

Autonomic modulation of chronic kidney patients on hemodialysis

Modulação autonômica de pacientes renais crônicos em hemodiálise

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Abstract

Chronic kidney Disease may progress to cardiovascular complications just as much as these complications can result in further deterioration of the renal function, with dialysis as an extreme therapeutical option. Heart Rate Variability is a noninvasive method for the evaluation of sympathovagal imbalance of the heart beat control, aiding on the early detection of cardiovascular malfunctions. Our purpose was to identify heart rate variability patterns in chronic kidney disease patients undergoing hemodialysis treatment, both by linear and nonlinear analysis. Were sampled a group of 27 renal failure patients under hemodialysis care, and a control group of 21 healthy individuals. The RR intervals were captured with a Polar® device from subjects lying in supine position for 20 minutes. A total of 1000 consecutive intervals were selected, and both linear and nonlinear parameters were considered for the heart rate variability analysis. Were used Shapiro-Wilk test, Mann-Whitney test, and Spearman test. Among the findings with statistical significance, reductions were found in RMSSD and pNN50, and SD1 and SD2 indexes whereas increases in the recurrence percentage and in entropy could be observed. A significant negative correlation between age and the values of SD1 index was also found. Patients with renal failure present a lower autonomic modulation of the parasympathetic branch, as highlighted by both the linear and nonlinear analysis. The nonlinear indexes in the Chaos domain were more precise in identifying autonomic dysfunctions, can reflect more clearly the complexity of the organic systems.

Keywords: Heart rate variability; Autonomic Nervous System; Chronic Kidney Disease; Dialysis.

Resumo

A doença renal crônica pode evoluir para complicações cardiovasculares e essas complicações podem resultar em maior deterioração da função renal, sendo a diálise uma opção terapêutica extrema. A Variabilidade da Frequência Cardíaca é um método não invasivo para avaliação do desequilíbrio simpato-vagal do controle dos batimentos cardíacos, auxiliando na detecção precoce de disfunções cardiovasculares. O objetivo foi identificar padrões de variabilidade da frequência cardíaca em pacientes com doença renal crônica em tratamento hemodialítico, tanto por análise linear quanto não linear. Foram amostrados um grupo de 27 pacientes com insuficiência renal em tratamento de hemodiálise e um grupo controle de 21 indivíduos saudáveis. Os intervalos RR foram capturados com um aparelho Polar® com indivíduos em decúbito dorsal por 20 minutos. Um total de 1.000 intervalos consecutivos foram selecionados e parâmetros lineares e não lineares foram considerados para a análise. Foram utilizados o teste de Shapiro-Wilk, o teste de Mann-Whitney e o teste de Spearman. Entre os achados com significância estatística, foram encontradas reduções nos índices RMSSD e pNN50, e nos índices SD1 e SD2, ao passo que se observaram aumentos

na porcentagem de recorrência e na entropia. Há uma correlação negativa significativa entre a idade e os valores do índice SD1. Pacientes com insuficiência renal apresentam menor modulação autonômica do ramo parassimpático. Os índices não lineares no domínio Caos foram mais precisos na identificação de disfunções autonômicas, refletindo melhor a complexidade dos sistemas orgânicos.

Palavras-chave: Variabilidade da frequência cardíaca; Sistema Nervoso Autônomo; Doença Renal Crônica; Diálise.

Resumen

La enfermedad renal crónica puede progresar a complicaciones cardiovasculares y estas complicaciones pueden resultar en un mayor deterioro de la función renal, siendo la diálisis una opción terapéutica extrema. La variabilidad de la frecuencia cardíaca es un método no invasivo para evaluar el desequilibrio simpátovagal en el control de la frecuencia cardíaca, lo que ayuda a la detección temprana de trastornos cardiovasculares. El objetivo fue identificar patrones de variabilidad de la frecuencia cardíaca en pacientes con enfermedad renal crónica en hemodiálisis, tanto mediante análisis lineal como no lineal. Se muestreó un grupo de 27 pacientes con insuficiencia renal en hemodiálisis y un grupo control de 21 individuos sanos. Los intervalos RR se capturaron con un dispositivo Polar® con los sujetos en posición supina durante 20 minutos. Se seleccionaron un total de 1000 intervalos consecutivos y se consideraron parámetros lineales y no lineales para el análisis. Se utilizaron la prueba de Shapiro-Wilk, la prueba de Mann-Whitney y la prueba de Spearman. Entre los hallazgos estadísticamente significativos, se encontraron reducciones en los índices RMSSD y pNN50, y en los índices SD1 y SD2, mientras que se observaron aumentos en el porcentaje de recurrencia y entropía. Existe una correlación negativa significativa entre la edad y los valores del índice SD1. Los pacientes con insuficiencia renal tienen menor modulación autonómica de la rama parasimpática. Los índices no lineales en el dominio Caos fueron más precisos en la identificación de disfunciones autonómicas, reflejando mejor la complejidad de los sistemas orgánicos.

Palabras clave: Variabilidad de la frecuencia cardíaca; Sistema Nervioso Autônomo; Enfermedad Renal Crónica; Diálisis.

1. Introduction

Chronic Kidney Disease (CKD) it is currently defined as the presence of alterations in the structure or function of the kidneys, for more than three months, compromising health. The main problems in patients with CKD are its complications resulting from the functional loss of the kidneys, renal failure (RF) - more advanced stage, and death (mainly from cardiovascular events) (Porto, et al., 2017). This condition is currently considered one of the most relevant health issues in the world. Dialysis is one of the possible therapeutic approaches for RF, and according to the Brazilian Dialysis Census in 2020 there were about one hundred and thirty three thousand people in treatment.

Patients with RF have a higher risk of cardiovascular complications, especially those in dialysis. They are also more prone to develop heart arrhythmias secondary to autonomic dysfunction, as shown by the reduction in the heart rate variability (HRV) (Chandra, et al., 2012).

The autonomic nervous system, through two antagonistic systems (the sympathetic and the parasympathetic), is essential for body homeostasis, maintaining the body's balance (Task, 1996). Autonomic dysfunction is due to alteration of autonomic function in a way that adversely affects health (Angelis, et al., 2004). So, oscillation between a normal heart rhythm, known as Heart Rate Variability (HRV), has been considered a marker of body homeostasis (Vanderlei, et al., 2009; Shaffer, 2014).

Considering the importance of HRV as an indicator of cardiac autonomic activity and also as a clinical tool to evaluate and identify health problems, its analysis may offer important physiological information, both in diagnostic and prognostic terms, which may be used by health professionals dealing with varied clinical conditions (Schroeden et al., 2003).

One of the elements responsible for homeostasis lies on the adequate balance of the sympathetic-parasympathetic branches of the ANS. Many reports suggest that an autonomic dysfunction promotes a loss in the chaotic behavior of the organism and a more linear behavior (Ferreira et al., 2009).

Thus, the aim of this work was to identify HRV patterns in time, frequency and nonlinear domains in patients with RF undergoing dialysis therapy, and compare them with healthy subjects to emphasize the relevance of HRV variables in the early evaluation of patients with kidney disease.

2. Methodology

This is a descriptive, quantitative and cross-sectional study. A convenience sampling ($N = 32$) corresponding to a renal failure group (RFG) was selected with RF patients undergoing dialysis treatment in the Kidney Transplantation Unit at the Clinical Hospital of the Federal University in Uberaba (Brazil). From these, four patients were excluded from the sample for reasons such as death, smoking habits and refusal to participate in the study

The RFG was composed of 27 patients (12 females and 15 males; 47.4 ± 16.2 years old), who observed the inclusion criteria: diagnosis of RF, undergoing hemodialysis treatment three times per week for at least six months, with clinical and hemodynamic stability, and no regular physical activities.

The control group (CG) consisted of 21 individuals (12 females e 9 males; 42.2 ± 11.6 years), with adequate renal function, with no cardiovascular or respiratory condition and no osteomyoarticular or metabolic disease. Also, participants from the CG were nonsmokers who were not undergoing any kind of pharmacological treatment and were not practicing regular physical activities.

Participants from both groups signed a voluntary consent, in accordance with the Resolution 266/2012 from the National Council of Health. The study was approved by the Human Research Ethics Committee (2075/2011).

HRV measures were registered in a rest, supine position, with spontaneous breathing, avoiding both excessive body movements and talking during the registration. For the RFG, registration was performed before the dialysis procedure.

The R-R intervals (iR-R) and the heart rate were registered beat to beat during 20 minutes with a Polar® device (RS800CX model) (Quintana, Heathers & Kemp 2012). The time series were digitally filtered in order to eliminate premature and/or ectopic beats, as well as noises, and then followed by manual reanalysis for the exclusion of residual artifacts. For the final analysis, 1000 iR-R from consecutive beats were selected from temporal series with more than 95% of sinus beats (Santos et al., 2016). The signal processing was performed by ‘Kubios HRV’ and ‘Visual Recurrence Analysis’ softwares.

The analysis of HRV was performed for both linear and nonlinear measures. The linear index in the time domain were the square root of mean squared differences of successive NN intervals (RMSSD) and the division of the number of interval differences of successive NN intervals greater than 50 ms by number of NN intervals (pNN50). In the frequency domain, the spectral densities of high (HF) and low (LF) frequencies, and the LF/HF ratio were considered. As for the nonlinear indexes, we had the recurrence percentage (%REC), qualitative and quantitative analysis of the Poincaré Plot (SD1, SD2) and Shannon Entropy.

At first, data were analyzed by the Shapiro-Wilk test for normal distribution. The comparison of data was accomplished by Mann-Whitney nonparametric test, and Spearman test was used for nonparametric correlations.

The analysis and the graphic representations were achieved through *Statistica 7.0* and *SPSS 17.0* softwares, considering a significance level of 5%.

3. Results

There was no significant statistical difference ($P=0.22$) between ages in the two groups. The RFG presented 51.8 ± 41.9 months of hemodialysis treatment, creatinine level of 10.8 ± 4.9 mg/dL, glycemic level of 147.3 ± 63.9 mg/dL. For RFG, the body weight at pre dialysis was 68.0 ± 14.0 kg and at post dialysis was 65.2 ± 14.6 kg.

When HRV was analyzed in the linear domain, the values for RMSSD and pNN50 indicate an improved heart autonomic modulation for the CG when compared to the RFG, i.e., the patients with renal disease present a lower parasympathetic autonomic modulation (Table 1).

Table 1. Median values for HRV linear and nonlinear indexes in patients (RFG) and control group (CG).

Linear Indexes	RFG	CG	p
	Md	Md	
RMSSD (ms)	7.1	23.6	0.000005*
pNN50 (%)	0.0	2.1	0.000005*
HF Spectral Density (nu)	29.7	36.0	0.99
LF Spectral Density (nu)	70.3	63.9	0.97
LF/HF ratio	2.36	1.77	0.25
Nonlinear indexes	RFG	CG	p
%REC	42.0	39.7	0.03*
Shannon Entropy (bits)	5.03	4.69	0.01*
SD1 (ms)	5.00	16.7	0.000002*
SD2 (ms)	20.2	49.4	0.000008*

CG- control group; HF- high frequency component; HRV- Heart Rate Variability; LF- low frequency component; Md- median; nu- normalized unities; p- level of significance; pNN50- division of the number of interval differences of successive NN intervals greater than 50 ms by number of NN intervals (%); RFG- group for chronic renal failure; RMSSD- square root of mean squared differences of successive NN intervals (ms); ms- millisecond; RFG- group for chronic renal failure; SD1- short term dispersion; SD2- long term dispersion; *statistically significant difference; %REC- recurrence percentage. p- level of significance; *statistically significant difference. Source: Authors.

For the nonlinear domain, we noticed that the RFG had a low parasympathetic heart modulation, indicated by the lower HRV and represented by a higher recurrence percentage (REC%), higher entropy and lower values for SD1 and SD2, as presented in Table 1.

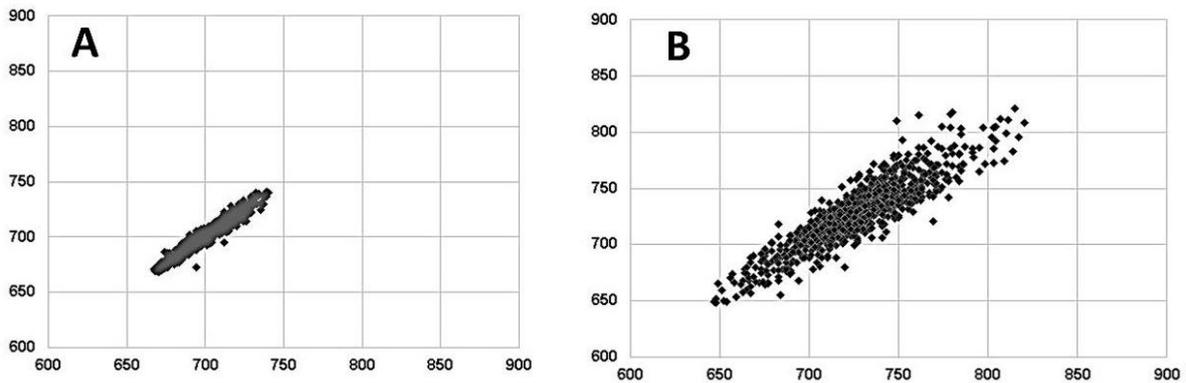
Correlation tests were performed for age, time under dialysis treatment and HRV indexes for the RFG. Significant negative correlation was observed between age and SD1 results ($r = -0,33$, $P=0,02$). Time under treatment had no correlation with HRV indexes. Correlations concerning linear and nonlinear HRV indexes are shown in Table 2.

Table 2. Correlation coefficients and levels of significance for HRV in the RFG.

Correlations for Variables	R	P
RMSSD x %REC	- 0.639	0.000*
RMSSD x Entropy	- 0.698	0.000*
RMSSD x SD1	0.990	0.000*
RMSSD x SD2	0.790	0.000*
pNN50 x %REC	- 0.422	0.003*
pNN50 x Entropy	- 0.479	0.001*
pNN50 x SD1	0.918	0.000*
pNN50 x SD2	0.789	0.000*
%REC x SD1	- 0.632	0.000*
%REC x SD2	- 0.218	0.155
Entropy x SD1	- 0.697	0.000*
Entropy x SD2	- 0.295	0.052

p- level of significance; pNN50- division of the number of interval differences of successive NN intervals greater than 50 ms by number of NN intervals (%); r- correlation coefficient ; RMSSD- square root of mean squared differences of successive NN intervals (ms); SD1- short term dispersion; SD2= long term dispersion; *statistically significant difference; %REC- recurrence percentage. Source: Authors. Source: Authors.

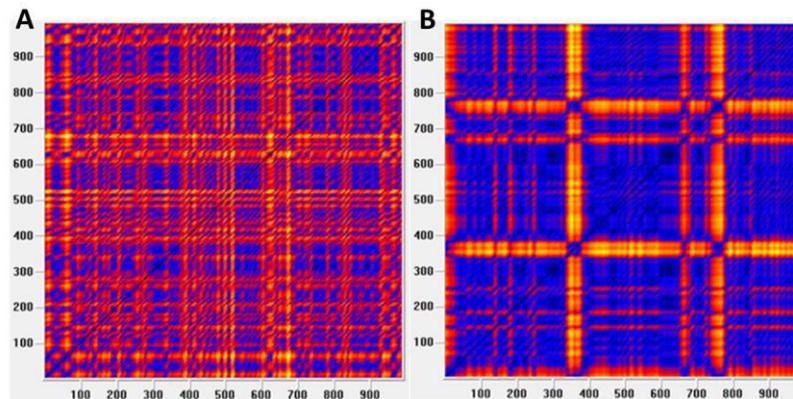
Figure 1.



Source: Authors.

Figure 1A represents the visual pattern for the Poincaré plot corresponding to a subject from the RFG, with a less dispersed distribution of the plotted points (torpedo pattern plot). while Figure 1B represents the visual pattern for the Poincaré plot corresponding to a subject from the CG, with a noticeably augmented dispersion for the iR-R plotted points (comet pattern plot).

Figure 2.



Source: Authors.

Figure 2A represents the visual pattern for the Recurrence Plot corresponding to a subject from the CG, where a more diffuse pattern indicates a low recurrence behavior and a better functioning. Figure 2B represents a patient from the RFG, clearly showing the presence of a mosaic and repetitive pattern, which indicates higher linearity, coherent with an unhealthy condition and dysfunction.

4. Discussion

The present study investigated the autonomic behavior from renal failure patients under haemodialysis treatment (RFG) compared to healthy subjects with the same age (CG). The main findings concerning the RFG were 1) significant reductions in RMSSD and pNN50; 2) significantly augmented recurrence percentage and Shannon entropy, and significantly reduced SD1 and SD2 indexes; 3) significant negative correlation between age and SD1 index, i.e., lower SD1 values correlating with older subjects, indicating a poorer parasympathetic heart modulation.

Patients with CKD have a high prevalence of death from cardiovascular events, with higher mortality in the dialysis stage, in which an autonomic imbalance is evidenced (Bardaran et al., 2015). Linear and non-linear HRV analysis is an important tool for assessing cardiac autonomic function, thus enabling early prognosis and preventive therapeutic interventions to prevent future cardiovascular events in this population (Chiang et al, 2016 & Rodrigues et al 2021).

RMMSD and pNN50 indexes represent the vagal heart modulation, suggesting that individuals under haemodialysis treatment may present some degree of impairment related with the parasympathetic branch of the ANS activity. Reduction of parasympathetic activity was evidenced by low values of RMMSD and HF indexes, also verified by Ferreira, et al. (2009)

According to Schlaich et al (2009), the low HRV may be a marker of sympathetic activation, directly related to adverse outcomes for the RFG, such as elevation on atherosclerosis, vasoconstriction, arrhythmias, sodium retention, renin liberation and raise in blood pressure. Results in this direction have been found by Drawz, et al. (2013), who reported lower HRV associated to multiple cardiovascular risk factors for CKD. They also describe RMSSD as an independent predictor for mortality. This same study also stated that reduction in HRV was associated with higher phosphorus levels in CKD patients. Effects of elevated phosphorus on HRV may be mediated by vascular calcification and arterial rigidity, which are associated with a reduction of baroreflex sensitivity, resulting in a raise of arterial blood pressure (Okada, et al., 2012).

It should be noted that the length of time under hemodialysis treatment has not presented significant correlation with the HRV indexes, indicating that a low HRV is not dependent on the time of exposure to this mode of therapy. It suggests that

the sole presence of RF may determine damage in cardiac autonomic balance, in the same way this damage can result from ageing.

Studies dealing with HRV in CKD patients present a restricted number of papers addressing nonlinear analysis of HRV. In our study, nonlinear indexes were considered. Recurrence percentage and Shannon entropy evaluated the complexity in cardiac autonomic modulation, and SD1 and SD2 indexes represented the complexity by the global variability (SD2) and by parasympathetic modulation (SD1). Chiang, et al. (2016) reported that an impaired cardiac autonomic modulation was observed when HRV nonlinear indexes were compared to linear indexes. In our study, linear indexes haven't shown sensibility to detect alterations in the autonomic modulation for CKD patients.

Considering nonlinear indexes, Recurrence percentage and Shannon entropy have shown, with statistical significance, higher values for the RFG ($P=0.03$ and $P=0.01$, respectively). Higher values for entropy indicate a higher determinism, i.e., a more linear behavior with less variability (Kowidi, et al., 2010). Variability is the basic condition which allows a living cell to dynamically respond to the challenges of the environment, in a self-organized process, swinging between destruction and rebuilding.

The human body may be understood as an extremely sensible mechanism, with both self-regulating and self-conservative characteristics aiming to keep its internal balance despite eventual changes of diverse magnitudes in the environment. Thus, variability is a supporting mechanism that enables the maintenance of life. Entropy, on the other hand, follows the arrow of time, i.e., higher entropy leading to disease and death (Hoshi, et al., 2013).

In this study the Shannon Entropy was a sensitive marker of severity for CKD. Similar results were found by Godoy et al., (2012) in whose study, nonlinear parameters were used to analyze patients with congenital heart disease. As for SD1 and SD2 nonlinear indexes, statistically lower values were present in RFG, meaning lower vagal modulation during hemodialysis (Rajendra, et al., 2006 & Lerma, et al., 2003).

In our study, the analysis of Recurrence was shown in Figure 1. Figure 1A presents a more diffuse pattern, indicating a low recurrent behavior, as expected for the CG. Figure 1B shows a mosaic and repetitive behavior, indicative of higher periodicity and a low HRV. These findings agree with Ferreira et al.⁹, whose analysis were also related with CKD patients in hemodialysis therapy.

In Figure 1B, corresponding to the Recurrence Plot of individuals with CKD, we can observe results similar to the findings by Takakura, et al., (2017) who demonstrated Recurrence Plots, what makes it possible to consider the graph as periodic, indicating a low HRV, close to that found in encephalic death (linear plot).

Our results show high correlation between the HRV indexes. This condition is particularly more relevant when data in HRV time domain were compared with nonlinear indexes. Negative correlations found for RMSSD and Recurrence percentage indicates that higher Recurrence correlates with lower values of RMSSD. The same negative correlation was found for RMSSD and Entropy. Conversely, a positive correlation with statistical significance was found for RMSSD and SD1, both representative of parasympathetic modulation.

Significant correlations between the HRV indexes show their complementary role in cardiac autonomic modulation. The main limitation in this study was the reduced number of participants. Some incompatibilities were found for data collection and differences between standards of care within the services designated for CKD patients were also identified.

Nevertheless, this study presents new methodologies for HRV analysis, which may be considered more important and more sensitive in detecting early alterations in cardiac autonomic modulation.

5. Conclusion

Patients with CKD are more likely to have lower parasympathetic autonomic modulation, which is well evidenced by linear and non-linear HRV.

Nonlinear parameters are more expressive in the identification of autonomic dysfunctions in this population, reinforcing their importance in the evaluation since they can reflect the chaotic behavior of organic systems in a more comprehensive way.

The potential use of HRV as a measure of early diagnosis and prognosis is highlighted. Therefore, we suggest new studies that show early evidence of cardiovascular diseases in this population.

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