Heart Rate Variability and Pulmonary Infections after Myocardial Revascularization

Paulo Rogério Corrêa[1], Aparecida Maria Catai[2], Isabela T. Takakura[1], Maurício N. Machado[1], Moacir F. Godoy[3]

Fundação Faculdade Regional de Medicina de São José do Rio Preto - FUNFARME[1]; Universidade Federal de São Carlos - UFSCar[2]; Faculdade de Medicina de São José do Rio Preto - FAMERP[3], São Paulo - Brazil

Abstract

Background: **Heart rate variability (HRV) is a noninvasive diagnostic method used in the assessment of the autonomic modulation of the heart. The assessment of HRV using nonlinear dynamics methods in the preoperative period of surgical myocardial revascularization could be predictive of morbidity such as pulmonary infections in the postoperative period.**

Objective: **To evaluate the behavior of HRV using nonlinear dynamics in the preoperative period of surgical myocardial revascularization and its relation to the occurrence of pulmonary infections in the in-hospital postoperative period.**

Methods: **A total of 69 patients with coronary artery disease (mean age of 58.6 ± 10.4 years) and indication for elective surgical myocardial revascularization were studied. In order to quantify the nonlinear dynamics of HRV, the following procedures were performed: detrended fluctuation analysis (DFA); analysis of the short (α1) and long-term (α2) components of DFA; approximate entropy (ApEn); Lyapunov exponent (LE); and Hurst exponent (HE) of time series of RR intervals of the ECG, as captured by the Polar S810i instrument on the day before surgery.**

Results: **At the cut-off levels set by the ROC curve, there was a significant difference between the groups with and without pulmonary infections in the postoperative period of myocardial revascularization for total DFA, approximate entropy and Lyapunov exponent with p = 0. 0309, p = 0.0307 and p = 0.0006, respectively.**

Conclusion: **The nonlinear dynamics methods, at their respective cut-off levels, allowed for the identification of patients developing pulmonary infection in the postoperative period of surgical myocardial revascularization, thus suggesting that these methods may have a prognostic value for this group of patients. (Arq Bras Cardiol 2010; 95(4): 448-456)**

Key words: **Heart rate; lung diseases, fungal; postoperative complications; myocardial revascularization.**

Introduction

The heart rhythm in normal adults is not strictly regular, and shows periodical fluctuations known as heart rate variability (HRV)[1-3]. It behaves as complex deterministic nonlinear systems with a complex variability that follows the chaos theory and is modulated by the autonomic nervous system[4].

Several studies have applied the concept of nonlinear dynamics in an attempt to characterize changes and/or loss of body functions. Thus, the loss or reduction of HRV indirectly reflects the reduction in the chaotic behavior, which could translate into impaired homeostasis[5]. In adult individuals with heart diseases or those older than 70 years, there is a clear trend to a loss of HRV and, therefore, loss of the chaotic pattern[4,6] in favor of a linear behavior. Thus, changes in the cardiovascular autonomic function characterize adjuvant causes and/or conditions for numerous diseases[1,3].

Studies on HRV of patients undergoing surgical myocardial revascularization (SMR) showed that its reduction in the postoperative period is associated with a higher risk of complications such as arrhythmias and death[7,8]. Godoy et al's study[5], in turn, showed that the analysis of HRV in the nonlinear domain in the preoperative period of patients undergoing elective SMR makes it possible to detect subgroups at a high risk for postoperative complications, which makes this analysis a new tool for the prediction of clinical complications in the assessment of patients undergoing major surgeries.

Pulmonary changes resulting from cardiac surgery have been reported in the literature and may be attributed to factors such as pain, changes in the ventilatory mechanics secondary to sternotomy, and the harmful effects of general anesthesia[9,10].

However, we did not find studies in the literature reporting whether patients with loss of the chaotic behavior in the preoperative period of SMR tend to have a higher risk of pulmonary infections in the postoperative period.

Assuming that patients with decreased HRV, as assessed by

Mailing address: Paulo Rogério Corrêa •
Rua Duarte Pacheco, 1401/casa 26 - Higienópolis - 15085-140 - São José do Rio Preto, SP - Brazil
E-mail: paulocorre@gmail.com
Manuscript received December 4th, 2009; revised manuscript received February 18, 2010; accepted March 15, 2010.

chaos domain methods in the preoperative period of SMR, tend to have higher morbidity and mortality, the analysis of the chaotic behavior of individuals eligible for cardiac surgery may be of the utmost importance in the prediction of the risk of pulmonary infections in the postoperative period.

Thus, the objective of the present study was to evaluate the behavior of heart rate variability by means of nonlinear analysis in the preoperative period of SMR, and its relation to the occurrence of pulmonary infections in the postoperative period.

Patients and methods

Patients

A total of 69 unselected patients were included in the study; their mean age was 58.6 ± 10.4 years, and 43 (61.4%) were males. The inclusion criteria were patients diagnosed with coronary artery disease, normal sinus rhythm, and indication for elective SMR, whether on or off-pump. The surgeries were performed by the same team, at the Department of Cardiac Surgery of *Hospital de Base de São José do Rio Preto* - SP.

The study was explained to all patients, and they gave written informed consent. The protocol was approved by the Research Ethics Committee of *Faculdade de Medicina de São José do Rio Preto*, report no. 408/2004.

Methods

RR intervals recording

Electrocardiographic (ECG) RR intervals were captured and recorded for 30 minutes on the day before surgery, with the volunteers awake, at rest in the supine position, their hands along their bodies, and the upper body elevated at between 35 and 45 degrees. Recordings were made by the Polar™ Advanced S810i™ device. This device detects ECG RR intervals with a sampling frequency of 500 Hz, and time resolution of one millisecond (ms), and has already been validated[11,12].

The RR interval series were analyzed and premature beats and interferences were eliminated. Only recordings with more than 95% of qualified sinus rhythm were included in the analysis, the time series comprising 1,000 RR intervals.

Data processing

In order to quantify the nonlinear HRV dynamics, detrended fluctuation analysis (total DFA); analysis of the short ($\alpha 1$) and long-term ($\alpha 2$) components of DFA; approximate entropy (-ApEn); Lyapunov exponent (LE); and Hurst exponent (HE) were performed.

Detrended fluctuation analysis (total DFA)

This analysis quantifies the presence or absence of fractal correlation property of the RR intervals and has been validated for time series data. This measurement is partially related to changes in the spectral characteristic of the heart rate behavior[13]. In each segment, the short-term (4 to11 beats, $\alpha 1$) and the long-term scaling exponents (> 11 beats, $\alpha 2$) are assessed by DFA[14].

Approximate entropy (-ApEn)

Approximate entropy describes the predictability or randomness of physical systems that change with time: the higher the entropy value, the more complex is the process[15,16]; but we should point out the minus sign of the variable, i.e., the one actually corresponding to the so-called negentropy.

Lyapunov exponent (LE)

LE measures the system sensitivity to baseline conditions and the amount of a system's instability or predictability. The presence of a positive LE indicates chaos, whereas in linear systems there is a tendency to values close to zero[17].

Hurst exponent (HE)

HE evaluates the loss of the natural order of the intervals between beats as a result of the rupture of the natural quantitative relation between the spaces of all time series. HE values close to one quantitatively indicate a disordered state, whereas values close to zero indicate an ordered, harmonic or stable state (chaos)[18].

Demographic data, mechanical ventilation time, use of extracorporeal circulation, Additive EuroScore, Logistic EuroScore[19], and pulmonary infection index of the participants were also recorded in the postoperative period, in addition to the previously mentioned nonlinear behavior reference variables in the preoperative period. The Additive EuroScore and Logistic EuroScore values were recorded by the surgical team physician.

In the postoperative period, the occurrence of pulmonary infections was considered in patients whose chest radiography showed pulmonary infiltrates and/or presence of yellow sputum on tracheal aspirate with positive culture with cut-off (growth) of 10^6 cfu[20], and/or fever, and/or leukocytosis, and need for antibiotic therapy.

The analyses of nonlinear HRV dynamics were carried out using the CDA_PRO software and DFA. Cut-off points for sensitivity and specificity were set using the ROC (receiver operator characteristics) curve.

Statistical analysis

For the statistical analysis, Fisher's exact test was used to compare the occurrence of events. Quantitative variables with non-Gaussian distribution were compared using the Mann-Whitney non-parametric test. Sensitivity, specificity, positive predictive value, negative predictive value and odds ratio with 95.0% confidence interval for the occurrence of events were also recorded. An α error of 5.0% was considered acceptable, and the level of significance was set at $p \leq 0.05$.

Results

Clinical characteristics of the study participants

Demographics, clinical characteristics and postoperative complications of the study patients are shown in Table 1.

Table 1 - **Demographics, clinical characteristics and postoperative complications of patients undergoing on-pump or off-pump SMR**

Characteristics	Total	On-pump (n = 44)	Off-pump (n = 25)	p value
Age		58.6 (± 10.6)	58.5 (±10.1)	0.966
Gender		27 males and 17 fem.	16 males and 9 fem.	0.828
Comorbidities				
Diabetes mellitus	13	9	4	0.756
Hypertension	15	10	5	1.000
COPD	02	0	2	0.128
Clinical complications				
Neurological complications	03	3	0	0.549
Renal complications	13	10	3	0.349
Tachyarrhythmias	11	9	2	0.305
Death	6	6	0	0.080
Postoperative pulmonary infections	18	14	4	0.253

Of the 69 patients evaluated, 18 developed pulmonary infection in the postoperative period; these patients had a longer mechanical ventilation time (846.05 min) in comparison to those who did not develop pulmonary infection (594.26 min), p = 0.0173 (Figure 1).

Figure 2 shows the comparative analysis between mechanical ventilation time of the individuals undergoing on and off-pump SMR. Those undergoing on-pump SMR (n = 44) had a longer mechanical ventilation time in comparison to those undergoing off-pump SMR (n = 25), and the difference was statistically significant (p = 0.0078).

The joint analysis of the results of the assessment between mechanical ventilation time of the individuals undergoing on or off-pump SMR, and who developed or not pulmonary infections in the postoperative period is shown in Table 2.

The differences were not statistically significant.

Results of the surgical risk assessment using the variables Additive EuroScore and Logistic EuroScore among individuals with or without pulmonary infections in the postoperative period are shown in Table 3. No statistical difference was found between their mean values in individuals with or without pulmonary infection in the postoperative period of SMR; therefore, these variables were not considered significant predictors.

Data from the nonlinear heart rate variability analysis

Table 4 shows values of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), cut-off point, odds ratio, 95.0% CI and p for the following variables: Hurst exponent (HE); Lyapunov exponent (LE); approximate entropy (-ApEn); total DFA; short-term DFA component ($\alpha 1$); and long-term DFA component ($\alpha 2$) between the groups with or without pulmonary infections.

Cut-off values of LE ≤ 0.832, -ApEn ≤ 0.480 and total DFA ³ 1.036 can be observed in Figures 3, 4, 5 and 6. These variables were proven to be significant predictors of pulmonary infections in individuals in the postoperative period of surgical myocardial revascularization.

Discussion

In the present study, the nonlinear dynamics indexes at their respective cut-off levels allowed for the differentiation of cases that developed pulmonary infection in the postoperative period of surgical myocardial revascularization.

We point out that, to the best of our knowledge, this is the first study using nonlinear dynamics assessment tools as an object of prognostic information on the individual

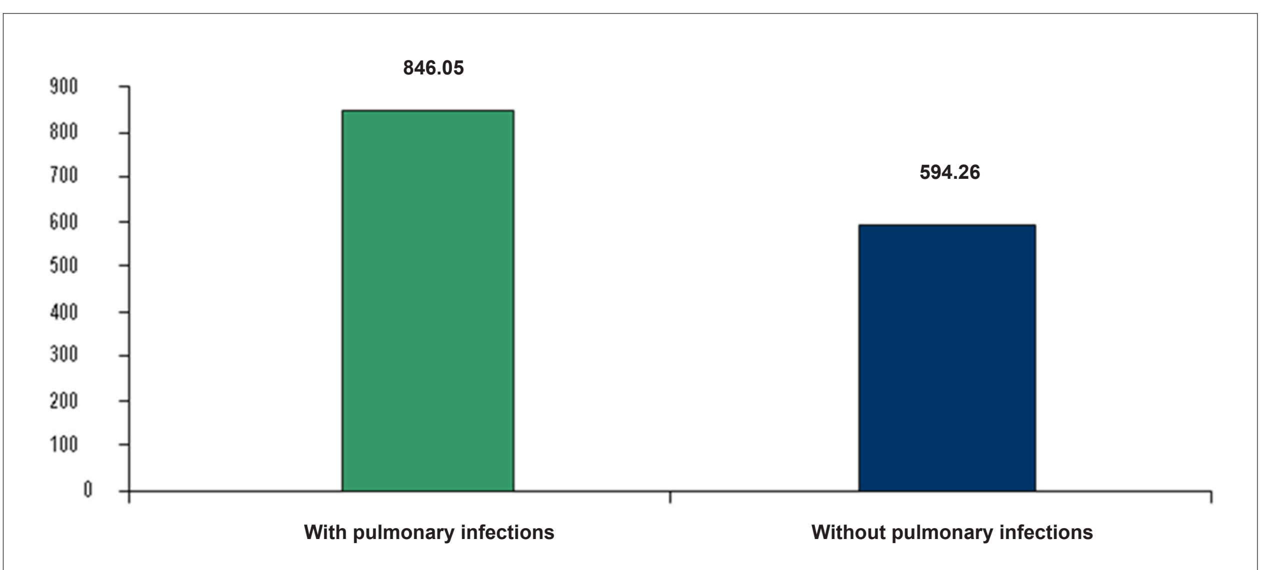

Figure 1 - Mechanical ventilation time (in minutes) and the presence of pulmonary infections.

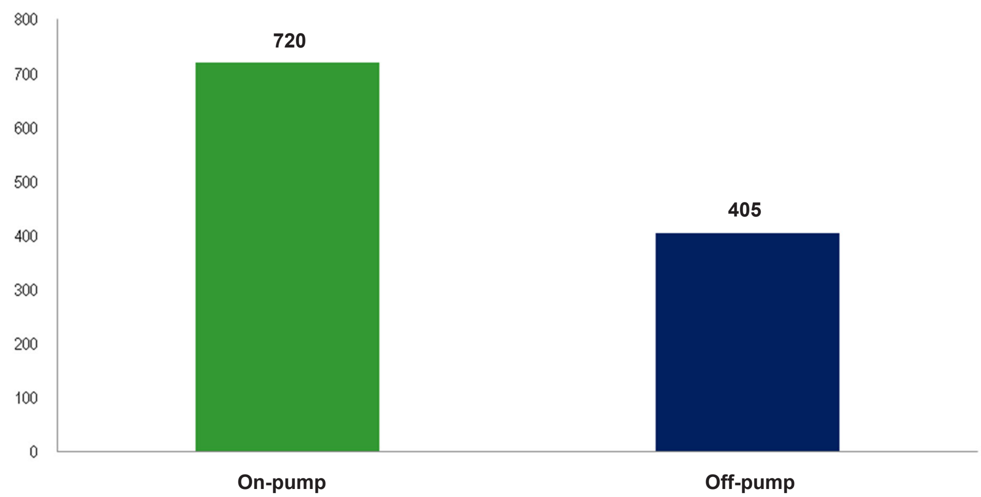

Figure 2 - Mechanical ventilation time (in minutes) of patients undergoing on-pump or off-pump myocardial revascularization.

Table 2 - Mean values of mechanical ventilation time of on-pump and off-pump SMR in individuals with or without pulmonary infection in the postoperative period

	With pulmonary infection	Without pulmonary infection	p value
MV time on-pump	725	705	0.3991
MV time off-pump	615	405	0.4487

MV - mechanical ventilation.

Table 3 - Mean values of the variables Additive EuroScore and Logistic EuroScore of individuals with or without pulmonary infection in the postoperative period of SMR

	With pulmonary infection	Without pulmonary infection	p value
Additive EuroScore	3	2	0.1486
Logistic EuroScore	2.16	1.81	0.1687

Table 4 - Sensitivity and specificity values; PPV; NPV; cut-off point; odds ratio; 95.0% CI, and p value of the variables Hurst exponent (HE); Lyapunov exponent (LE); approximate entropy (-ApEn), total DFA, short-term DFA component (α1); and long-term DFA component (α2) between the groups with or without pulmonary infections

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Cut-off	Odds ratio	95.0%CI	p value
Hurst exponent	0.6842	0.4528	0.3095	0.8000	≤ 0.210	1.793	0.5918 A 5.433	0.4173
Lyapunov exponent	0.6842	0.7736	0.5200	0.8723	≤ 0.832	7.403	2.316 A 23.661	0.0006
Approximate entropy	1.000	0.2075	0.3115	1.000	≤ 0.480	10.553	0.5909 A 188.45	0.0307
Total DFA	0.4737	0.8113	0.4737	0.8113	≥ 1.036	3.870	1.246 A 12.024	0.0309
DFA - short-term component (α1)	0.9474	0.2264	0.3051	0.9231	≥ 0.727	5.268	0.6359 A 43.648	0.1621
DFA - long-term component (α2)	0.6316	0.6226	0.3750	0.8250	≥ 0.906	2.829	0.9555 A 8.374	0.0655

Original Article

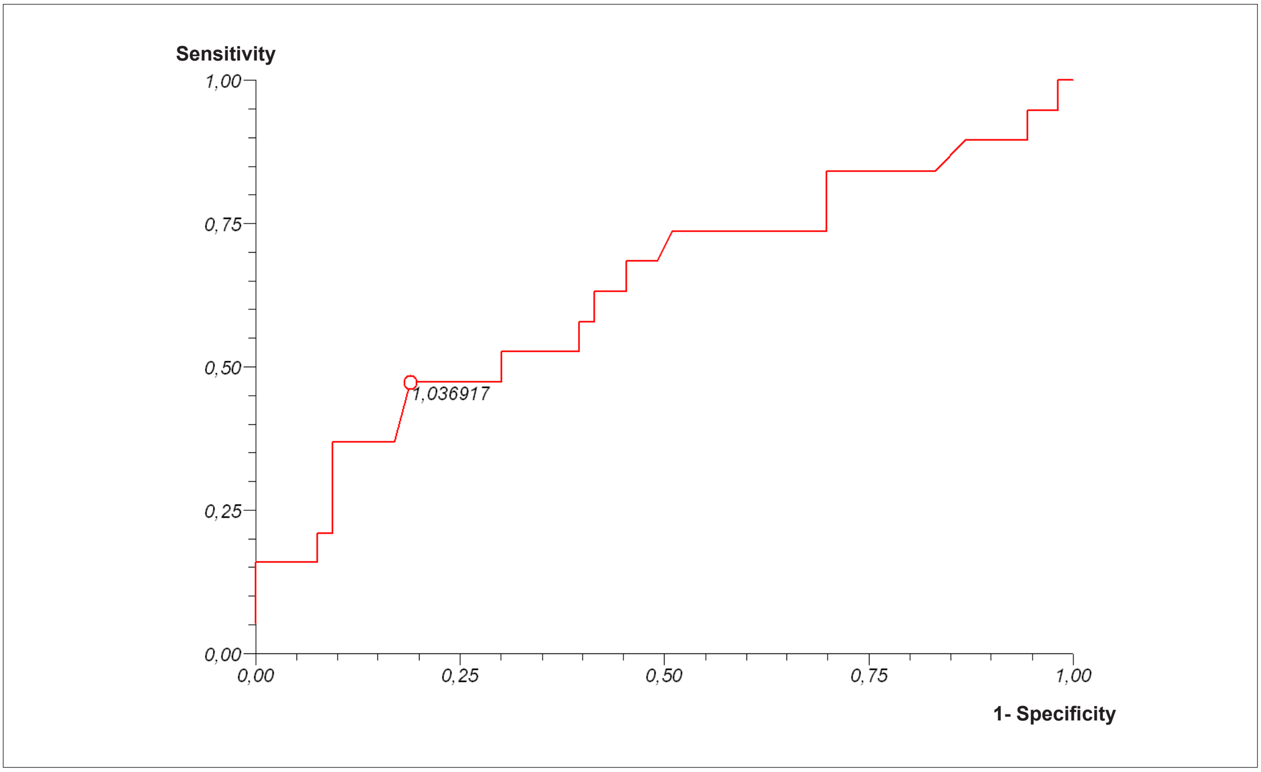

Figure 3 - Graphic representation of the ROC curve of detrended fluctuation analysis (total DFA).

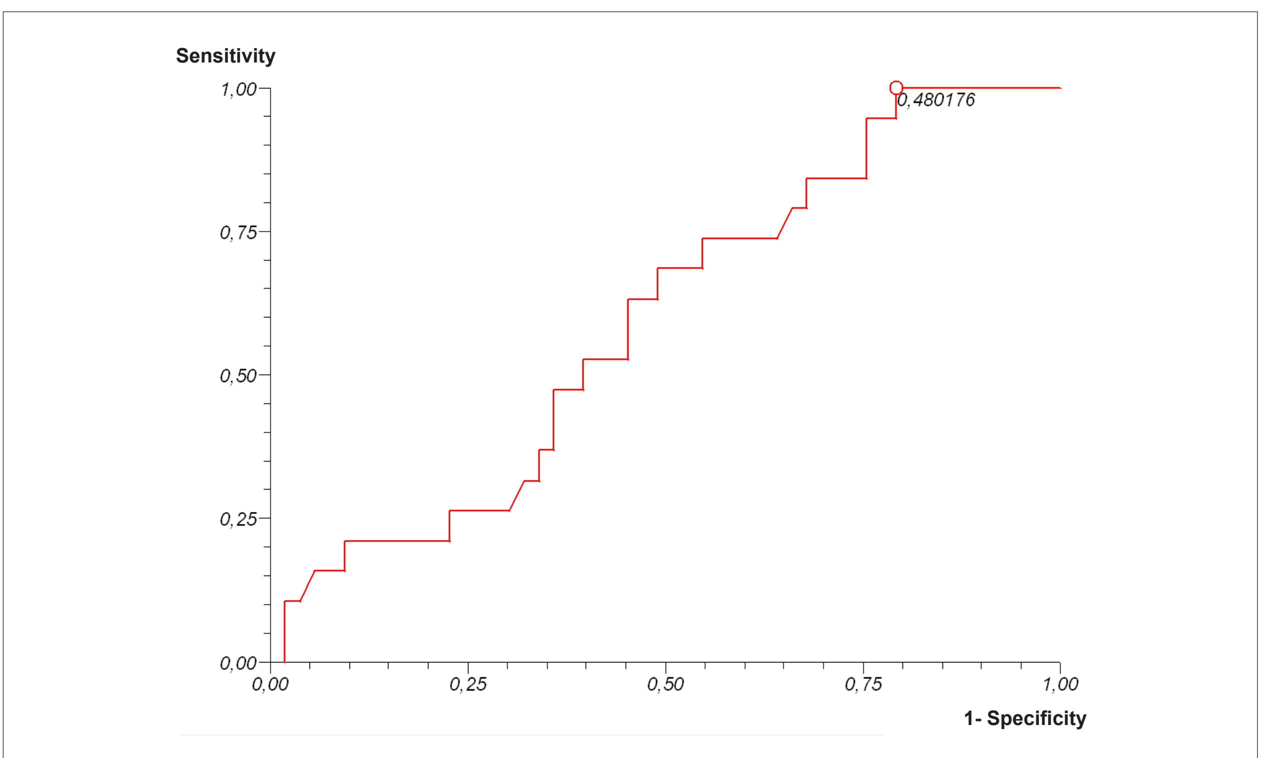

Figure 4 - Graphic representation of the ROC curve of approximate entropy (-ApEn).

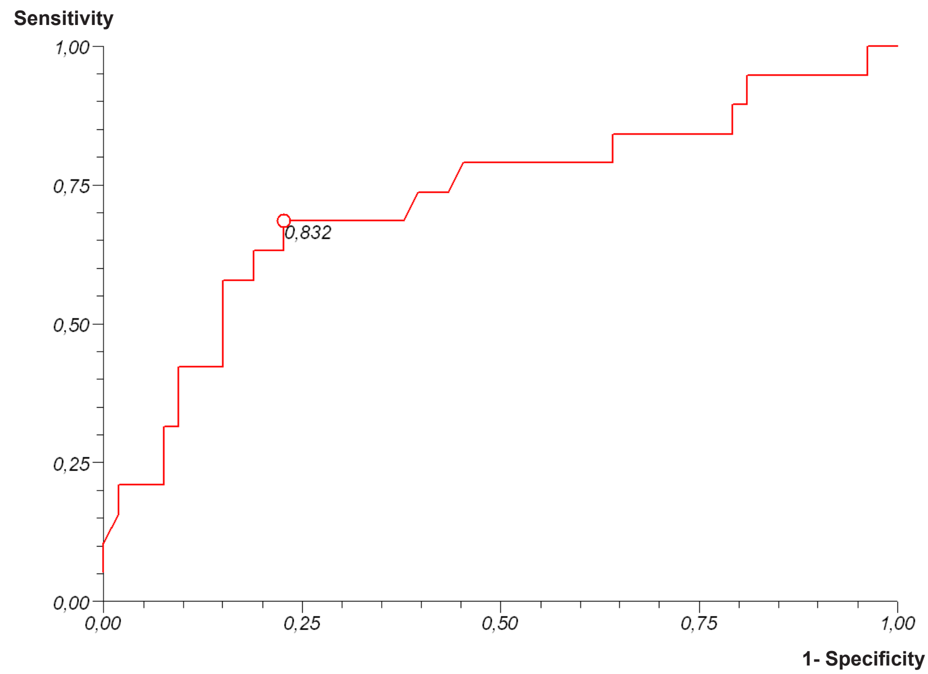

Figure 5 - Graphic representation of the ROC curve of the Lyapunov exponent (LE).

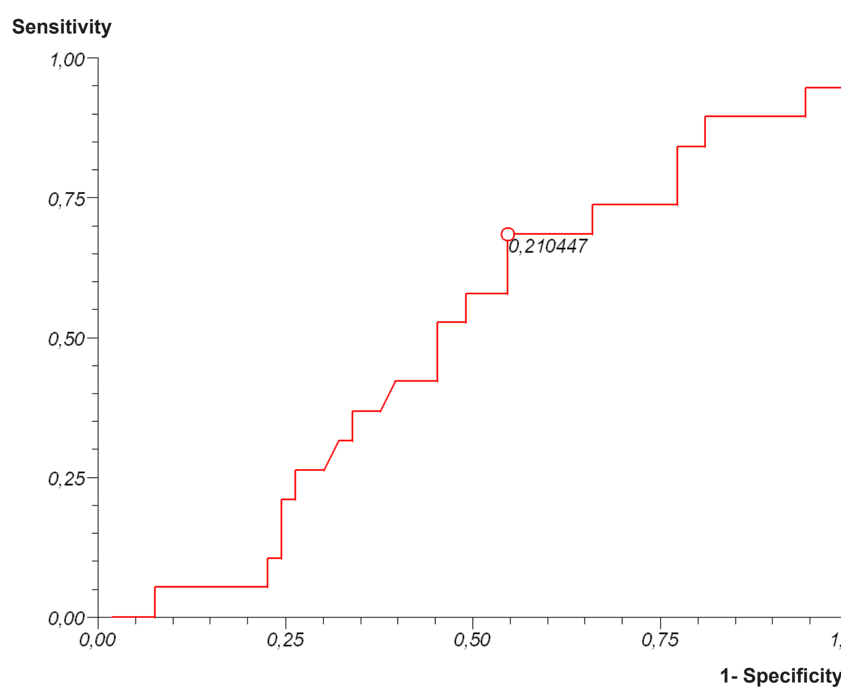

Figure 6 - Graphic representation of the ROC curve of the Hurst exponent (HE).

risk of the development of pulmonary infections in patients undergoing SMR.

Although several options are available for the treatment of coronary artery disease (CAD), surgical myocardial revascularization (SMR) has precise indications and provides favorable mid and long-term outcomes. Indications for SMR have been widely discussed based on clinical observations, and the outcomes and prognosis for these patients seem to be related to the presence of specific preoperative risk factors such as gender, age, presence of cardiogenic shock, and Q-wave infarction[21,22].

The only criterion for inclusion in the present study for all individuals evaluated in preoperative period was the elective indication for SMR; the level of postoperative risk was not used as an inclusion criterion.

The analysis of nonlinear heart rate variability dynamics has been used for risk stratification of mortality in patients with coronary artery disease with depressed left ventricular function following acute myocardial infarction[23]. In relation to HRV of patients undergoing surgical myocardial revascularization (SMR), in turn, studies have shown that its reduction in the postoperative period is associated with a higher risk of complications such as arrhythmias and death[7,8].

On the other hand, the recent Godoy et al's study[5] showed that the HRV analysis in the nonlinear domain in the preoperative period of patients undergoing elective SMR may detect subgroups at a high risk for postoperative complications.

In the present study, we verified that the nonlinear analyses of HRV indexes were adequate for the characterization of the presence or absence of pulmonary infections in the postoperative period of surgical myocardial revascularization.

Based on the cut-off levels determined by the ROC curve, significant differences could be observed between the groups with and without pulmonary infections in the postoperative period of surgical myocardial revascularization for the variables detrended fluctuation analysis (total DFA), approximate entropy, and Lyapunov exponent. There was no significant difference for the variables short-term ($\alpha 1$) and long-term ($\alpha 2$) DFA components, and Hurst exponent.

Total DFA quantifies the fractal properties of the time series. Values close to 1.0 indicate a chaotic behavior. Values close to 1.5 and 0.5 correspond to linearity and randomness, respectively[24]. Total DFA values showed statistically significant differences between the groups: they were close to 1.5 in the group with pulmonary infections, thus confirming what was theoretically expected for situations of loss of chaos and progression to linearity.

In relation to approximate entropy (-ApEn), it has been said that the more complex (chaotic) the series, the higher the -ApEn value, and the more regular and predictable the series, the lower the -ApEn value[15].

Our findings are consistent with these authors' observation, because values lower than or equal to 0.4802 were significantly associated with pulmonary infections in the postoperative period of myocardial revascularization. The approximate entropy (-ApEn) decreases with the loss of homeostasis or chaos, i.e., it gets closer to linear behaviors.

As regards the Lyapunov exponent (LE), higher values have been related to a chaotic behavior, and linearity shows a tendency to the value zero[17]. In our study, values lower than or equal to 0.832 in the preoperative period more frequently occurred in patients who developed pulmonary infections in the postoperative period of SMR.

This corroborates the importance of the use of nonlinear dynamics analysis in the prognostic assessment of morbid states, for its ability to evaluate the degree of loss of the patient's homeostatic behavior, considering the whole and not only the severity of the diseases alone.

In cardiac surgery, pulmonary changes deserve special attention because, except for underlying pulmonary diseases, factors such as pain, changes in the ventilatory mechanics secondary to sternotomy, and the harmful effects of general anesthesia are believed to contribute to changes in pulmonary function[9,10].

The *"Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia"*[25] report that, in mechanically ventilated patients, the occurrence of pneumonia increases with duration of ventilation. The risk of mechanical ventilation-associated pulmonary infection is higher in the first days of hospital stay and is estimated at 3% per day within the 5th to 10th day, dropping to 1% per day after the 10th day.

In this study, patients undergoing on-pump MR had a longer mechanical ventilation time, with a statistically significant difference; however, when a joint analysis of the mechanical ventilation time of individuals undergoing on and off-pump SMR, and with or without postoperative pulmonary infections was carried out , no statistically significant differences were observed.

Patients who developed postoperative pulmonary infections had a statistically significant longer mechanical ventilation time, not lasting more than two days, though. Nonetheless, the presence of pulmonary infections was not detected while the patients were on mechanical ventilation, but only when they had already resumed spontaneous breathing with the aid of a low-flow oxygen mask.

In this study, an important methodological parameter used in the identification of pulmonary infections was the result of the quantitative culture of tracheal aspirate (TA). Several studies have suggested that the diagnostic value of quantitative culture of TA may be the same as that of techniques using bronchoalveolar lavage and protected specimen brush[25].

Carvalho et al[20] reported that, for the diagnostic evaluation of pulmonary infections, clinical criteria and the progression of the radiographic infiltrate should be analyzed together, in association with the analysis of direct examination of a secretion specimen from the lower respiratory tract, and quantitative cultures of TA and/or bronchoalveolar lavage.

In the present study, in addition to the quantitative TA culture, the presence of lung infiltrates on chest radiography and/or use of specific antibiotic therapy, and/or presence or yellow secretion were analyzed. Thus, we consider that this analysis may indicate the presence or absence of pulmonary infection in the individuals assessed.

In the present study, we also evaluated the Additive and Logistic EuroScore, which are assessment systems of the cardiac surgery risk by means of a logistic model used as a significant predictor of mortality and postoperative complications both in the short and the long-term for hospitalized patients undergoing cardiac surgery intervention[19,26].

The questionnaires were administered by one single professional not related to the research as soon as the patient was admitted to the Intensive Care Unit. However, these indexes were not able to discriminate patients at a higher risk for pulmonary infections in the postoperative period of myocardial revascularization, thus corroborating the importance of the HRV analysis used in the present study.

As for the study limitations, we should mention the influence of drug therapy and its discontinuation on HRV because this situation was observed in the patients studied; also, the study sample was heterogeneous in terms of risk factors. Although we consider that the analysis of the influence on HRV of each risk factor individually is very important, this has proved impossible in the clinical practice, because the patients usually present with associated diseases and/or risk factors.

In conclusion, the nonlinear dynamics methods at their respective cut-off levels allowed for the identification of patients who developed pulmonary infection in the postoperative period of SMR. This identification seems to confirm that, by studying complex nonlinear dynamics systems, the Chaos Theory assesses the patients as a whole, determining the degree of loss of the homeostatic behavior and is, therefore, able to be applied for prognostic purposes in view of their global impairment.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of doctoral submitted by Paulo Rogério Corrêa, from *Faculdade de Medicina de São José do Rio Preto* - FAMERP.

Referências

1. Goldberger AI. Nonlinear dynamics, fractals, and chaos theory: Implications for neuroautonomic heart rate control in health and disease. Geneva: World Health Organization; 1999.
2. Reis AF, Bastos BG, Mesquita ET, Romeu Filho LJM, Nóbrega ACL. Disfunção parassimpática, variabilidade da frequência cardíaca e estimulação colinérgica após infarto agudo do miocárdio. Arq Bras Cardiol. 1998; 70 (3): 193-9.
3. Rossi BRO, Mazer D, Silveira LCR, Pelegrino CJ, Di Sacco THR, Blanco JHD, et al. The physical exercise attenuates the cardiac autonomic deficit induced by nitric oxide synthesis blockade. Arq Bras Cardiol. 2009; 92 (9): 32-8.
4. Sugihara G, Allan W, Sobel D, Allan K. Nonlinear control of heart rate variability in human infants. Proc Natl Acad Sci USA. 1996; 93 (6): 2608-13.
5. de Godoy MF, Takakura IT, Corrêa PR, Machado MN, Miranda RC, Brandi AC. Preoperative nonlinear behavior in heart rate variability predicts morbidity and mortality after coronary artery bypass graft surgery. Med Sci Monit. 2009; 45 (3): CR117-122.
6. Yambe T, Nanka S, Kobayashi S, Tanaka A, Owada N, Yoshizawa M, et al. Detection of the cardiac function by fractal dimension analysis. Artif Organs. 1999; 23 (8): 751-6.
7. Bronner F, Douchet MP, Quiring E, Charpentier A, Vi-Fane R, Eisenmann B, et al. Evolution de la vatiabilite de la frequence cardiaque après chirurgie cardiaque sous circulation extra – corporelle. Ann Cardiol Angeiol (Paris). 1998; 47 (8): 549-54.
8. Singh S, Jonhson PI, Lee RE, Orfei E, Lonchyna VA, Sullivan HJ, et al. Topography of cardiac ganglia in the adult human heart. J Thorac Cardiovasc Surg. 1996; 112 (4): 943-53.
9. Maciel SS, Cavalcanti ACW, Aristóteles LRC, Maciel AMS. Método fisioterapêutico de terapia intensiva no pós-operatório de revascularização miocárdica. Rev Bras Ciênc Saúde. 2003; 7 (1): 87-98.
10. Leguisamo CP, Kalil RAC, Furlani AP. Effectiveness of a preoperative physiotherapeutic approach in myocardial revascularization. Braz J Cardiovasc Surg. 2005; 20 (2): 134-41.
11. Ruha A, Sallinen S, Nissila S. A real-time microprocessor QRS detector system with a 1-ms timing accuracy for the mensurement of ambulatory HRV. IEE Trans Biomed Eng. 1997; 44 (3): 159-67.
12. Gamelin FX, Berthoin S, Bosquet L. Validity of polar S810i heart rate monitor to measure R-R intervals at rest. Med Sci Sports Exerc. 2006; 38 (5): 887-93.
13. Huikuri HV, Makikallio TH, Perkiomaki J. Measurement of heart rate variability by methods based on nonlinear dynamics. J Electrocardiol. 2003; 36 (Suppl): 95-9.
14. Fukuta H, Hayano J, Ishihara S, Sakata S, Ohte N, Takahashi H, et al. Prognostic value of nonlinear heart rate dynamics in hemodialysis patients with coronary artery disease. Kidney Int. 2003; 64 (2): 641-8.
15. Pincus SM, Huang WM. Approximate entropy: statistical properties and applications. Commun Statist Theory Meth. 1992; 21: 3061-77.
16. Brown LK. Entropy isn't what it used to be. Chest. 2003; 123 (1): 9-11.
17. Yeragani KV, Rao KARK, Smitha MR, Pohl RB, Balon R, Srinivasan K. Diminished chaos of heart rate time series in patients with major depression. Biol Psychiatry. 2002; 51 (9): 733-44.
18. Dioguardi N, Grizzi F, Franceschini B, Bossi P, Russo C. Liver fibrosis and tissue architectural change measurement using fractal-rectified metrics and Hurst's exponent. World J Gastroenterol. 2006; 12 (14): 2187-94.
19. Roques S, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J. 2003; 24: 881-2.
20. Carvalho MVCF, Winkfler GFP, Costa FAM, Bandeira TJG, Pereira EDB, Holanda MA. Concordance between tracheal aspirative and bronchoalveolar lavage in the diagnosis of ventilador associated pneumonia. J Bras Pneumol. 2004; 30 (1): 26-38.
21. Almeida RMS, Lima Jr JD, Martins JF, Loures DRR. Revascularização do miocárdio em pacientes após a oitava década de vida. Rev Bras Cir Cardiovasc. 2002; 17 (2): 8-14.
22. Jatene FB, Nicolau JC, Hueb AC, Atik FA, Barafiole LM, Murta CB, et al. Fatores prognósticos da revascularização na fase aguda do infarto agudo do miocárdio. Rev Bras Cir Cardiovasc 2001; 16 (3): 195-202.
23. Stein PK, Reddy A. Non-linear heart rate variability and risk stratification in

cardiovascular disease. Indian Pacing Electrophysiol J. 2005; 5 (3): 210-20.

24. Acharya RU, Lim CM, Joseph P. Heart rate variability analysis using correlation dimension and detrended fluctuation analysis. ITBM-RBM. 2002; 23: 333-9.

25. American Thoracic Society Documents. Guidelines for the management of adults with hospital-acquired, ventilador-associated, and healthcare-associated pneumonia. AM J Respir Crit Care Med. 2005; 171 (4): 388-416.

26. Lafuente S, Trilla A, Bruni L, Gonzalez R, Bertran MJ, Pomar JL, et al. Validation of the EuroSCORE probabilistic model in patients undergoing coronary bypass grafting. Rev Esp Cardiol. 2008; 61 (6): 589-94.