

Nonlinear Analysis of Heart Rate Variability: A Comprehensive Review

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ABSTRACT

The traditional techniques for Heart Rate Variability (HRV) analysis in time and frequency domains are often not sufficient to characterize the complex dynamics of the heartbeat, since the mechanisms involved in cardiovascular regulation probably interact with each other in a nonlinear manner. There are already dozens of techniques for non-linear evaluation of HRV. However, until now, systematic studies of large groups of patients using this approach have not been conducted. We present the current state of knowledge in this area based on nonlinear variables more prevalent in existing publications. It can be concluded that the analysis of HRV in the nonlinear domain provides very useful information to characterize the appropriate autonomic balance and is a more reliable marker of complications and mortality in patients with cardiovascular disease.

Key words: Heart Rate Variability; Nonlinear Dynamics; Autonomic Nervous System; Invariant Domain; Informational Domain

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TOPIC HIGHLIGHT

The heart rate variability (HRV) is habitually quantified by using methods of the time and frequency domains, which measures the overall magnitude of fluctuations in intervals between consecutive heartbeats (RR interval) around its average value or the magnitude of fluctuations in some predetermined vibration frequencies.

The traditional data analysis techniques in the time and frequency domains are often not sufficient to characterize the complex dynamics of generation of the heartbeat since the mechanisms involved in cardiovascular regulation probably interact with each other in a nonlinear way.

Then, various attempts have been reported to apply the concept of nonlinear dynamics to this problem, arousing increasing interest. These new methods related to nonlinear dynamics are, in general, clinically more relevant for a better interpretation of pathophysiological behavior of HRV under various conditions and, consequently, its prognostic value, complementing the information obtained with traditional assessments. However, systematic studies of large groups of patients using this approach, have not been conducted^[1-2].

In a recent publication of the European Society of Cardiology, the authors reviewed the literature available from 1996 until December 2013, looking for relevant articles addressing the use of non-conventional methods, which had been used in a significant number of patients (more than 200 cases) finding only 21 studies from the thousands already published. This highlights the importance of the issue addressed here, which aims to characterize and quantify the real practical use of nonlinear methods for assessing HRV^[3-4].

Nonlinear analysis methods differ from the conventional HRV methods because they do not assess the magnitude of variability but rather the quality, scaling, and correlation properties of the signals^[5]. In other words, they are related with the unpredictability, fractability and complexity of the signal.

The concepts related to chaos theory, the fractal mathematics and the dynamic complexity of heart rate variability behavior are still far from large application in medical clinical practice, although they constitute a fruitful field for research and expansion of knowledge in both health and disease^[6].

In particular, it has been demonstrated, for example, that the short period fractal-scaling exponent measured by the Detrended Fluctuation Analysis (DFA α) method predicts fatal cardiovascular events in several populations. The Approximate Entropy (-ApEn) also a nonlinear index of dynamic heart rate, which describes the complexity of the RR interval behavior has provided information about the vulnerability for atrial fibrillation. There are many other nonlinear indices such as the Lyapunov Exponent (LE) and Correlation Dimension (CD), which also provide information on the characteristics of HRV, but their clinical utility has not been fully established^[6].

Meyerfeldt *et al.*^[7] in 2002 evaluated whether changes in HRV represented or not early signs for the occurrence of ventricular tachycardia in patients with implantable defibrillators. They analyzed 1000 RR intervals occurring immediately before the onset of a ventricular tachycardia (131 episodes) compared to a control period distant of the arrhythmia (74 series) in 63 patients with heart failure, and implanted defibrillator device. They found that none of the linear parameters was able to detect significant differences between groups. However, nonlinear parameters detected short periods of low variability prior to the occurrence of tachyarrhythmia suggesting the possibility of creating defibrillators sensitive to algorithms based on nonlinear dynamics.

More recently, there has also been an effort in trying to demonstrate the effect of gender and age on nonlinear indexes. Beckers *et al.*^[5] (2005) evaluated 135 women and 141 men (age 18 -71) using Holter monitoring system for 24 hours subdividing the analysis into two periods: daytime (8 AM-9 PM) and nighttime (11 PM-6 AM). They studied variable nonlinear scaling properties like $1/f$ slope (where " f " is frequency), fractal dimension, and detrended fluctuation analysis with short (α_1) and long-term (α_2) correlations being the nonlinear complexity described with correlation dimension (CD), Lyapunov exponent (LE), and approximate entropy (ApEn). They found that like with the linear variables, nonlinear variables also feature a day-night variation, except for the CD in the female population. Higher nonlinear behavior was evident during the night. No clear differences between men and women were found with the nonlinear indexes. They concluded that nonlinear indexes decline with age and this could be related to the concept of decreasing autonomic modulation with advancing age.

Souza *et al.*^[8] (2014) evaluated healthy women aged 18-30 years studying the behavior of HRV in response to the postural change maneuver, using linear and nonlinear variables. They observed that the short-term alpha-1 exponent was significantly increased at all moments investigated compared to seat. Increase in the properties of short-term fractal correlations of heart rate dynamics accompanied by a decrease in the parasympathetic modulation and global HRV was observed in response to the postural change maneuver.

An interesting and exhaustive historic of the initial studies about nonlinear dynamics can be found in Voss A *et al.*^[11] (2009).

We will do from now, a general approach on the current state of clinical application and prognostic relevance of the main nonlinear methods for assessing HRV. We will use the classification proposed by Bravi A *et al.*^[9] (2011). These authors comment that the growth and complexity of techniques applicable to the study of heart rate variability have made interpretation and understanding of variability more challenging. Then after review, carefully, the theory and the clinical applications of more than 70 variability techniques, they proposed a revised classification for the domains of variability techniques, which include statistical, geometric, energetic, informational, and invariant types.

The domains related to Linear Analysis of HRV in that classification are the statistical, the geometric and the energetic. The domains related to the Nonlinear Analysis of Heart Rate Variability are the Informational and the Invariant. In each one of these last two domains, we will make some comments about the more prevalent ones in published clinical studies.

1. INVARIANT DOMAIN

A. Detrended Fluctuation Analysis (DFA) with α_1 and α_2 components

B. Fractal Dimension (FD)

C. Hurst Exponent (HE)

D. Largest Lyapunov Exponent (LLE)

E. Correlation Dimension (CD)

1A. DFA(α)

The complex physiological signals although typically not stationary, they are not random. The Detrended Fluctuation Analysis (DFA) was developed by Peng CK *et al.*^[10] in 1995 and is used to measure the presence or absence of fractal correlation properties. With the aid of this method, it is possible to detect the occurrence of intrinsic self-similarity in certain types of nonstationary time scales^[6,10-11].

Self-similarity means that one subunit of RR intervals resembles a series of larger time scale, i.e., there is a long-term correlation between RR intervals, in which the intervals in a given time interval are partially dependent of previous segments^[3]. The mathematical concept of this index can be easily found in a large quantity of publications^[11-13].

In general are considered two components as part of this index α , the short-term (α_1) involving correlations from four to 16 heartbeats and long-term (α_2) involving from 16 to 64 beats.

The long-range correlations should correspond to sympathetic modulation, whereas short-term correlations should correspond to both sympathetic and vagal modulation^[5].

It is considered that alpha coefficient values close to 0.5 ("White Noise") imply the absence of correlation between the RR interval and consequently greater randomness in the dynamics of the time series. Values closer to 1.0 (" $1/f$ or Pink Noise") have characteristics of both random and high correlations, indicating fractal heart dynamics. Values close to 1.5 ("Brownian Noise"; integration of "White Noise") are associated to signs with strongly correlated behavior^[1,14].

It was observed that an acceptable estimative of the scaling alpha exponent can be obtained from the analysis of a data set interval with only 256 intervals (equivalent to about 3.5 min RR data in a heart rate of 70 beats/min). Therefore, it would be expected that the analysis of RR data from an ECG recording period of 10 min, could provide an adequate measure of the scaling exponent. However, the alpha value obtained from this calculation can be under the influence of both the short-term level reflecting the parasympathetic control, as the long-term level reflecting the sympathetic control and therefore may fail to distinguish the completely parasympathetic and sympathetic influences. A separate analysis of both short-term scale and long-term should cancel the mutual effect and reveal the exact range of the scale. Thus, Roy and Ghatak (2013)^[15] proposed for analysis of the short-term component (α_1) to use using only 25 intervals and for the analysis of the long-term component (α_2) from 30 to N/4 intervals but this procedure has not been in widespread use. Buccelletti *et al.*^[2] (2012) when commenting on the method claim that "A singular ECG derivation is recorded continuously and the R-R distance is calculated in milliseconds until it is possible to get an amount of 8000 R-R (!),

that are necessary to assure an adequate interval of time". As can be noted, there are no consensus yet about the adequate interval to use.

Mäkikallio *et al.*^[16], 1998 showed that this dynamic fractal behavior of RR intervals, changes in patients with stable angina. They compared 38 consecutive patients with stable angina, with a control group detecting reduction of fractal correlation in the first group.

Analysis of the short-term fractal properties have also shown greater prognostic power compared to the conventional measurements in patients with acute myocardial infarction with or without depressed ventricular function^[17].

Mäkikallio TH *et al.* (1999) using traditional measurements of time and frequency domains beyond the analysis of short-term fractal properties studied 159 patients post myocardial infarction who had depressed ventricular function (EF < 35%) stating that at the end of four years of follow-up 72 patients had died (45%). The exponent alpha of short-term scale differed significantly when comparing the group who survived with the group who died (1.07 ± 0.26 vs 0.90 ± 0.26 ; $p < 0.001$) and none of the conventional variables was able to make that separation. Moreover, among all variables, the exponent α_1 at the cut-off < 0.85, was the best single predictor of mortality with a relative risk of 3.17 (95% CI 1.96 to 5.15; $p < 0.0001$) even after adjusting for multiple clinical variables^[18].

In obese children, reduction of α_1 values when compared to normal children may suggest an early loss of fractal dynamics and the consequent risk of future development of heart disease^[19].

Buccelletti *et al.*^[21] (2012) compared two groups of patients matched for age (57 ± 14 years versus 54 ± 20 years), formed respectively by 45 individuals who came to the Emergency Department for elucidation of chest pain and 20 seriously ill patients hospitalized in a ICU after open heart cardiac surgery or treatment of septic shock. These values were 0.98 ± 0.31 and 0.76 ± 0.43 for α_1 with 1.01 ± 0.09 and 0.99 ± 0.18 for α_2 , respectively.

Krstacic G *et al.* (2012) tested the applicability of nonlinear methods for HRV performance evaluation in patients with stress-induced cardiomyopathy (Takotsubo Syndrome or "Broken Heart Syndrome") whose pathogenesis is possibly related to acute release of large amounts of stress hormones leading to effect known as 'catecholamine induced myocardial stunning'. Twenty-five female patients (60.2 ± 8.3 years) with symptoms and signs of stress-induced cardiomyopathy, were identified and included in the study and the control group consisted of 50 randomly selected age-matched (mean age 63.1 ± 7.2 years) healthy women. The values found for α_1 and α_2 were 1.11 ± 0.05 and 1.18 ± 0.04 for the control group and 1.31 ± 0.06 and 1.25 ± 0.05 for the group with cardiomyopathy showing a fractal behavior in the controls and a trend to strongly correlated behavior in the study group^[19].

What one finds is that regardless of the studied disease or age, and even sample size and acquisition methodology, values that deviate from the normal value of 1.0 (increasing or decreasing) are associated with higher morbid gravity or worse prognosis revealing loss of fractal behavior toward random or strongly correlated behavior.

The above-cited methodological differences could explain some of the discrepancies between results found in several studies with the index pointing to the need for greater standardization aiming comparability of results.

1B. Fractal Dimension (FD)

Fractals are irregular elements that do not fit in any of the conventional geometric figures. As fractals are considered the clouds, mountains, coastlines, snowflakes and in the context of this topic, the contours of tachograms derived from the heartbeat of healthy or

diseased individuals.

One of the fundamental characteristics of fractals is their dimension, called fractal dimension (FD). It is a statistical measure based on an algorithm proposed by Katz in 1988^[20] which gives an indication of how fully a particular element fills the space in which it is located. In the case of an RR interval tachogram derived from the heartbeat, that algorithm describes the planar extension of the time series.

FD is a measure of the regularity of a signal. It corresponds to the self-similarity of the signal. Thus, the greater the value of fractal dimension more irregular will be the signal indicating increased complexity or how much the system has in terms of self-similarity. It has been linked to vagal modulation of heart rate^[5].

1C. Hurst Exponent (HE)

The Hurst exponent (HE) is a useful statistical method for inferring the properties of a time series without making assumptions about stationarity. Hurst exponent is responsible for a measure of predictability of a time series. Hurst exponent values range between zero and 1 with higher values indicating a smoother trend, less volatility, and less roughness. A value of 0.5 indicates a true random walk (a Brownian motion time series). In a random walk, there is no correlation between any elements and future element^[21].

An H exponent $\neq 0.5$ implies that the time series is fractal. Hurst exponent is related to the fractal self-similarity dimension (D) by the equation $H = 2 - D$. The method is shown to be robust even for relatively short time series (data length < 1,000), obtained from human subjects^[22-24].

Values $0 < H < 0.5$ indicates anti-persistent behavior, in that one can expect whatever direction of change is current, is unlikely to continue^[25]. In an anti-persistent time series (also known as a mean-reverting series) an increase will most likely be followed by a decrease or vice-versa (i.e., values will tend to revert to a mean). This means that future values have a tendency to return to a long-term mean. A value $0.5 < H < 1$ indicates persistent behavior. In a persistent time series, an increase in values will most likely be followed by an increase in the short term and a decrease in values will most likely be followed by another decrease in the short term. For pink noise, $H = 1$. H is directly related to fractal dimension, D, where $1 < D < 2$, such that $D = 2 - H$. Alternatively the local Hurst Exponent is related to the exponent α of the DFA method by the relationship $\alpha = 1 + H$ ^[26].

Krstacic G *et al.*^[19] (2012) testing the applicability of nonlinear methods for HRV performance evaluation in patients with stress-induced cardiomyopathy (Takotsubo Syndrome or "Broken Heart Syndrome") evaluated twenty-five female patients (60.2 ± 8.3 years) with symptoms and signs of stress-induced cardiomyopathy and 50 randomly selected age-matched (mean age 63.1 ± 7.2 years), healthy women, employing a measure of the Hurst exponent. The value found for the control group was 0.84 ± 0.05 and 0.58 ± 0.09 for the group with cardiomyopathy ($P < 0.001$). The findings are in agreement with the expected since Random Brownian motion produces the value $H = 0.5$ (uncorrelated events) and an exponent H other than 0.5 implies that the time series is fractal.

1D. Largest Lyapunov Exponent (LLE)

The Lyapunov exponent is a non-linear measure that quantifies how chaotic is the system. Presence of positive LLE Indicates chaotic system sensitive to the initial conditions. Periodic signals will have an exponent of zero. It has limited applicability because it requires the use of long and stable time series, which is often impossible to get in biological systems^[6,27].

The Lyapunov exponent Measures the "Butterfly Effect", or the changes in the final results in relation to changes in initial data, even though these are very small. Mathematically, the more the result is close to one, the greater the chaotic pattern (related to health and homeostasis), and the closer to zero, the greater is the linear pattern (related to disease).

Selig FA *et al* (2011) studied Heart Rate Variability in preterm (PTN) and term neonates (TN) using linear and nonlinear variables. Among the nonlinear variables, Lyapunov Exponent in PTN was significantly different from TN, with P -value < 0.001 . Still, regarding absolute values, the TN group had mean LE values closer to 1 than the PTN group; this fact is explained by the probable immaturity of the autonomic nervous system in the PTN group, with more linear time series than the term neonates^[28].

1E. Correlation Dimension (CD)

The correlation dimension gives the information about the number of independent functional components necessary to describe the underlying system and the degree of nonlinear coupling between these components. The correlation dimension is a measure that overcomes the limitations of the need for large time series since it allows evaluation of short series and also non-stationary^[6].

In biological systems, the higher the CD is, the more degrees of freedom the system has and, therefore, the greater range of possible adaptive responses are present. Correlation dimension is a useful measure of self-similarity of a signal. Correlation dimension will have higher value if RR intervals vary more and it decreases when autonomous balancing shifts towards sympathetic regulation.

There is also an inverse relationship with age with higher values in adolescent group (8 to 17 years) and lesser values starting with age group of 22 to 35 years due to increased sympathetic activity^[29].

2. INFORMATIONAL DOMAIN

A. Approximate Entropy (ApEn)

B. Sample Entropy (SampEntropy)

C. Shannon Entropy (ShanEntropy)

D. Multiscalar Entropy (MSE)

2A. Approximate Entropy (ApEn)

ApEn a widely used nonlinear tool to analyze biological data. It was proposed by Pincus SM (1991)^[30] and quantifies the likelihood that runs of patterns, which are close, will or not be followed by additional similar observations in subsequent incremental comparisons^[31-33].

In brief, given a time series with N points (SN), Approximate Entropy [ApEn(S_N, m, r)], is approximately equal to the negative average natural logarithm of the conditional probability that two sequences that are similar for m points (where m is called the embedding dimension) remain similar, within a tolerance r , at the next point^[31-32,34].

It can be used to assess the complexity, randomness or unpredictability of fluctuations in a time series. High values of ApEn indicate high irregularity and complexity in time-series data^[1,5].

ApEn lack two important expected properties. First, ApEn is heavily dependent on the record length and is uniformly lower than expected for short records. Second, it lacks relative consistency. That is, if ApEn of one data set is higher than that of another it may not remain higher for all conditions tested so causing difficulty when comparisons are needed^[6,34].

With regard to its relationship with the autonomic nervous system, it is said that ApEn is mostly linked with vagal modulation^[5].

Yeragani *et al*^[33] (2005) have shown that ApEn correlates significantly with the HF power time series and can be regarded as a nonlinear measure of cardiac vagal function.

Krstacic G *et al*^[19] (2012) studied with nonlinear methods the behavior of HRV in patients with stress-induced cardiomyopathy (Takotsubo Syndrome or "Broken Heart Syndrome") evaluating twenty-five female patients with Symptoms and signs of stress-induced cardiomyopathy and 50 randomly selected age- matched healthy women employing the measurement of approximate entropy. The value of ApEn found for the control group was 1.10 ± 0.11 and 0.92 ± 0.12 for the group with cardiomyopathy ($P < 0.001$). These findings agree with the expected since larger ApEn values correlate with increased complexity in the system.

2B. Sample Entropy (SampEntropy)

As mentioned above, the results for the Approximate Entropy rely heavily on the sample size and are relatively inconsistent. To circumvent these drawbacks Richman JS and JR Moorman (2000) developed a new related measure of time series regularity that they called sample entropy (SampEn)^[34].

SampEn displays the property of relative consistency in situations where ApEn does not. That is, if one record shows lower SampEn than another with one set of values of m and r , it also shows lower SampEn with different values.

Low SampEn characterizes regular time series, whereas high SampEn characterizes random time series.

Lake DE *et al*^[35] (2002) evaluated 89 infants admitted consecutively to the NICU over a period of 9 months with Sepsis or sepsis like illness. SampEn was significantly associated with upcoming sepsis and sepsis like illness (ROC area 0.64, 95% CI 0.56-0.74, $P = 0.001$). Moreover, SampEn significantly added diagnostic information to the variables gestational age and birth weight ($P < 0.001$).

Porta A *et al*^[36] (2007) studied SampEn during graded head-up tilt test in 17 healthy nonsmoking humans (age from 21 to 54 years, median = 28; 7 women and 10 men) over short heart period variability series (near 250 cardiac beats). They found that SampEn showed a progressive decrease of complexity as consequence of the tilt table inclination, producing a progressive shift of the sympathovagal balance toward sympathetic predominance through a sympathetic activation and vagal withdrawal.

Bay *et al*^[37] (2009) evaluated in sixteen healthy female college students with a mean \pm SD age of 23.8 ± 2.7 yrs. and body mass index of 20.8 ± 1.2 kg/m², complexity measures along with the spectral components of HRV during both the follicular phase (day 11.9 ± 1.4) and the luteal phase (day 22.0 ± 1.4). SampEn and high frequency (HF) components decreased from the follicular phase to the luteal phase, whereas normalized low frequency (LF) components and the LF-to-HF ratio as well as resting HR increased.

Mani *et al* (2009)^[38] studied eighty patients with cirrhosis [53 men, 27 women; mean (\pm 1SD) age 54 ± 10 year], classified as neuropsychiatrically unimpaired or as having minimal or overt hepatic encephalopathy, and 11 healthy subjects, using nonlinear analysis of HRV. They found significant reduction in SampEnt in liver disease group compared to healthy subjects (2.33 ± 0.67 versus 2.89 ± 0.52 ; $P < 0.01$) and association with the severity of the condition with SampEnt values in Child A, B and C respectively 2.47 ± 0.69 ; 2.14 ± 0.55 and 2.05 ± 0.60 .

The improved accuracy of SampEn statistics should make them useful in the study of experimental clinical and other biological time series.

2C. Shannon Entropy (ShanEntropy)

Shannon Entropy is usually estimated after the transformation of the dataset into bins or a symbolic sequence. Counting the relative frequency of each bin or word, the Shannon entropy will be equivalent to the sum of the relative frequencies weighted by the logarithm of the inverse of the relative frequencies (i.e. when the frequency is low, the weight is high, and vice versa)^[9].

However, when reading a paper about utilization of Shannon Entropy as a complexity measure we must be aware about the methodology of the data extraction. Therefore, when SE is derived from the Symbolic Dynamic Analysis method, it is true that the higher the values more complexity is present and from the clinical point of view, the more physiological are the conditions and probably healthier is the patient. In the other hand when SE is derived from the Recurrence Plot method, the higher are the values, the less complexity will be present and from the clinical point of view, less physiological will be the conditions and probably more diseased will be the patient. The explanation of this apparent paradox is the following: with Symbolic Dynamic, SE is a measure of the complexity of the possible “words” of the system and then, if we have more words we have more complexity. With Recurrence Plots, SE is a measure of the complexity of the “diagonals” present in the system and as diagonals are representing the determinism, the higher the values are, more determinism and so more linearity and less homeostasis.

To illustrate this different interpretation, we present below, the works of Guo R *et al.*^[38] (2002) and Kunz VC *et al.*^[39] (2011). In the first study, the authors compare, using Recurrence quantification analysis (RQA), the pulse morphological changes in 37 inpatients with coronary heart disease and 37 normal subjects. Shannon entropy of the frequency distribution of diagonal line lengths showed significantly higher values for patients with CHD (4.464 ± 0.194) than for normal subjects (4.262 ± 0.199 ; $P < 0.05$). In the second study, the authors compare, using Symbolic Analysis the presence of autonomic dysfunction in patients with coronary artery disease (CAD) and to compare them with normal subjects. A sample of 52 men (mean age 54 ± 5.39 years) was allocated into three groups: obstructive CAD $\geq 50\%$ (CAD+ $n = 18$), obstructive CAD $< 50\%$, (CAD- $n = 17$) and apparently healthy controls (CG $n = 17$). The CAD+ group presented lower SE values compared to CAD- and control groups (3.28, 3.51 and 3.53, respectively, $p < 0.05$).

CONCLUSION

It can be concluded that the analysis of HRV in the nonlinear domain provides very useful information to characterize the appropriate autonomic balance and is a more reliable marker of complications and mortality in patients with cardiovascular disease.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

- Voss A, Schulz S, Schroeder R, Baumert M, Caminal P. Methods derived from nonlinear dynamics for analysing heart rate variability. *Phil. Trans. R. Soc. A* 2009; **367**: 277-296; DOI: 10.1098/rsta.2008.0232;
- Buccelletti F, Bocci MG, Gilardi E, Fiore V, Calcinaro S, Fragnoli C, Maviglia R, Franceschi F. Linear and Nonlinear Heart Rate Variability Indexes in Clinical Practice. *Computational and Mathematical Methods in Medicine*, Article ID 219080, 5 pages, 2012. doi:10.1155/2012/219080).
- Sassi R, S Cerutti, Lombardi F, Malik M, Huikuri HV, Peng CK, Schmidt G, Yamamoto Y, Document Reviewers, Gorenek B, Lip GH, Grassi G, Kudaiberdieva G, Fisher JP, Zabel M, Macfadyen R. Advances in heart rate variability signal analysis: joint position statement by the e-Cardiology and the ESC Working Group European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. *Europace* DOI: <http://dx.doi.org/10.1093/europace/euv015> First published online: 15 July 2015
- Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. *Eur Heart J*. 1996 Mar; **17**(3): 354-381
- Beckers F, Verheyden B, Aubert AE. Aging and nonlinear heart rate control in a healthy population. *Am J Physiol Heart Circ Physiol* 20026; **290**: H2560–H2570, First published December 22, 2005; doi:10.1152/ajpheart.00903.2005.
- Huikuri HV, Mäkilä TH, Perkiömäki J. Measurement of heart rate variability by methods based on nonlinear dynamics. *J Electrocardiol*. 2003; **36**. Suppl: 95-99
- Meyerfeldt U, Wessel N, Schutt H, Selbig D, Schumann A, Voss A, Kurths J, Ziehmann C, Dietz R, Schirdewan A. Heart rate variability before the onset of ventricular tachycardia: differences between slow and fast arrhythmias. *Int J Cardiol*. 2002 Aug; **84**(2-3): 141-151
- Souza AC, Cisternas JR, de Abreu LC, Roque AL, Monteiro CB, Adami F, Vanderlei LC, Sousa FH, Ferreira LL, Valenti VE. Fractal correlation property of heart rate variability in response to the postural change maneuver in healthy women. *Int Arch Med*. 2014 May 15; **7**: 25. doi: 10.1186/1755-7682-7-25. eCollection 2014
- Bravi A, Longtin A, Seely AJE. Review and classification of variability analysis techniques with clinical applications. *Biomed Eng Online*. 2011; **10**: 90. Published online 2011 Oct 10. doi: 10.1186/1475-925X-10-90
- Vanderlei LCM, Pastre CM, Freitas Júnior IF, Godoy MF. Fractal correlation of heart rate variability in obese children. *Autonomic Neuroscience*. 2010; **155**(1-2): 125-129 doi:10.1016/j.autneu.2010.02.002
- Peng CK, Havlin S, Stanley HE, Goldberger AL. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos*. 1995; **5**(1): 82-87
- Penzel T, Kantelhardt JW, Grote L, Peter JH, Bunde A. Comparison of detrended fluctuation analysis and spectral analysis for heart rate variability in sleep and sleep apnea. *IEEE Transactions on Biomedical Engineering*. 2003; **50**: 1143-1151. doi: 10.1109/TBME.2003.817636. doi: 10.1063/1.166141
- Melillo P, Bracale M, Pecchia L. Nonlinear Heart Rate Variability features for real-life stress detection. Case study: students under stress due to university examination *Biomed Eng Online*. 2011; **10**: 96. Published online 2011 Nov 7. doi: 10.1186/1475-925X-10-96
- Stubsjoen SM, Bohlin J, Skjerve E, Valle PS, Zanella AJ. Applying fractal analysis to heart rate time series of sheep experiencing pain. *Physiology & Behavior*. 2010; **101**: 74-80
- Roy B, Ghatak S. Nonlinear Methods to Assess Changes in Heart Rate Variability in Type 2 Diabetic Patients *Arq Bras Cardiol* 2013; **101**(4): 317-327
- Mäkilä TH, Ristimäe T, Aeraksinen KEJ, Peng CK, Goldberger AL, Huikuri HV. Heart rate dynamics in patients with stable angina pectoris and utility of fractal and complexity measures. *Am J Cardiol* 1998; **81**: 27-31
- Tapanainen JM, Thomsen PE, Køber L, Torp-Pedersen C, Mäkilä TH, Still AM, Lindgren KS, Huikuri HV. Fractal analysis of heart rate variability and mortality after an acute myocardial infarction. *Am J Cardiol*. 2002 Aug 15; **90**(4): 347-352
- Mäkilä TH, Hoiber S, Køber L, Torp-Pedersen C, Peng CK, Goldberger AL, Huikuri HV. Fractal analysis of heart rate dy-

- namics as a predictor of mortality in patients with depressed left ventricular function after acute myocardial infarction. TRACE Investigators. TRAndolapril Cardiac Evaluation. *Am J Cardiol.* 1999 Mar 15; **83**(6): 836-9
- 19 Krstacic G, Parati G, Gamberger D, Castiglioni P, Krstacic A, Steiner R. Heart rate variability and nonlinear dynamic analysis in patients with stress-induced cardiomyopathy. *Medical & Biological Engineering & Computing.* 2012; **50**(10): 1037-1046.
- 20 Katz M. Fractals and the analysis of waveforms. *Comput Biol Med* 1988; **18**: 145-156
- 21 Mittal A. & Bhardwaj R. Predictability Index, Fractal Dimension And Hurst Exponent Estimation Of Indian Air Pollution Parameters. *International journal of Advanced Scientific and Technical Research.* 2011; **2**(1): 363-375
- 22 DePetrillo PB, Speers A, Ruttimann UE. Determining the Hurst exponent of fractal time series and its application to electrocardiographic analysis. *Computers in Biology and Medicine* 1999; **29**: 393-406
- 23 Sherman LD, Callaway CW, Menegazzi JJ. Ventricular fibrillation exhibits dynamical properties and self-similarity. *Resuscitation* 2000; **47**: 163-173
- 24 Das M, Gebber GL, Barman SM, Lewis CD. Fractal Properties of Sympathetic Nerve Discharge. *J Neurophysiol* 2003; **89**: 833-840
- 25 Kamalanand K & Jawahar PM. Predictability Analysis on HIV/AIDS System using Hurst Exponent. *International Journal of Medical and Biological Sciences.* 2012 <http://www.waset.org/journals/ijmbs/v6/v6-60.pdf>
- 26 Goldberger AL, Amaral LAN, Hausdorff JM, Ivanov PC, Peng C-K, Stanley HE. Fractal dynamics in physiology: Alterations with disease and aging. *PNAS* 2002; **99** (suppl 1): 2466-2472; doi:10.1073/pnas.012579499
- 27 Vuksanovic V, Gal V. Nonlinear and chaos characteristics of heart period time series: Healthy aging and postural change. *Autonomic Neuroscience: Basic and Clinical* 2005; **121**: 94-100)
- 28 Selig FA, Tonolli ER, Silva EVCM, Godoy MF. Heart rate variability in preterm and term neonates. *Arq. Bras. Cardiol.* 2011; **96**(6): <http://dx.doi.org/10.1590/S0066-782X2011005000059>
- 29 Koichubekov B, Korshukov I, Omarbekova N, Riklifs V, Sorokina M, Mkhitarian X. Computation of Nonlinear Parameters of Heart Rhythm Using Short Time ECG Segments. *Computational and Mathematical Methods in Medicine.* 2015, ID 983479, <http://dx.doi.org/10.1155/2015/983479>
- 30 Pincus SM. Approximate entropy as a measure of system complexity. *Proc. Natl. Acad. Sci. USA.* 1991; **88**: 2297-2301
- 31 Tarvainen MP. Approximate Entropy in Kubios HRV 2.2 User's Guide. http://kubios.uef.fi/media/Kubios_HRV_2.2_Users_Guide.pdf. 2014; 14-15.
- 32 Moody GB. Approximate Entropy (ApEn). [01/24/2015]. <http://www.physionet.org/physiotools/ApEn/>
- 33 Yeragani VK, Krishnan S, Engels HJ, Gretebeck R. Effects of caffeine on linear and nonlinear measures of heart rate variability before and after exercise. *Depression and Anxiety.* 2005; **21**: 130-134
- 34 Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *American Journal of Physiology - Heart and Circulatory Physiology* 2000; **278**(6): H2039-H2049
- 35 Lake DE, Richman JS, Griffin MP, Moorman JR. Sample entropy analysis of neonatal heart rate variability. *American Journal of Physiology - Regulatory, Integrative and Comparative Physiology.* 2002; **283**(3): R789-R797 DOI:10.1152/ajpregu.00069.2002
- 36 Porta A, Gnecchi-Ruscone T, Tobaldini E, Guzzetti S, Furlan R, Montano N. Progressive decrease of heart period variability entropy-based complexity during graded head-up tilt. *Journal of applied Physiology.* 2007; **103**(4): 1143-1149; DOI: 10.1152/jap-physiol.00293.2007
- 37 Bay X, Li J, Zhou L, Li X. Influence of the menstrual cycle on nonlinear properties of heart rate variability in young women. *American Journal of Physiology - Heart and Circulatory Physiology.* 2009; **297**(2): H765-H774 DOI: 10.1152/ajpheart.01283.2008
- 38 Guo R, Wang Y, Yan J, Yan H. Recurrence quantification analysis on pulse morphological changes in patients with coronary heart disease. *J Tradit Chin Med* 2012 December 15; **32**(4): 571-577
- 39 Kunz VC, Souza RB, Takahashi ACM, Catai AM, Silva E. The relationship between cardiac autonomic function and clinical and angiographic characteristics in patients with coronary artery disease. *Brazilian Journal of Physical Therapy.* 2011; **15**(6): 503-510. <http://dx.doi.org/10.1590/S1413-35552011005000020>

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