Débora Martins da Silva, Murilo Carneiro Macedo, Lucas Brasileiro Lemos, Fernando Costa Vieira, Uanderson Silva Pirôpo, Helder Brito Andrade, Niels Wessel and Rafael Pereira*

Reliability analysis of the heart autonomic control parameters during hemodialysis sessions

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Abstract: The study of heart autonomic control (HAC) in patients with chronic kidney disease (CKD) undergoing dialysis treatment has been carried out, however, there are no studies reporting the reliability of measurements of HAC parameters involving the mentioned samples and conditions. The reliability of many HAC parameters was evaluated from patients with CKD during two sessions of hemodialysis. The successive R-R intervals were recorded during two sessions of hemodialysis from 14 CKD patients that were undergoing dialysis for at least 6 months and with no history of recurrent hypotensive events. HAC parameters were obtained with time and frequency domain analysis, as well as with nonlinear methods. The reliability was measured with the intraclass correlation coefficient (ICC). The results showed excellent reliability (ICC=0.90–0.98) for most heart rate variability (HRV) parameters, especially the parameters obtained in the time domain [square root of the mean squared differences between successive R-R intervals (RMSSD), percentage of adjacent R-R intervals that differ by more than 50 ms (pNN50), mean of the 5-min standard deviations of R-R intervals (SDNNi), and triangular index] and with non-linear methods [standard deviation of the instantaneous variability beat-to-beat (SD1), standard deviation in long-term continuous R-R intervals (SD2), detrended fluctuation analysis (DFA) $\alpha 1$ and $\alpha 2$, approximate and sample entropies, and correlation dimension (D2): ICC=0.86–0.96]. Among the parameters obtained in the frequency domain (normalized magnitude from the spectrum of low-frequency components (LFnu), normalized magnitude from the spectrum of high-frequency components (HFnu), and LF/HF ratio), the LF/HF ratio showed better reliability (ICC=0.96 vs. ICC=0.70). Measurements of HAC parameters have excellent test-retest reliability for the studied samples and conditions.

Keywords: chronic renal insufficiency; heart rate variability; hemodynamics.

***Corresponding author: Rafael Pereira,** Research Group in Neuromuscular Physiology, Department of Biological Sciences, State University of Southwest Bahia (UESB), Rua José Moreira Sobrinho s/n, Jequiezinho, Jequie, BA 45210-506, Brazil, E-mail: rafaelpereira@uesb.edu.br; and Medicine School, State University of Southwest Bahia (UESB), Jequie, Bahia 45210-506, Brazil
Débora Martins da Silva and Murilo Carneiro Macedo: Medicine School, State University of Southwest Bahia (UESB), Jequie, Bahia 45210-506, Brazil; and Research Group in Neuromuscular Physiology, Department of Biological Sciences, State University of Southwest Bahia (UESB), Jequie, Bahia 45210-506, Brazil
Lucas Brasileiro Lemos and Fernando Costa Vieira: Medicine School, State University of Southwest Bahia (UESB), Jequie, Bahia 45210-506, Brazil; and Kidney Disease Center of Jequie (CDRJ), Jequie, Bahia, Brazil
Uanderson Silva Pirôpo and Helder Brito Andrade: Research Group in Neuromuscular Physiology, Department of Biological Sciences, State University of Southwest Bahia (UESB), Jequie, Bahia 45210-506, Brazil
Niels Wessel: Department of Physics, Humboldt-Universität zu Berlin, Berlin, Germany

Introduction

Analysis of reliability of biological variables is common, and an important step, in many areas of research. The reliability from variables collected with repeated measures (e.g. repeated measurements of blood pressure, heart rate, body temperature, etc.) is critical to the knowledge about the consistency of the data, which impacts directly in statistical inferential methods.

Variables with great inter and intra-subject variability, such as parameters of heart autonomic control (HAC), may require a large sample size in order to achieve good reliability of measures, especially when it involves complex samples or complex experimental conditions. Sacre et al. [23] claims that the reliability of the HAC measures tends to decline as the subject's clinical status becomes worse. Likewise, cardiovascular stress conditions, such as hypovolemic conditions, may also increase the inter- and intra-subject variability of HAC.

The study of HAC through analysis of the variability of R-R intervals has been widely used in researches involving patients with chronic kidney disease (CKD) during daily activities [4, 5, 8, 28] and during hemodialysis sessions [3, 5, 22], which is justified by the autonomic dysfunction commonly observed in this population [5, 22] and the increased risk of sudden death from cardiac complications in these patients [1, 8, 11, 32]. Although widely used in scientific research, to our knowledge, there are no studies evaluating the reliability of the parameters of HAC from patients with chronic kidney disease during hemodialysis sessions.

In this context, it is plausible to hypothesize that the HAC of patients with CHD during hemodialysis sessions are poorly reliable, because it involves a complex clinical condition, combined with a stressor procedure to the cardiovascular system, which would limit the use of this variable in scientific research by compromising data consistency, especially when involving a small sample size. Thus, the aim of this study was to evaluate the test-retest reliability of HAC parameters from patients with CKD during two hemodialysis sessions.

Materials and methods

Sample

The sample consisted of 14 patients, eight women and six men (33±9 years old), diagnosed with CKD, undergoing hemodialysis treatment for at least 6 months and without history of recurrent hypotensive crises during hemodialysis sessions. Exclusion criteria were diabetes mellitus (DM), since DM is a major cause of autonomic dysfunction, uncontrolled hypertension [systolic blood pressure (SBP)≥200 mm Hg and/or diastolic blood pressure (DBP)≥120 mm Hg], and previous diagnosis of cardiac arrhythmia. Table 1 presents a sample description.

Proceedings and measurements

All data were recorded in the Kidney Disease Center of Jequie (CDRJ), Bahia, Brazil, from December 2012 to June 2013. The sample consisted of patients with CKD and undergoing hemodialysis treatment. Only patients submitted to hemodialysis in the morning were included, owing to the influence of circadian rhythm on HAC.

Participants were invited to take part in the study and were informed about the study procedures; those who agreed to participate in the study signed an informed consent. The study was approved by the Research Ethics Committee of the State University of Southwest Bahia (protocol#: 09635912.3.0000.0055).

R-R interval recording

All patients who met the sample selection criteria and agreed to participate were subjected to recording R-R intervals through a heart rate monitor (Polar® RS800CX, Finland) with a sampling frequency of 1000 Hz, providing a temporal resolution of 1 ms for each R-R interval, in two hemodialysis sessions with a window of at least 48 h between them. The hemodialysis sessions lasted for 233±10 and 235±6 min, for the first and second session, respectively. The mean weight loss in the sessions (2.61±0.89 and 2.45±0.89 kg for the first and second session, respectively) exhibited an excellent reliability between sessions, measured through the intraclass correlation coefficient ICC [ICC=0.94 (95% confidence interval: 0.80–0.98); standard error of mean (SEM)=0.31 kg].

Heart rate monitors were previously validated for analysis of HAC [9]. The RR interval data were analyzed in the time and frequency domain and with nonlinear analysis methods, and all analyses were performed with the Kubios HRV analysis software 2.1 (Department of Applied Physics, University of Eastern Finland) [31]. The recorded data were pre-processed using a smoothing procedure with a cut-off frequency of 0.035 Hz to remove disturbing low-frequency baseline trend components as used and suggested by Luque-Casado et al. [13]. The smoothness priors method is basically a time-varying high-pass

Table 1: Etiology of CKD[a]/primary disease, comorbidities, dialysis time (months), urea, and parameters of hemodialysis adequacy (URR and Kt/V) for each patient included in the study.

Patient	Sex	Etiology of CKD[a]/primary disease	Comorbidity	Dialysis time (months)	Urea (mg/dl)[b]	URR (%)[c]	Kt/V[d]
1	F	Hypertensive nephrosclerosis	Hypertension	66	138	72	1.37
2	F	CKD with unknown etiology	–	50	126	74	1.41
3	F	Hypertensive nephrosclerosis	Hypertension	8	114	74	1.42
4	M	CKD with unknown etiology	Hypertension	63	105	69	1.30
5	M	CKD with unknown etiology	–	34	142	59	1.06
6	F	Chronic glomerulonephritis	Hypertension	78	119	76	1.46
7	F	Lupus nephropathy	Hypertension	17	148	72	1.37
8	M	Chronic glomerulonephritis	Hypertension	143	93	63	1.17
9	F	CKD with unknown etiology	Hypertension	106	104	68	1.30
10	M	CKD with unknown etiology	Hypertension	72	127	68	1.28
11	M	Chronic glomerulonephritis	–	66	101	71	1.34
12	M	Hypertensive nephrosclerosis	Hypertension	7	108	63	1.10
13	F	Chronic glomerulonephritis	Hypertension	228	110	76	1.45
14	F	CKD with unknown etiology	–	82	168	75	1.43

[a]CKD, Chronic kidney disease; [b]average from the last 12 months; [c]URR, urea reduction rate; [d]Kt/V, fractional clearance of body water for urea.

filter and its cut-off frequency can be adjusted with the Lambda parameter (i.e. the bigger the value of lambda, the smoother is the removed trend) as exposed by Tarvainen et al. [31]. Then, the used cut-off frequency was below the frequency ranges examined in this study.

The analysis procedures followed the recommendations of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [32] and Tarvainen et al. [31]. It is important to note that the number of data points (i.e. the number of recorded R-R intervals) obtained in each hemodialysis session was not significantly different (1st session=13913±956 data points; 2nd session=13962±567 data points).

Time domain analysis

The time domain analysis was performed to obtain the following parameters: square root of the mean squared differences between successive R-R intervals (RMSSD), percentage of adjacent R-R intervals that differ more than 50 ms (pNN50), standard deviation of the average R-R intervals calculated over the 5-min segments (SDANN), the mean of the 5-min standard deviations of R-R intervals (SDNNi), and triangular index, calculated by dividing the area (corresponding to the total number of RR intervals used in the histogram construction) by the height (corresponding to the number of RR intervals with modal frequency) of the triangle.

Frequency domain analysis

The analysis of the frequency domain was performed using the fast Fourier transform (FFT) to obtain the following parameters: normalized magnitude from the spectrum of the low frequency components (LFnu) and the high frequency (HFnu), and LF/HF ratio. The low- and high-frequency power was set as 0.04–0.15 and 0.15–0.4 Hz, respectively. The window width was set to 256 s and overlapped to 50%.

Nonlinear methods

The analysis of Poincaré plot allowed obtaining the standard deviation of the instantaneous variability beat to beat (SD1) and standard deviation in long-term continuous RR intervals (SD2) parameters as proposed by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [32] and Voss et al. [35]. The detrended fluctuation analysis (DFA) ($\alpha 1$ and $\alpha 2$), correlation dimension (D2), approximate entropy, and sample entropy were also obtained in accordance with the proposal by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology [32], Voss et al. [35], Wagner and Persson [36], Zurek et al. [39] and Tarvainen et al. [31].

Statistical analysis

Data were analyzed descriptively as mean±standard deviation. The reliability of the HAC parameters were determined from the ICCs by means of the two-way model ($ICC_{2,1}$ – a two-way repeated-measures analysis of variance) [12, 27].

The ICC is a suitable method to measure the reliability of two or more measures and is interpreted as the proportion of the total variability attributed to the measured variable [25]. Among the available methods to infer the reliability of variables with repeated measurements, the ICC is referred as the preferable method, mainly because it can be applied to small samples [12, 27]. Additionally, this statistical approach has been widely used to evaluate reliability from data with stochastic characteristics, as HAC parameters [19, 20]. ICC was used to express relative reliability of the measures because it expresses the ratio of between-subject variance to total variability with a unitless value [27].

The reliability was defined as excellent for ICC values between 0.80 and 1.00, good between 0.60 and 0.80, and low when <0.60, as proposed by Shrout and Fleiss [27]. In addition, we calculated the average standard error of repeated measurements (SEM=square root of the mean square error term from the ANOVA) as proposed by Weir [37]. SEM was used to express absolute reliability of the measure, where smaller values of SEM reflect more reliable measures. All statistical procedures were performed using SPSS 21.0 (SPSS Inc., IBM, Chicago, IL, USA).

The SEM can be estimated as the square root of the mean square error term from the ANOVA.

Results

Figure 1 presents the R-R intervals behavior, from a volunteer, along the first and second hemodialysis sessions.

All HAC parameters obtained with the nonlinear methods showed excellent reliability, with ICC values above 0.85. Among the parameters obtained with the analysis in frequency domain, the LF/HF showed excellent reliability, while the results of LFnu and HFnu were only good (ICC=0.70). The majority of parameters obtained with analysis in the time domain showed excellent reliability, except the SDANN, which showed very low ICC (ICC=0.53). All ICC values, as well as mean±standard deviation of each parameter are presented in Table 2.

Figure 2 shows the correlation between the first and second hemodialysis sessions from the HAC parameters with best (pNN50 and DFA $\alpha 1$) and worst (LFnu and SDANN) reliability.

Discussion

This study aimed to assess the test-retest reliability of HAC parameters from patients with CKD in two hemodialysis sessions, and the results showed great consistency for the most of the studied parameters, especially those obtained through analysis in the time domain and with nonlinear methods.

Previous studies shown the impairment of the heart autonomic control from CKD patients when RR intervals are recorded from 24 h (i.e. during the daily routine) [4, 5];

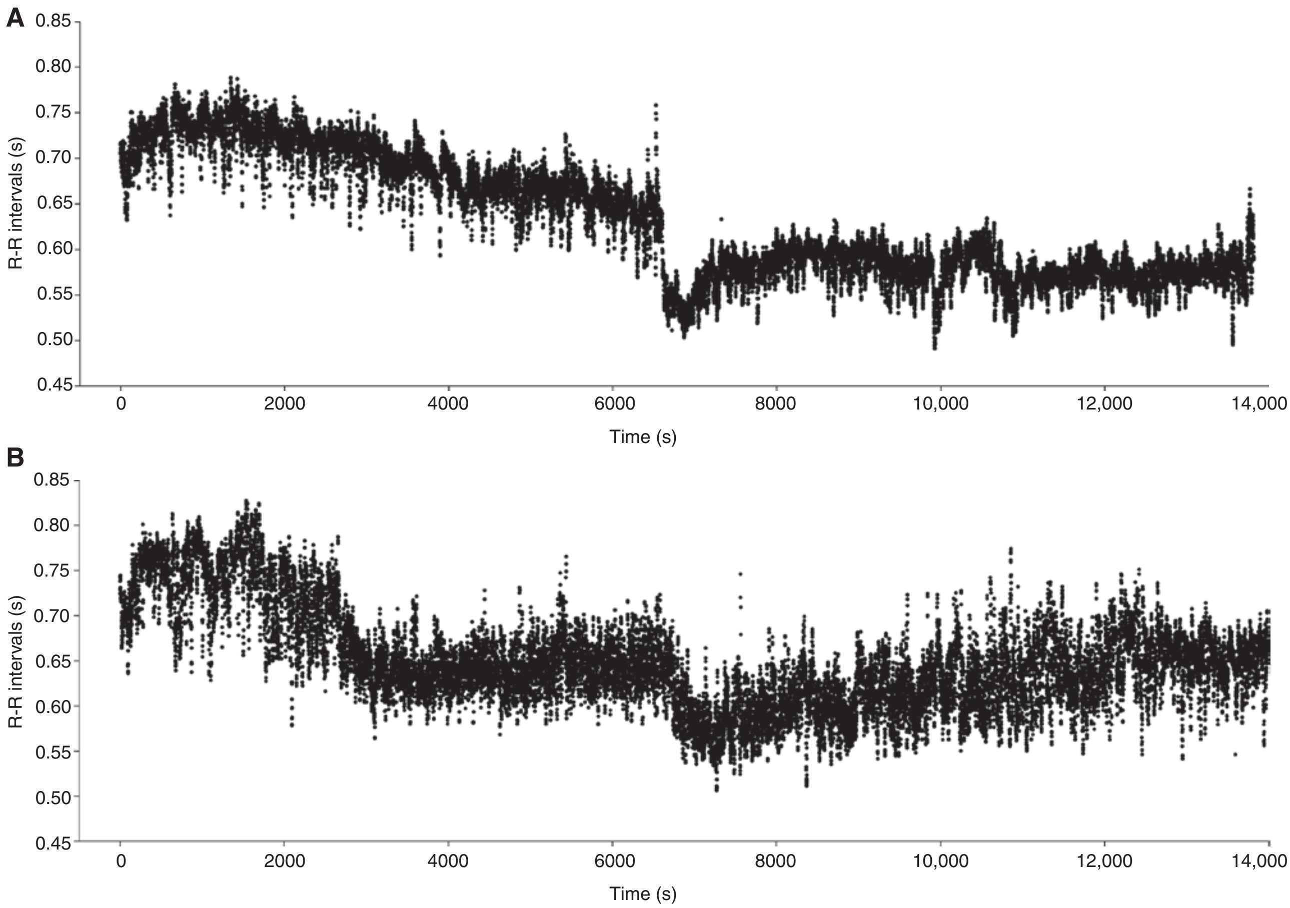

Figure 1: R-R intervals from a patient during two hemodialysis sessions.

Table 2: Mean±standard deviation, intraclass correlation coefficient (ICC) with 95% confidence interval, and standard error of mean (SEM) of the heart autonomic control parameters obtained in two hemodialysis sessions.

Analysis method	Variable	1st session	2nd session	SEM	ICC [95% CI]
Time domain	RMSSD (ms)	19.58±13.08	23.03±12.22	5.08	0.90 [0.68–0.97]
	pNN50 (%)	4.54±8.01	5.04±7.86	1.75	0.98 [0.93–0.99]
	SDANN (ms)	56.30±26.59	55.59±22.32	19.84	0.53 [0.00–0.85]
	SDNNi (ms)	32.15±10.60	36.04±11.77	4.07	0.90 [0.62–0.97]
	Triangular index (ms)	5.62±2.76	6.50±2.96	0.80	0.94 [0.70–0.98]
Frequency domain	LF n.u.	66±21	58±23	14.80	0.70 [0.10–0.89]
	HF n.u.	34±20	42±23	14.45	0.70 [0.10–0.89]
	LF/HF ratio	3.61±4.37	2.91±4.45	1.18	0.96 [0.87–0.99]
Nonlinear methods	SD1 (ms)	13.84±9.25	16.29±8.64	3.59	0.90 [0.68–0.97]
	SD2 (ms)	27.31±10.85	31.46±12.04	5.16	0.86 [0.54–0.96]
	DFA α_1	1.19±0.30	1.15±0.30	0.08	0.96 [0.88–0.99]
	DFA α_2	0.61±0.14	0.55±0.11	0.04	0.90 [0.32–0.98]
	Correlation dimension (D2)	0.57±0.84	0.69±1.06	0.30	0.95 [0.84–0.98]
	Approximate entropy	1.39±0.12	1.37±0.16	0.05	0.93 [0.77–0.97]
	Sample entropy	1.53±0.20	1.50±0.25	0.08	0.94 [0.80–0.98]

however, analysis of HAC during hemodialysis sessions is of great importance from a clinical point of view, since it is a cardiovascular stress condition owing to the volume withdrawal that can induce hypovolemia [2].

Previous studies have shown a clear trend to increased sympathetic activity along the hemodialysis session [3, 6], which is justified by the volume withdrawal during the dialysis session. The failure to

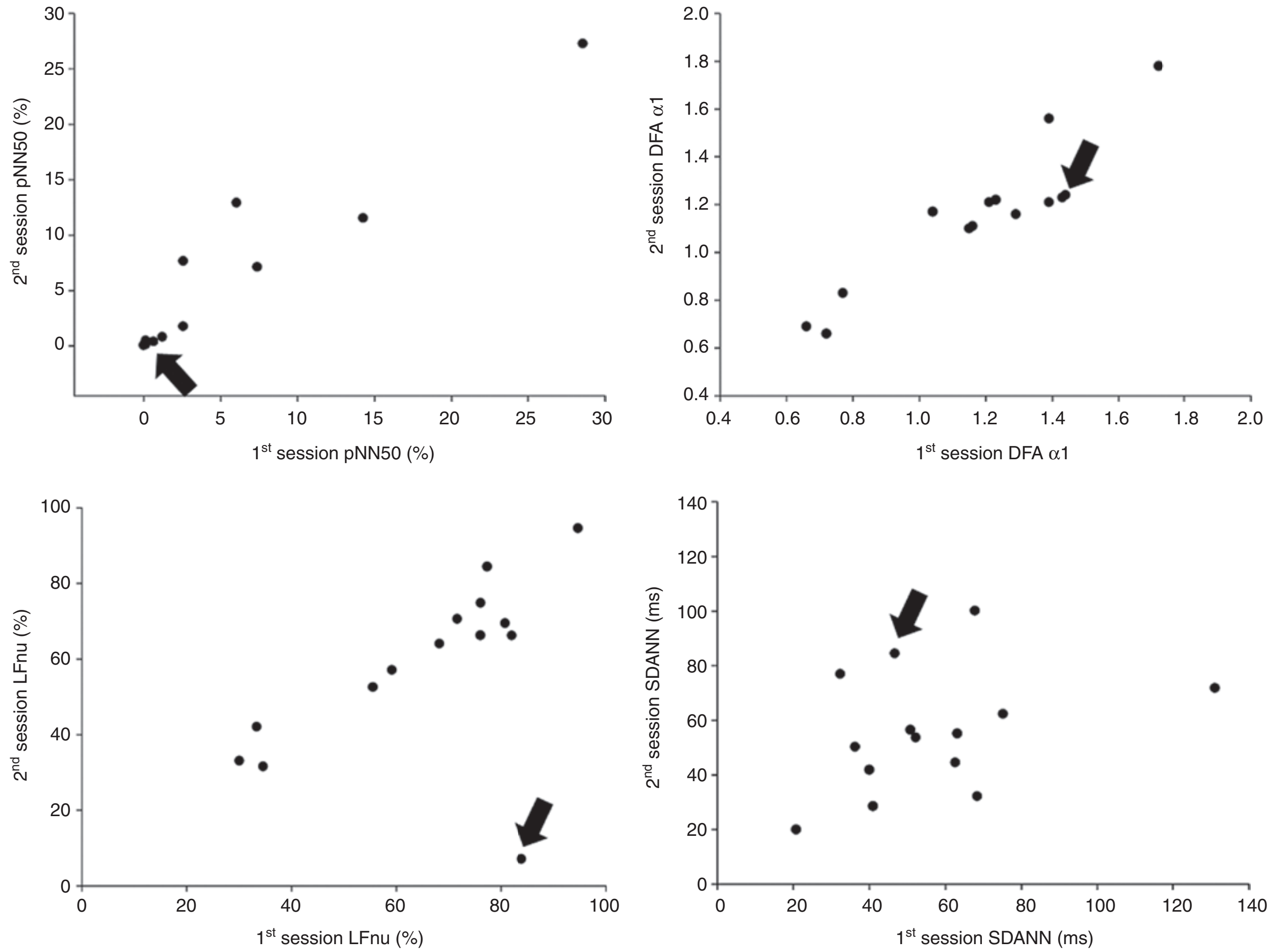

Figure 2: Scatter plot showing the correlation from the best (pNN50 and DFA α1) and worst (LFnu and SDANN) reproducibility and reliability of heart autonomic control parameters during the first and second hemodialysis sessions.
Arrows indicate the patient with discrepant behavior at LFnu, but normal behavior at DFAα1 and pNN50.

respond to the blood volume reduction by the increase of sympathetic activity may predispose to hypotension, which is the most frequent complication during hemodialysis sessions [6, 24, 26, 33]. Notwithstanding, the reduced vagal activity, common in patients with CKD, predisposes these patients to an increased risk of sudden death [1, 8, 11, 34].

The predominance of a low-frequency spectral band has been related to sympathetic activity, and therefore, a more stable hemodynamic behavior during hemodialysis sessions [3, 24]. Our results showed a predominance of this spectral band in both sessions, which may explain the hemodynamic stability of included patients, as an inclusion criterion was the absence of recurrent hypotensive crisis during hemodialysis sessions.

Although the known results about the HAC during hemodialysis sessions are based mainly on analysis in the frequency domain [3, 16], our results showed that the HF and LF spectral bands had poorer reliability when compared to the results of analysis in the time domain or obtained by nonlinear methods. Figure 2 allows identifying a volunteer with discrepant behavior for spectral parameters between the first and second sessions. This is a young woman (27 years old), the single patient with the diagnosis of lupus nephropathy, an immunological renal disease, which is a complex clinical condition and may present exacerbations and remissions. Interestingly, despite of this and differently of the spectral parameters, the results from nonlinear methods were reliable and not influenced by the primary disease, as discussed below.

The LF/HF ratio, reported in the literature as a sympathovagal balance indicator [32] showed excellent reliability, and is therefore preferable when wanting to include parameters obtained in the frequency domain. The high levels of LF/HF ratio obtained in both hemodialysis sessions could indicate a clear sympathetic predominance, necessary to offset the falling blood pressure, induced by volume withdrawal. However, the analysis of dynamical changes in time series, as R-R intervals, using time and frequency methods are often not sufficient to describe physiological events, especially in complex conditions or in diseases [14, 38]. For example, breathing rate, what is hard to control during hemodialysis sessions, may influence heart rate fluctuations [17, 38], and then, the parameters obtained with frequency domain analysis. Instead of this, nonlinear methods involve robust mathematical concepts and proceedings, which may be more suitable to categorize and understand complex behavior of the cardiovascular system [38].

The reliability of HAC parameters from healthy subjects was evaluated by Schroeder et al. [25] and Pinna et al. [20], and as well as in our study, the results show better ICC for the parameters obtained in the time domain compared to those obtained in the frequency domain, which can be explained by the significant influence of external stimuli (e.g. pain, breathing rate, menstruation, etc) over the parameters obtained with frequency domain analysis [10].

The analysis in the time domain has the advantage of being obtained through simple mathematical procedures, allowing obtaining statistical and geometric indices easy to apply and interpret [32]. This fact, coupled to an excellent reliability obtained with this method of analysis leads us to recommend the use of these statistical and geometric indexes to study HAC during hemodialysis sessions, instead of frequency domain-based parameters. However, as explained previously, both, the analysis methods (i.e. in the time and frequency domains), could not be suitable to describe complex physiological events, what may be achieved with nonlinear methods. The large time series (i.e. 4-h recordings) favors the time domain parameters, owing to the statistical and geometric methods used. It is clear for pNN50, which is a statistical parameter at a large time series, but not applicable to SDANN, which is the standard deviation of the average 5-min RR intervals along the recorded time series. Figures 1 and 2 help to understand the poor reliability of SDANN; it is plausible to think that the same trend isn't present for all subjects when this time window (intervals of 5 min) is used for R-R intervals recorded during the hemodialysis sessions.

The analysis of R-R intervals with nonlinear methods have been widely used and recommended in literature [7, 15, 18, 21, 30]. Owing to its complex and dynamic nature, biological phenomena, such as the variation of successive R-R intervals, are better described through analysis with nonlinear methods [32, 38]. The fact that we obtained excellent reliability (ICC=0.86–0.96) with the nonlinear parameters of HAC supports the use of these parameters in studies aiming to evaluate the autonomic behavior during hemodialysis sessions. It is important to note that, differently from the time and frequency domain methods, all the nonlinear parameters quantified the complexity of the time series in a global way, showing up more stable and less influenced by factors as breathing rate and primary disease, among others factors. Thus, we state that this is the most reliable approach to study the HAC during hemodialysis sessions.

Additionally, nonlinear parameters are reported as important predictors of cardiac events, such as ventricular fibrillation and sudden death, in studies with animals and humans [15, 28–30].

Suzuki et al. [30] showed that the analysis with detrended fluctuations, specifically the parameter $\alpha 1$, increases the risk stratification capacity for mortality in patients requiring hemodialysis. The cited study was carried out with electrocardiogram recordings for 24 h, and unfortunately, we have not identified in the literature studies using this parameter during hemodialysis sessions. Our results provide support for future studies aimed to investigate the predictor power of nonlinear parameters, obtained during hemodialysis, to outcomes as mortality and cardiovascular complications, since an excellent reliability of the parameters in this condition was found.

In conclusion, our study indicates that despite the cardiovascular stress resulting from volume withdrawal induced by hemodialysis in clinically critical patients, the test-retest reliability from the HAC parameters is great for most of the parameters obtained in the time domain and by nonlinear methods, especially the ones obtained with nonlinear methods, which provides reliability to use these variables in studies with similar samples and conditions as used here. One major limitation of our study is the relative small sample size; further prospective studies have to be conducted to validate the results we obtained.

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