Chapter

Characterization of Homeostatic Level Based on Non-linear Variables of Heart Rate Variability

Moacir Fernandes de Godoy and Michele Lima Gregório

Abstract

Heart Rate Variability (HRV) has been frequently cited as an indicator of homeostatic status. Low levels of HRV are associated with aging, disease, or increased risk of death. The authors based this chapter on an alphanumerical classification for the levels of homeostasis, structured on three linear variables (Heart Rate, RMSSD, and HF ms2) by analyzing a bigdata with more than 30 million pieces of data collected from literature. It was possible to confirm the clinical validity of this alphanumeric classification. It has been mentioned that HRV analysis in time and frequency domains are often not sufficient to characterize the complex dynamics of the heartbeat. Thus, the primary objective of this study was to verify whether or not there are correlations between the variables of the non-linear domain with variables and indices of the linear domain and also with the homeostatic level of individuals. It was found, contrary to expectations, that the variables ApEn, SampEntr and DFA α1 were not useful in characterizing the homeostatic level, since they do not differentiate between healthy and highly compromised individuals. Regarding the parasympathetic, sympathetic and stress indexes, only DFA a1 detected a correlation with the sympathetic index and the stress index.

Keywords: heart rate variability, non-linear, autonomic nervous system, homeostasis, big data

1. Introduction

Heart rate variability has been frequently cited as a relevant indicator of homeostatic status, since low levels of heart rate variability, especially those related to the parasympathetic component, are repeatedly associated with the presence of aging, disease, or increased risk of death [1].

Generally, the evaluated variables are categorized as belonging to the time domain, frequency domain and non-linear domain. Among the linear variables with clinical importance, most mentioned in the literature, heart rate, RMSSD (root mean square of successive differences between normal heartbeats) and HFms2 (high-frequency component), stand out.

Both the time domain and frequency domain methods assume that HRV signals are linear, and thus cannot quantify the dynamic structure of the signal.

More recently, there has been an increase in references suggesting that variables in the non-linear domain of HRV would be more sensitive in detecting alterations in homeostasis.

Sassi et al., in 2015 [2] evaluated the available literature over a period of 18 years (1996 to 2013) and found only 21 studies with more than 200 cases, in which non-linear HRV assessment methods were used.

In addition, a lot of discrepancy between studies has been observed, calling attention to the lack of standardization and proper validation of some methods used [3].

To assess the non-linear properties, several methods have been proposed in the past, including Fractal Dimension, Lyapunov Exponent, Hurst Exponent, Correlation Dimension, Approximate Entropy, Sample Entropy, Shannon Entropy and Detrended Fluctuation Analysis. All these methods quantify some non-linear property of HRV [3]. Among these various HRV variables belonging to the non-linear domain, three stand out in the world Literature, namely Approximate Entropy (ApEn), Sampling Entropy (SampEnt) and the alpha 1 component of the Detrended Fluctuation Analysis (DFA α1).

ApEn is a statistic quantifying regularity and complexity of a stationary signal [4]. This means that ApEn quantifies the predictability of fluctuations in the time series. The main idea behind approximate entropy is that a sequence is regular if a subsequence and an expansion of the subsequence are similar [5].

Byum et al. in 2019 [6], studied a total of 33 patients with major depressive disorder (MDD) based on the DSM-IV criteria, and 33 healthy controls, matched for age and gender. Four entropy indices, approximate entropy, sample entropy, fuzzy entropy and Shannon entropy, were extracted. There were no significant differences in entropy features between the control and patient groups at the base line. The authors considered that this inconsistency was likely a result of the heterogeneous presentation and multifactorial etiology of MDD.

Garner et al., in 2021 [7] examined 38 subjects with Chronic Obstructive Pulmonary Disease (COPD) and 38 matched controls. They measured heart rate variability, through Approximate Entropy (ApEn), during 30 minutes, in the supine position, without any physical, sensory or pharmacological stimuli. They concluded that ApEn was capable of optimally identifying the decrease in chaotic response in COPD but, despite this, ApEn should be considered a relatively unpredictable mathematical marker and the use of other techniques to evaluate a healthy or pathological condition needs to be encouraged.

Beckers et al., [3], evaluated the Approximate Entropy behavior in 21 patients in advanced stages of heart failure (NYHA class III and IV) compared to 21 healthy individuals, age and sex matched. Twenty-one heart failure (CHF) patients (NYHA class III and IV; all males; age: 54.5 ± 2.9 years) were included. An age and sex matched group of 21 healthy subjects (all males; age: 54.5 ± 4.1 years) was used as a control population. No statistically significant differences were found between groups regarding Approximate Entropy.

Sample Entropy (SampEn) has been proposed as a method to overcome limitations associated with approximate entropy (ApEn). Para Aboy et al., [8], SampEn is more consistent and agrees more closely with theory for known random processes than ApEn.

Al-Angari and Sahakian in 2008 [9] used Sample Entropy, as a measure of signal complexity to evaluate the behavior of heart rate variability in Obstructive Sleep Apnea Syndrome (OSAS). They found that healthy subjects have significantly more complex HRV pattern than the OSA subjects and that the sample entropy had an accuracy of 70.3%. They stressed, however, that the sample entropy approach does not show major improvement over the existing methods. In fact, its accuracy in detecting sleep apnea was relatively low in those well classified patients.

The alpha 1 exponent of the Detrended Fluctuation Analysis (DFA α1) is a non-linear domain variable in the analysis of heart rate variability and represents the observed self-similarity or fractal nature between the RR intervals in a time series. Tapanainen et al., in 2002 [10] showed the evolution of 697 survivors after acute myocardial infarction, through the analysis of conventional variables in the time and frequency domains, in addition to the non-linear variable DFA α1. They found that (49) 7% of cases died after a mean follow-up of 18.4 ± 6.5 months. The DFA alpha 1 exponent with a value below 0.65 was an independent predictor of death, both in univariate as in multivariate analysis, regardless of the presence or absence of left ventricular dysfunction.

Schaffarczyk et al., in 2022 [11] evaluated the usefulness of DFA α1 with cutoff values of 0.75 and 0.50 in determining aerobic and anaerobic thresholds, in 26 female volunteers aged between 20 and 59 years, having found a good correlation of values according to the intensity of the exercise. At low exercise intensity, DFA α1 values indicated a well-correlated fractal pattern remaining close to 1.0 or slightly above. As the effort intensity was increased, they noticed a decrease in the index to approximately 0.75, approaching the uncorrelated random patterns, represented by values close to 0.50 or even below, in the case of even more intense work. It was inferred that this index may reflect the state of systemic internal load.

These sometimes conflicting observations, highlight the importance of the issue addressed here, which aims to characterize and quantify the real practical use of the most widespread and clinically applicable non-linear methods for assessing HRV.

2. Method

2.1 Validation

In 2022, Godoy and Gregório [1] evaluated the Heart Rate Variability as a Marker of Homeostatic Level, proposing an alphanumeric classification, after collecting about 10.5 million data from a bigdata, based on specific changes in three variables of the linear domain of the HRV. At that moment 465,966 data from those variables were detected, 387,638 related to heart rate, 45,545 related to RMSSD and 32,783 related to HFms2.

A total healthy individual, with an excellent Homeostatic Level and, therefore, with very low risk, would receive the A1B1C1 classification. An individual with a high basal heart rate, a very low RMSSD and HF power values would be classified as A3B3C3 indicating high severity, low homeostatic level and, therefore, at high risk. Several intermediate combinations would be possible characterizing the current state of each case. The cutoff values for each variable were:

Level A: Heart Rate (bpm)
- Stage Al: Heart Rate less than 70 bpm
- Stage A2: Heart Rate between 70 and 85 bpm
- Stage A3: Heart Rate above 85 bpm

Level B: RMSSD (ms)
- Stage B1: RMSSD above 32 milliseconds
- Stage B2: RMSSD between 32 and 28 milliseconds
- Stage B3: RMSSD less than 28 milliseconds

Level C: HF ms2
- Stage C1: HF ms2 above 468 ms2

Stage C2: HF ms2 between 468 and 156 ms2
Stage C3: HF ms2 less than 156 ms2

In the present study, we initially sought to validate these data based on an update of available big data. Our database now has more than 31.6 million pieces of data, of which 10,671,458 were related to the three classic linear variables (554,483 to Heart Rate; 5,176,138 to RMSSD; 4,940,837 to HFms2) and 30,723 to the three non-linear chosen variables (6670 to ApEn, 6785 to SampEntr and 17,268) from DFA α1. The complementary amount of data refers to other variables not included in this study. The references that enabled the construction of this bigdata can be made available upon request.

The variables analyzed in the present study and components of the bigdata were grouped according to the clinical status of the participating individuals as belonging to the group of healthy individuals and the group with significant impairment of the homeostatic level, such as, for example, cases of neoplasms, liver dysfunctions or advanced kidney disease, hospitalizations in intensive care units in critical situations, prematurity and conditions of imminent death. **Figure 1** presents the distribution of the quantities of analyzed variables in these two situations.

It can be seen that, the cut-off levels proposed with the initial sample remained equivalent in the current magnified sample and, therefore, become validated.

2.2 Study sample

Based on the proposed alphanumeric code, an unselected group of 123 individuals from the personal casuistic was evaluated, regardless of sex and age, with different clinical states, from apparently healthy to severely compromised health status. **Figure 2** specifies the classification of cases in each impairment group, either at level I, involving patients with three stages 1 or two stages 1 or without duplication of stages; at level II, involving patients with three stages 2 or two stages 2; at level III, involving patients with three stages 3 or two stages 3.

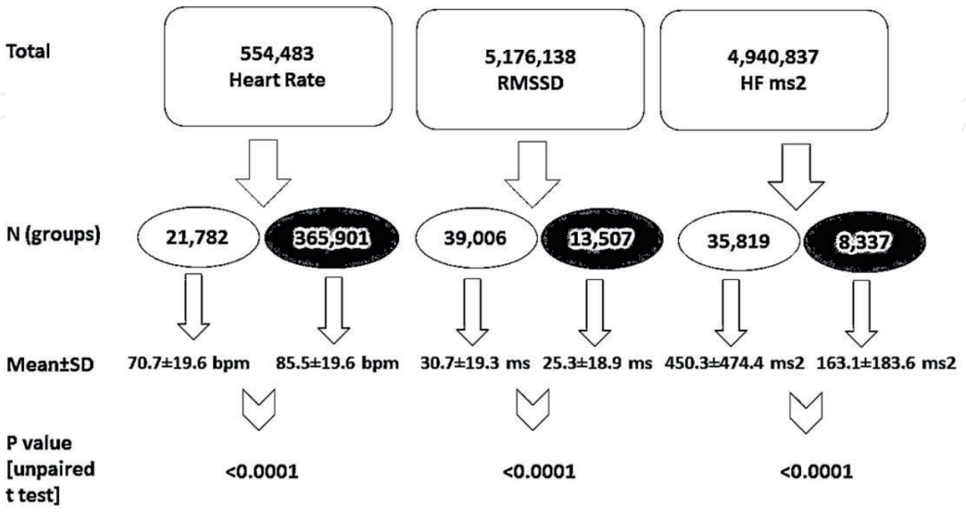


Figure 1.
Data distribution, from the bigdata of 31.6 million pieces of data, with segmented relation to the three selected variables, and according to the group of healthy individuals (light sets) and the group with severe homeostatic impairment (dark sets). The complementary amount of data refers to variables not included in this study. Variable values are presented as mean ± standard deviation. P values are relative to intergroup comparisons of homeostatic impairment.

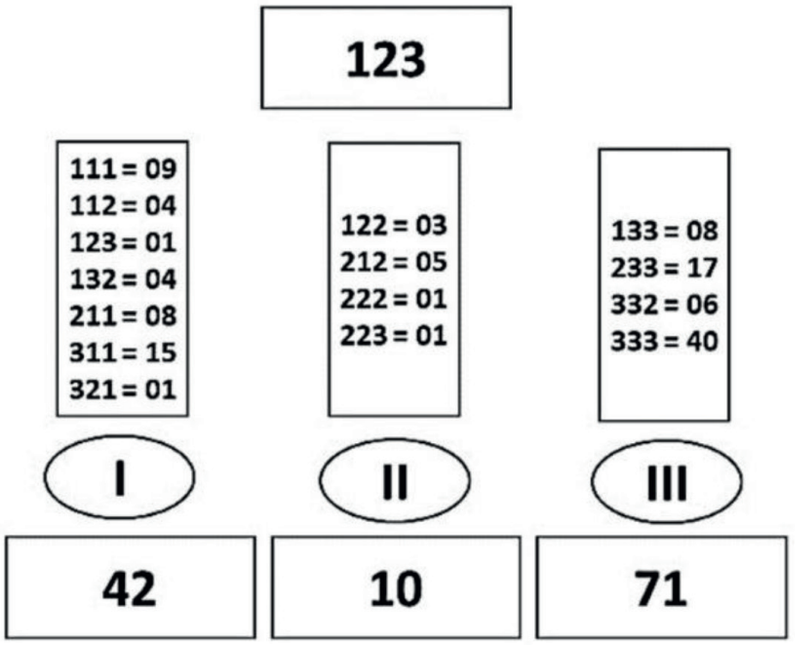


Figure 2.
Distribution of homeostatic level classifications of 123 non selected patients, based on the alphanumeric coding proposed by Godoy and Gregório (2022) [1].

2.3 Statistical analysis

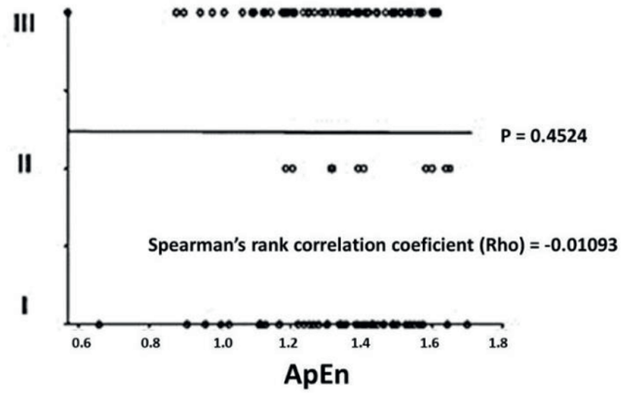
Continuous quantitative data were analyzed using the unpaired Student's t-test. Discrete or non-Gaussian quantitative data were analyzed using the Mann-Whitney test. For correlations, both Pearson's correlation and Spearman's correlation were applied, depending on the type of variable. The graphical representation was made using Boxplot and linear regression graphs. An alpha error of 5% was admitted, with P values lower than or equal to 5% being considered significant. The statistical software used was StatsDirect version 3.3.5. To quantify the HRV variables, the Kubios HRV Scientific application version 4.0.1 of October 2022 was used.

3. Results

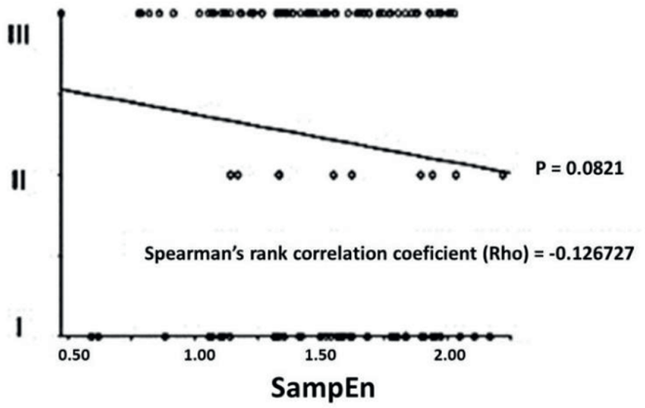
We sought to assess whether each of the three non-linear variables (ApEn, SampEn and DFA alpha 1) were correlated or not with the level of homeostatic impairment. It was observed that none of the evaluations detected a significant correlation between the variable and the homeostatic level (Spearman's rank correlation coefficient); **Figure 3**(a-c).

Comparisons were also made of each of the three non-linear variables between individuals considered healthy (Group I, light sets) and those with severe health impairment (Group III, dark sets). It was possible to collect a total of 30,723 pieces of information on these three variables. It was found that none of the three non-linear variables studied was able to discriminate these opposing groups of homeostasis impairment (**Figures 4**–**7**).

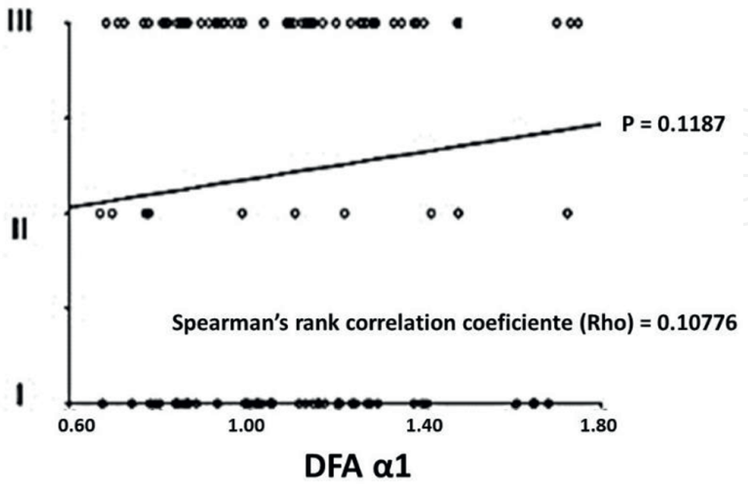
Finally, Pearson's correlations were sought between the non-linear and the linear variables, between the non-linear and the parasympathetic, sympathetic and stress



(a)



(b)



(c)

Figure 3.
a. Spearman's rank correlation coefficient between the non-linear variable ApEn and the homeostatic levels. b. Spearman's rank correlation coefficient between the non-linear variable SampEn and the homeostatic levels. c. Spearman's rank correlation coefficient between the non-linear variable DFA α1 and the homeostatic levels.

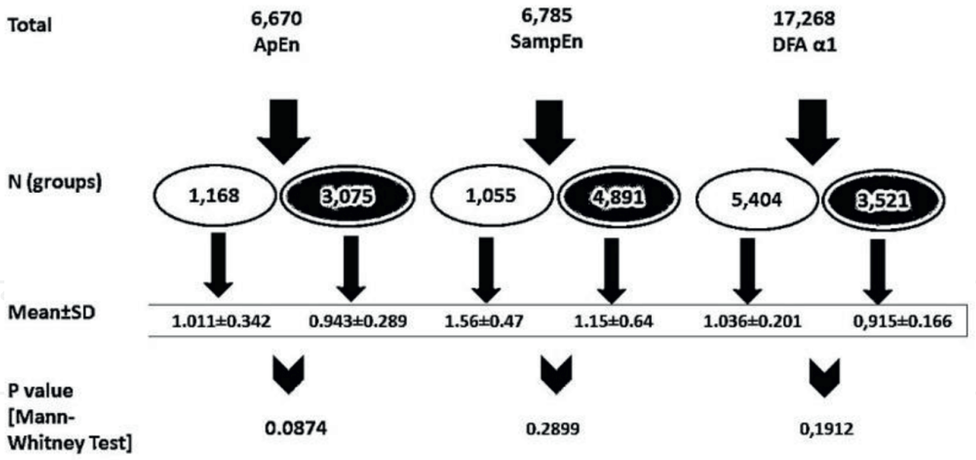


Figure 4.
Statistical comparison by the non-parametric Mann-Whitney test on the ability of the non-linear variables, ApEn, SampEn and DFA alpha 1 to distinguish between healthy individuals and individuals with significant homeostatic impairment.

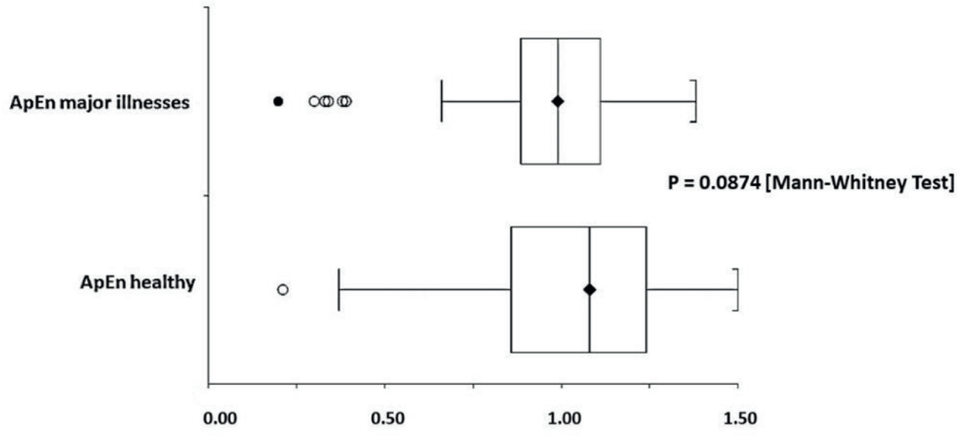


Figure 5.
Boxplot comparing the values of the non-linear variable ApEn, in healthy individuals and in those with significant homeostatic impairment.

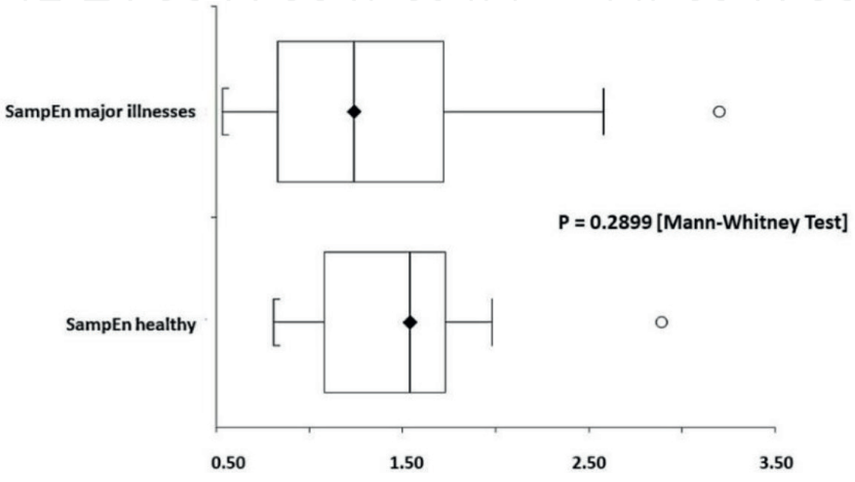


Figure 6.
Boxplot comparing the values of the non-linear variable SampEn, in healthy individuals and in those with significant homeostatic impairment.

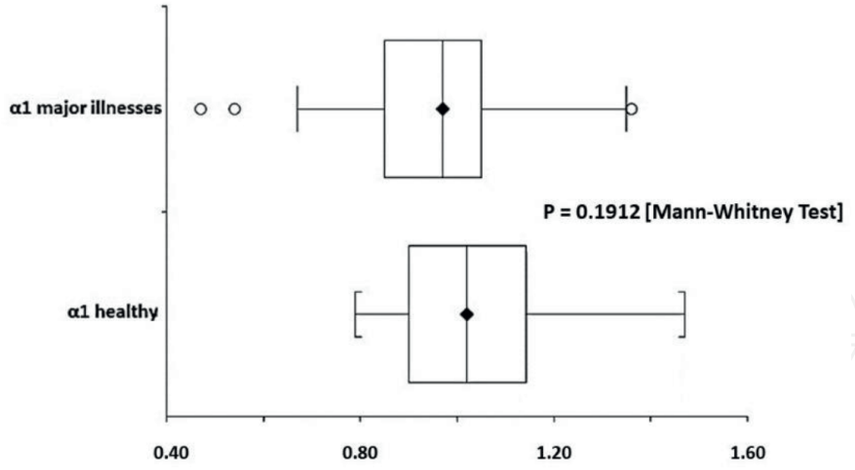


Figure 7.
Boxplot comparing the values of the non-linear variable DFAa1, in healthy individuals and in those with significant homeostatic impairment.

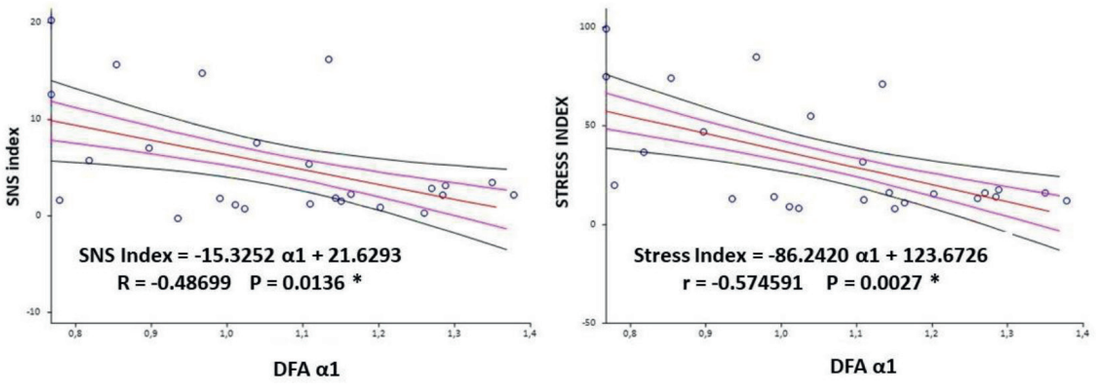


Figure 8.
Linear correlations between the non-linear variable DFA α1 and the sympathetic and stress indexes [= significant].*

	Heart Rate	RMSSD	HFms2	PNS	SNS	Stress Index	Groups
ApEn	0.0429	−0.0794	−0.0637	0.3385	−0.2474	−0.1763	−0.0025
Samp. Entr	−0.0568	−0.0949	−0.0983	0.3280	−0.2241	−0.1392	−0.1135
DFAα1	−0.0819	−0.1278	−0.1157	0.1729	−0.4869*	−0.5745*	0.1107

* = significant correlation.

Table 1.
Pearson correlation (r values) between non-linear variables and linear variables, autonomic indexes and clinical conditions.

indexes and also between the non-linear variables and the clinical classification of health states.

It is worth remembering that the PNS index (parasympathetic nervous system tone index) is derived from the association between the variables Mean RR, RMSSD and SD1 indicates a parasympathetic nervous system activity compared to normal resting values. The SNS index (Sympathetic nervous system tone index) is derived from the association between the variables Mean HR, Stress index and SD2 indicates Sympathetic

nervous system activity compared to normal resting values. The Stress index is the square root of the Baevsky's stress index with normal values ranging from 7 to 12.

In general, there were no significant correlations between the analyzed variables, that is, the correlation coefficients were not significantly different from zero, except for the negative correlations between DFA a1 and the sympathetic index ($r = -0.48699$; $P = 0.0136$) and DFA α1 with the Stress Index ($r = -0.574591$; $P = 0.0027$) (**Table 1** and **Figure 8**).

4. Conclusions

I. It was possible to confirm the clinical validity of an alphanumeric classification of homeostatic level, based on a big data with more than 30 million data related to variables of Heart Rate Variability, collected in the world Literature, by comparing the mean values obtained with the mean expected values.

II. The three classical variables of the linear domain (Heart Rate, RMSSD and HFms2), based on the suggested cut-off levels, are significantly different when comparing healthy individuals and individuals with significant impairment of homeostasis.

III. No correlation was detected, using Spearman's rank correlation coefficient, between each of the three non-linear variables (ApEn, SampEn and DFA α1) and the degree of homeostatic impairment.

IV. There are no correlations between the variables of the non-linear domain with variables of the linear domain, neither with the degree of global clinical impairment nor homeostatic level of individuals.

V. The three variables of the selected non-linear domain (ApEn, SampEn and DFA $\alpha 1$), are not statistically different when healthy individuals are compared with individuals with significant impairment of the homeostatic level.

VI. In general, there were no significant correlation by Pearson's correlation coefficient between the non-linear variables and the selected linear variables, as well as between the non-linear variables and the parasympathetic index. Only DFA $\alpha 1$ showed a significant correlation (negative and moderate) with the sympathetic index ($r = -0.48699$; $P = 0.0136$) and with the Stress Index ($r = -0.574591$; $P = 0.0027$).

VII. These findings suggest that the non-linear variable DFA $\alpha 1$ may be considered a marker of individual stress burden.

VIII. Finally, the relevance of the non-linear evaluation was demystified since the non-linear variables evaluated did not show significant discriminatory power.

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