24	0.09
SDNN	-0.15	0.28
RMSSD	-0.53	p<0.0001
SDNN/RMSSD	0.75	p<0.0001
pNN50	-0.53	0.0001
RRtri	-0.24	0.09
TINN	-0.01	0.97
LF(ms²)	0.15	0.28
LF(nu)	0.74	p<0.0001
HF(ms²)	-0.45	0.0007
HF(nu)	-0.74	p<0.0001
LF/HF	0.74	p<0.0001
SD1	-0.53	p<0.0001
SD2	-0.07	0.05
SD1/SD2	0.78	p<0.0001

Table 2. Correlation between the alpha-1 exponent and the HRV indices. Mean RR: Mean RR intervals; Mean HR: mean heart rate; SDNN: standard deviation of normal-to-normal R-R intervals; pNN50: the percentage of adjacent RR intervals with a difference of duration greater than 50ms; RMSSD: root-mean square of differences between adjacent normal RR intervals in a time interval. ms: millisecond. LF: low frequency; HF: high frequency; LF/HF: low frequency/high frequency ratio; RRtri – Triangular index; TINN – triangular interpolation of RR intervals; SD1 – standard deviation of the instantaneous variability of the beat-to beat heart rate; SD2 – standard deviation of long-term continuous RR interval variability; SD1/SD2 ratio – ratio between the short - and long - term variations of RR intervals. ms: milliseconds; nu: normalized units.

The alpha-2 exponent of the DFA presented only moderate negative correlation with the LF index in absolute units (ms^2) with no significant correlation with any other index (Table 3).

We also investigated the correlation of the alpha-1/alpha-2 ratio with the HRV indices and we observed positive moderate correlation with the SDNN/RMSD ratio and negative moderate correlation with the SD1 and SD1/SD2 ratio. There was also positive strong correlation of the alpha-1/alpha-2 ratio with the LF (nu) and LF/HF ratio (Table 4) and negative correlation with the HF (nu).

Index	r	p
Mean RR	0.03	0.86
Mean HR	-0.03	0.83
SDNN	-0.11	0.45
RMSSD	-0.17	0.22
SDNN/RMSSD	0.16	0.26
pNN50	-0.17	0.22
RRtri	-0.18	0.20
TINN	-0.08	0.58
LF(ms²)	-0.33	0.02
LF(nu)	-0.12	0.39
HF(ms²)	-0.19	0.18
HF(nu)	0.12	0.39
LF/HF	-0.12	0.41
SD1	-0.17	0.22
SD2	-0.09	0.53
SD1/SD2	-0.17	0.21

Table 3. Correlation between the alpha-2 exponent and the HRV indices. Mean RR: Mean RR intervals; Mean HR: mean heart rate; SDNN: standard deviation of normal-to-normal R-R intervals; pNN50: the percentage of adjacent RR intervals with a difference of duration greater than 50ms; RMSSD: root-mean square of differences between adjacent normal RR intervals in a time interval. ms: millisecond. LF: low frequency; HF: high frequency; LF/HF: low frequency/high frequency ratio; RRtri – Triangular index; TINN – triangular interpolation of RR intervals; SD1 – standard deviation of the instantaneous variability of the beat-to beat heart rate; SD2 – standard deviation of long-term continuous RR interval variability; SD1/SD2 ratio – ratio between the short - and long - term variations of RR intervals. ms: milliseconds; nu: normalized units.

IV. DISCUSSION

This study was undertaken to evaluate the association of the fractal exponents of HRV derived from DFA with the time and frequency domain and geometric indices of HRV in healthy men for a short period (minimal number of 256 RR intervals). We observed that the alpha-1 exponent was strongly associated with those indices, while the alpha-1/alpha-2 ratio was partially associated. On the other hand, the alpha-2 exponent was not associated with any index investigated. The DFA technique is a modified root-mean-square analysis of a random walk, and it quantifies the presence or absence of fractal correlation properties in the time series. In this method a fractal-like signal results in an exponent value of 1.0, a random signal results in a value of 0.5, and a strongly correlated signal behavior linear results in an exponent value of 1.5[18].

We reported that the alpha-1 index analyzed in a minimal number of 256 RR intervals presented negative and strong correlation with RMSSD, pNN50, HF in normalized and absolute units and SD1 indices. All those indices correspond to the parasympathetic modulation of the heart[1]. On the other hand, it presented strong and positive correlation with the LF (nu) and LF/HF ratio, indicating a positive association with the sympathetic-vagal balance[2]. The alpha-1 exponent was not correlated with the linear geometric indices of HRV, i.e. TINN and RRTri, but presented strong correlation with the nonlinear Poincaré plot indices, i.e. SD1, SD2 and SD1/SD2 ratio. The Poincaré plot analysis (also known as return map) is a simple technique, it was initially used as a qualitative tool[19] and it was considered later as a geometrical analysis by fitting an ellipse to the shape of the Poincaré plot in order to calculate HRV indices[20]. The literature considers it a nonlinear method, because it describes the nonlinear dynamics of a phenomenon that can recognize the hidden correlation patterns of a time series signal[21]. Our data reinforce the alpha-1 exponent as a nonlinear index to evaluate HRV[5, 8].

In this context, an elegant study[5] investigated the changes in the frequency-domain indices of HRV and in the alpha-1 fractal exponent induced by the passive head-up tilt test and dynamic exercise in healthy male volunteers for 10 minutes. An increase in the LF (nu) index was revealed during exercise; however, no significant changes were observed during the passive tilt test. They also found reduction in the HF power in the passive tilt test. In addition, the authors reported that the short-term fractal scaling exponent alpha-1 increased during low-intensity dynamic exercise and during passive head-up tilt test as observed in the LF (nu) index, supporting our data.

Interestingly, although the alpha-1 exponent presented correlation with the RMSSD index, we observed that it did not present correlation with the SDNN index. However, it presented strong correlation with the SDNN/RMSSD ratio. In this context, the SDNN/RMSSD ratio was already suggested to be a surrogate for the LF/HF ratio[22]. Previous studies investigated the relationship between SDNN/RMSSD and LF/HF ratios. One investigation presented a correlation coefficient ($r = 0.90$) at resting supine position[23]. Another study reported some correlation coefficients r ($r = 0.90$–0.94) on prefrontal cortex patients[24]. In view of the above consideration, the strong association between the fractal alpha-1 exponent and the SDNN/RMSSD ratio is supported by the strong correlation between the short-term fractal scaling exponent alpha-1 and the LF/HF ratio.

Regarding the long-term exponent (alpha-2), there was no significant correlation with any index evaluated in our study. Previous published studies also failed to observe significant changes in the alpha-2 exponent with at least 256 RR intervals in different conditions[7,8]. Vanderlei and colleagues[7] investigated heart rate dynamics through analysis of the alpha-1 and alpha-2 fractal exponents and HRV frequency domain indices in obese children. The authors noted reduced values of alpha-1 exponent, LF and HF indices in normalized units, but no change was observed in the alpha-2 exponent[7]. The same group[8] evaluated the alpha-1 and alpha-2 exponents as well as the time and frequency domain indices of HRV in subjects with COPD and reported decreased values of all time and frequency domain indices and decreased short-term fractal exponent, while there was no change in the alpha-2 exponent. Furthermore, it was suggested that the scaling exponent alpha-1 analysis may be useful for identifying high-risk patients while the alpha-2 exponent was not significantly associated with high-risk patients[25]. Nevertheless, a recent study found a significant decrease in the short-term scaling exponent alpha-1 and a significant increase in the long-term scaling exponent alpha-2 during heel lancing in newborns[9]. The possible influence of the lack of physiological maturity in newborns may be involved in this result.

Index	r	P
Mean RR	-0.27	0.05
Mean HR	0.28	0.04
SDNN	-0.12	0.38
RMSSD	-0.30	0.03
SDNN/RMSSD	0.41	0.01
pNN50	-0.29	0.03
RRtri	-0.01	0.96
TINN	0.01	0.96
LF(ms²)	0.28	0.04
LF(nu)	0.66	p<0.0001
HF(ms²)	-0.29	0.04
HF(nu)	-0.65	p<0.0001
LF/HF	0.65	p<0.0001
SD1	-0.30	0.03
SD2	-0.07	0.61
SD1/SD2	-0.41	0.01

Table 4. Correlation between the alpha-1/alpha-2 ratio and the HRV indices. Mean RR: Mean RR intervals; Mean HR: mean heart rate; SDNN: standard deviation of normal-to-normal R-R intervals; pNN50: the percentage of adjacent RR intervals with a difference of duration greater than 50ms; RMSSD: root-mean square of differences between adjacent normal RR intervals in a time interval. ms: millisecond. LF: low frequency; HF: high frequency; LF/HF: low frequency/high frequency ratio; RRtri – Triangular index; TINN – triangular interpolation of RR intervals; SD1 – standard deviation of the instantaneous variability of the beat-to beat heart rate; SD2 – standard deviation of long-term continuous RR interval variability; SD1/SD2 ratio – ratio between the short - and long - term variations of RR intervals. ms: milliseconds; nu: normalized units.

Although we did not find significant association of the alpha-2 exponent with the time and frequency domain and geometric indices of HRV, this exponent is indicated to correspond to Brownian motion, it is thought to indicate the total loss of the response loops and collapse of the processes that regulate heart rate during pain, resulting in highly correlated fractal dynamics that spread into many time scales[5]. This assumption supports the findings recently published by the Weissman group[9], which reported significant increase in the alpha-2 alpha during pain induction in newborns.

According to our findings, the alpha-1/alpha-2 ratio presented moderate to strong correlation with the SDNN/RMSSD ratio, LF and HF indices in absolute units as well as the LF/HF ratio and SD1/SD2 ratio. We believe that the association with some variables was partially due to the strong relationship of the alpha-1 exponent with the time and frequency domain and geometric indices of HRV, while the alpha-2 long-term scaling exponent was not associated with those HRV indices. The alpha-1/alpha-2 ratio was also investigated in obese children[7] and in COPD patients[8]. The authors observed changes in the time and frequency domain indices of HRV as well as in the alpha-1 exponent of the fractal dynamics, however, there was no significant alteration in the alpha-1/alpha-2 ratio. Taken together, we believe that this ratio does not provide relevant clinical data information. On the other hand, we suggest further studies to add new elements in this issue.

The HRV has been used as a resource of interventions evaluation, as pathological conditions common to clinical practice investigation and to physiological conditions interpretation in medicine with fetal research to elderly [12,16,28,29]. However, there is still a gap regarding the association of the fractal exponents of HRV with the time and frequency domain and geometric indices of HRV for short period. A recent study evaluated the effect of fetal respiratory movements on the heart rate fractal dynamics with an abdominal electrocardiogram and the authors considered that the heart rate short-term fractal properties are convenient for assessing the cardiovascular prenatal regulation[27]. Also, Nicolini and colleagues[28] considered studies on the prognostic value of HRV in elderly subjects, discussing the potential confounding effect of erratic rhythm, and concentrates on the conceptual distinction between autonomic tone and autonomic modulation.

Our study presents some limitations that are important to be raised. Our findings cannot be extrapolated to other populations with different characteristic because the study was conducted in men in order to avoid sex-dependent effects. The absence of data for plasma catecholamines levels would strengthen our findings. Moreover, there is not sympathetic analysis through other methods such as skin conductance resistance. Those methods could add further information regarding the fractal scaling exponents of HRV and the autonomic nervous system for short period, however, this was not the main aim of the study.

As a main finding, we showed that the alpha-1 exponent can be used for short period analysis of HRV (at least 256 RR intervals), while the alpha-1/alpha-2 ratio was associated with LF and HF indices in absolute units as well as the LF/HF ratio, SDNN/RMSSD and SD1/SD2 ratios. On the other hand, the alpha-2 exponent was not supported to be used for this analysis. If these exponents (alpha-1 and alpha-1/alpha-2 ratio) were indicated to be applied to short-term HRV analysis (more than 256 RR intervals) they may provide features regarding the changing effects of the autonomic nervous system on the heart and enable tracking of dynamic changes in real-time, e.g. medications with fast reaction periods and recovery from physical exercise[26].

V. CONCLUSIONS

The alpha-2 exponent of the HRV derived from DFA was not associated with the time and frequency domain and geometric indices of HRV, while the alpha-1 exponent presented strong correlation. Therefore, our data support the alpha-1 exponent is indicated for 256 RR interval analysis of HRV in healthy condition.

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