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Evaluation of the autonomic heart rate modulation of patients with chronic renal disease in hemodyalysis: preliminare study

Avaliação da modulação autonômica da frequência cardíaca de pacientes com doença renal crônica em hemodiálise: estudo preliminar

Evaluación de la modulación autónoma de la frecuencia cardíaca en pacientes con enfermedad renal crónica sometidos a hemodiálisis: estudio preliminar

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RESUMO | A doença renal crônica (DRC) é definida como dano à função renal. Doentes renais crônicos atingem alta prevalência de morte por eventos cardiovasculares antes dos estágios finais, sendo maior a mortalidade em estágio dialítico, em que é evidenciado um desequilíbrio autonômico. Objetivamos avaliar a modulação simpatovagal de pacientes com DRC em tratamento de hemodiálise ambulatorial. Foram avaliados 23 pacientes, divididos em: Grupo DRC com DRC no estágio 5D (DRC-5D) em tratamento regular de hemodiálise ambulatorial; Grupo-controle com indivíduos saudáveis. A variabilidade da frequência cardíaca (VFC) foi coletada por um cardiofrequencímetro e analisada por índices lineares do domínio do tempo e do domínio da frequência. 14 pacientes no Grupo DRC com média de idade 48±16; e 9 pacientes saudáveis no Grupo-controle com média de idade 64±5. Nos resultados pelo domínio de tempo, o Grupo DRC mostrou valores significativamente maiores da frequência cardíaca (FC) comparado ao Grupo-controle (83,49±13,09 bpm vs. 67,88±9,43 bpm). Todavia, os índices média dos intervalos R-R (735,82±121,54 ms vs. 898,94±123,58 ms), RMSSD (11,75±11,86 ms vs. 20,03±6,80 ms), SDNN (17,06±9,81ms vs. 28,42±7,62 ms) do Grupo DRC mostraram valores significativamente menores comparados aos do Grupo-controle, respectivamente. Nos resultados pelo domínio da frequência, o Grupo DRC mostrou valores significativamente menores em comparação ao Grupo-controle nos índices BFab (129,7±184,3 ms vs. 262,31±168,15 ms) e AFab (82,70±227,66 ms vs. 180,77±119,85 ms). Pacientes com DRC em hemodiálise apresentaram redução da modulação parassimpática quando comparados com indivíduos saudáveis, sugerindo prejuízo do balanço simpatovagal e, consequente, disfunção autonômica cardíaca.

Descritores | Insuficiência Renal Crônica; Sistema Nervoso Autônomo; Doenças Cardiovasculares.

ABSTRACT | Chronic kidney disease (CKD) is defined as damage to kidney function. Patients have high prevalence of death by cardiovascular events before the final stages of the disease, with higher mortality in dialytic stage, in which autonomic imbalance is evidenced. This study seeks to evaluate sympathovagal modulation of patients with CKD undergoing hemodialysis treatment. We evaluated 23 subjects, divided into: CDK-group with CKD-stage 5D in regular hemodialysis treatment; and Control-group with healthy individuals. Heart rate variability (HRV) was collected by a heart rate monitor and analyzed by linear time domain and frequency domain indices. CDK-group had 14 patients, mean age of 48±16; and Control-group had 9 healthy patients, mean age of 64±5. In the time domain, CDK-group showed significantly higher heart rate values compared with Control-group (83.49±13.09 bpm vs. 67.88±9.43 bpm). However, the mean indices of the

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R-R intervals (735.82±121.54 ms vs. 898.94±123.58 ms), RMSSD (11.75±11.86 ms vs. 20.03±6.80 ms), and SDNN (17.06±9.81 ms vs. 28.42±7.62 ms) from CDK-group showed significantly lower values compared with Control-group. In frequency domain results, CDK-group showed significantly lower values compared with Control-group in LFab (129.7±184.3 ms vs. 262.31±168.15 ms) and HFab (82.70±227.66 ms vs. 180.77±119.85 ms). Patients with CKD on hemodialysis had reduced parasympathetic modulation compared with healthy subjects, suggesting impairment of the sympathovagal balance and, consequently, cardiac autonomic dysfunction.

Keywords | Renal Insufficiency, Chronic; Autonomic Nervous System; Cardiovascular Diseases.

RESUMEN | La enfermedad renal crónica (ERC) se define como la pérdida de la función renal. Los pacientes renales crónicos tienen una alta prevalencia de muerte por eventos cardiovasculares antes de la etapa final, con mayor mortalidad en la etapa de diálisis, en la que se evidencia un desequilibrio autonómico. Este estudio tuvo como objetivo evaluar la modulación simpatovagal de pacientes con ERC sometidos a tratamiento de hemodiálisis ambulatoria. Se evaluaron 23 pacientes, lo cuales fueron divididos en: Grupo ERC con ERC en etapa 5D (ERC-5D) en tratamiento de hemodiálisis ambulatoria regular; Grupo de control con individuos sanos. Para identificar la variabilidad de la frecuencia cardíaca (VFC) se utilizó un monitor de frecuencia cardíaca y los datos obtenidos fueron analizados por los índices lineales de tiempo y de dominio de frecuencia. En el grupo ERC 14 pacientes tenían un promedio de edad de 48±16 años; y en el grupo control 9 pacientes sanos tenían un promedio de edad de 64±5. En los resultados para el dominio del tiempo, el grupo ERC mostró valores significativamente más altos de frecuencia cardíaca (FC) en comparación con el grupo control (83,49±13,09 lpm vs. 67,88±9,43 lpm). Sin embargo, los índices medios de los intervalos R-R (735,82±121,54 ms vs. 898,94±123,58 ms), RMSSD (11,75±11,86 ms vs. 20,03±6,80 ms), SDNN (17,06±9,81 ms vs. 28,42±7,62 ms) del grupo ERC demostraron valores significativamente más bajos en comparación con el grupo control, respectivamente. En los resultados para el dominio de la frecuencia, en el grupo ERC se obtuvo valores significativamente más bajos en comparación con el grupo control en los índices BFab (129,7±184,3 ms vs. 262,31±168,15 ms) y AFab (82,70±227,66 ms vs. 180,77±119,85 ms). Los pacientes con ERC sometidos a hemodiálisis mostraron una modulación parasimpática reducida en comparación con los individuos sanos, lo que sugiere un deterioro del equilibrio simpatovagal y, en consecuencia, una disfunción autonómica cardíaca.

Palabras clave | Insuficiencia Renal Crónica; Sistema Nervioso Autónomo; Enfermedades Cardiovasculares.

INTRODUCTION

Chronic kidney disease (CKD) is a global public health problem, with an average overall prevalence of 13.4%[1]. In Brazil, an estimated three to six million adults have the disease[2]. CKD is defined as gradual loss of renal function, regardless of structural alteration of tissue and causal diagnosis, based on the level of glomerular filtration rate (GFR)[3].

Chronic renal patients are considered individuals at high risk for cardiovascular diseases (CVD), because they have a higher prevalence of their traditional risk factors, such as advanced age, systemic arterial hypertension (SAH) and diabetes mellitus (DM), when compared with the general population. The literature also associates cardiovascular complications with non-traditional risk factors related to CKD, such as decreased GFR and extracellular volume overload[4].

Thus, studies show that this population has a high mortality rate from cardiovascular events even before the final stages of the disease; even higher for CKD (stage 5 - CKD-5D) cases on hemodialysis (HD) because at this stage a large imbalance of autonomic activity is evidenced[2,5]. This imbalance in the sympathovagal activity influences the control of the cardiovascular system, partially performed by the autonomic nervous system (ANS), which is influenced, among others, by information from baroreceptors, respiratory system, vasomotor system, thermoregulatory system, and kidneys, as they perform systemic hemodynamic regulation through the renin-angiotensin-aldosterone system (RAAS), prostaglandins and kidney kinins[6,7]. Individuals with CKD have other (non-traditional) risk factors that also influence autonomic dysfunction, such as inflammation, oxidative stress, and extracellular volume overload.

The control performed by the ANS is closely linked to heart rate (HR). The increase in HR is a consequence of greater sympathetic and decreased parasympathetic action, that is, vagal inhibition; and the reduction is a consequence

of the predominance of parasympathetic activity. Heart rate variability (HRV) is a noninvasive method capable of evaluating the sympathovagal interactions in the HR central control, and indicates the responsiveness of the heart to multiple environmental and physiological stimuli[7].

HRV is described as oscillations of the intervals between consecutive beats shown by R waves of the electrocardiographic tracing (iR-R). High HRV means good adaptation, characteristic of individuals with efficient autonomic mechanisms. On the other hand, low HRV is an indicator of abnormal and insufficient adaptation of the ANS, indicating a physiological malfunction in the individual. That is, changes in HRV patterns can be an early and sensitive indicator of health impairments[7].

HRV can be evaluated by linear methods, more common in clinical practice, since these can be obtained in short and/or long periods of time. Among those are the SDNN, SDANN and SDNNi indexes, which translate the overall variability of HR and the low frequency component (LF), which predominantly reflects sympathetic modulation. The RMMSD, pNN50 and high frequency component (HF) represent the parasympathetic activity. Finally, the LF/HF ratio represents the sympathovagal balance over the heart[7,8].

In the population with CKD, the reduction of HRV is related to damage to the parasympathetic system caused by functional alterations of the ANS due to uremic toxins and the structural impairment of the arteries[5]. This dysfunction causes a higher incidence of hospitalization in CKD patients with low HRV, suggesting that this autonomic imbalance may participate in the pathophysiology of the disease[9]. Authors also demonstrated that the reduction of SDNN, LF and LF/HF parameters in HD patients is an independent predictor of cardiovascular adverse events, such as arrhythmias, heart failure (HF) and sudden death[10-12].

Although initial evidence indicates that individuals with CKD have altered HRV, this assessment is not yet routinely used in this population, unlike what already occurs in other chronic diseases (such as chronic obstructive pulmonary diseases, heart diseases, etc.). This study aims to evaluate the sympathovagal modulation of patients with CKD on HD. In this sense, there is room for the conception and development of further research on cardiac autonomic modulation of CKD patients. Its clinical practice could support the implementation of physical therapy strategies, based on physical exercise protocols to reduce the impact of this autonomic dysfunction on cardiovascular risk.

METHODS

Participants

This is an experimental prospective cross-sectional observational study. For this, the volunteers were screened and stratified into two groups: CKD-group, represented by CKD patients on regular outpatient HD treatment at the Clementino Fraga Filho University Hospital (HUCFF) of the Universidade Federal do Rio de Janeiro (UFRJ); and Control-group, with healthy sedentary individuals. These studies, as well as the collections, were developed in the Research Group on Cardiorespiratory Evaluation and Rehabilitation (Gecare), of the Department of Physiotherapy of the Universidade Federal do Rio de Janeiro.

The inclusion criteria of the CKD-group were individuals over 18 years of age, of both sexes, sedentary, and CKD-5D for at least six months in outpatient treatment, undergoing hemodialysis (HD) three times a week and four hours per session. The Control-group was composed of individuals over 18 years of age, healthy according to clinical evaluation, of both sexes, and sedentary (with less than 150 minutes per week of physical exercise practice). Patients who were hospitalized three months prior to the study were excluded from the CKD-group. Regarding the Control-group, were excluded volunteers with a history of cardiovascular, neurological, orthopedic, muscular, metabolic and immunological disease; and clinical and/or functional evidence of chronic obstructive pulmonary disease (forced expiratory volume/forced vital capacity ratio – $FEV_1/FVC<70\%$).

All volunteers signed an informed consent form and the privacy of the research subjects and confidentiality of the data were fully guaranteed during all stages of the study.

Experimental protocol

The collections were performed in the nephrology sector, in an air-conditioned room with temperature

between 22°C and 24°C, and occurred in the same period of the day (between 5:30 and 6:00).

The volunteers were kept at rest for 10 minutes in the sitting position, to lower the HR to baseline values. After rest, HR and iR-R were collected, beat by beat, for 10 minutes in the sitting position, through a cardiofrequency meter (Polar® v800) with sampling frequency of 1000 Hz, fixed by an elastic belt in the lower third of the sternum and with simultaneous transmission to the clock in which they were stored. Later, the data were transported and stored, by using a USB interface, in a microcomputer with a specific software for the analysis.

Data analysis

The HRV was analyzed by linear mathematical and statistical models in the domain of time and of implemented frequency by using a specific routine developed for this purpose in the Kubius HRV 2.0 for Windows application. For this to be possible, the most stable stretch of the signal was selected, five minutes long and free of artifacts.

The analysis in the time domain was performed from the indexes: (1) mean HR and variations in the duration of R-R intervals (iR-R); (2) SDNN, which is the standard deviation of normal iR-R in milliseconds (ms); and (3) RMSSD that corresponds to the square root of the square sum of the difference between the consecutive iR-R of the electrocardiogram record, divided by the number of iR-R at a given time minus one – iR-R in ms[7,8].

The analysis in the frequency domain was performed from the high frequency bands (HF), low frequency bands (LF), both in absolute values (ab). HF reflects a predominance of vagal modulation and LF reflects a predominantly sympathetic modulation[7,8].

Statistical analysis

Statistical analysis was performed on SigmaPlot for Windows version 11.0, copyright© 2008 Systat Software, Inc. The data were submitted to the tests of normality (Shapiro-Wilk test) and homogeneity (Levene test). Then, when appropriate, an unpaired Student's t-test or Mann-Whitney test was applied for comparisons of the indexes in the time domain and in the HRV frequency domain. All measurements were expressed as mean and standard deviation with $p<0.05$.

RESULTS

The initial population of this study consisted of 24 eligible patients, and only one patient opted out of participating. Participants were selected from December 2017 to February 2018 at Nephrology Services and in the Physiotherapy Department of the Clementino Fraga Filho University Hospital of Federal University of Rio de Janeiro (Figure 1).

All participants completed the evaluations; 14 individuals were in the CKD-group, with a mean age of 48±16 years with 9 females; and 9 individuals in the Control-group, with a mean age of 64±5 years, 5 of which were female. In the CKD-group, consisting of individuals with CKD-5D, the associated comorbidities were: SAH (n=9), DM (n=5), HF (n=6), coronary artery disease (n=5) and chronic glomerulonephritis (n=2). All patients were non-smokers (table 1).

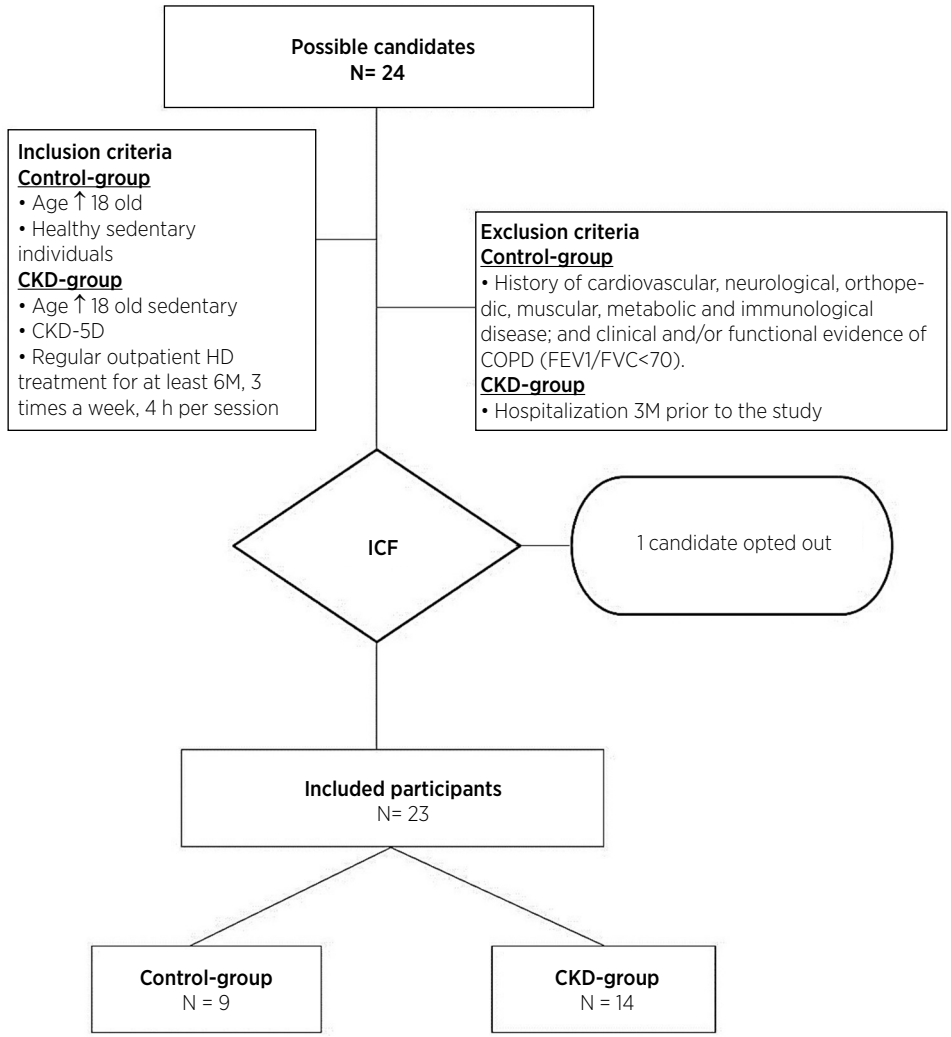

Figure 1. Study flowchart
CKD-5D: stage 5 chronic renal patients; 6M: 6 months; 3M: 3 months; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in the 1st minute; FVC: forced vital capacity; ICF: informed consent form.

Table 1. General characteristics of the participants

	CKD-group	Control-group
Patients analyzed (n)	14	9
Age (years)	48±16	64±5
Female – n (%)	8 (57.1)	5 (57.1)
BMI (kg/m^2)	26± 6	24±3
Beta-blockers – n (%)	3 (21.4)	-
Calcium channel blockers – n (%)	4 (28.5)	-
SAH – n (%)	9 (64.2)	-
DM – n (%)	5 (35.8)	-
HF – n (%)	6 (42.5)	-
CAD – n (%)	5 (35.7)	-
Chronic glomerulonephritis – n (%)	2 (14.3)	-

BMI: body mass index; SAH: systemic arterial hypertension; DM: diabetes mellitus; HF: heart failure; CAD: coronary artery disease.

Figure 2 (graphs A, B, C and D) shows the time and frequency domain indexes using HR, iR-R, SDNN and LF. We observed higher values with statistical significance of the mean HR in the CKD-group compared with the Control-group (83.49±13.09 bpm vs. 67.88±9.43 bpm) (p=0.006), and also worse cardiac autonomic adjustments and overall HRV of the CKD-group compared with the Control-group, observed by significantly lower values in the mean of iR-R (735.82±121.54 ms vs. 898.94±123.58 ms) (p=0.006), SDNN (17.06±9.81ms vs. 28.42±7.62 ms) (p=0.005), and LFab (129.7±184.3 ms vs. 262.31±168.15 ms) (p=0.001).

Graphs E and F, also in Figure 2, show the time and frequency domain indexes that represent predominance of parasympathetic activity (RMSSD and HFab). We observed significantly lower values in the CKD-group compared with the Control-group in the following parameters: RMSSD (11.75±11.86 ms vs. 20.03±6.80 ms) (p=0.003); and HFab (82.70±227.66 ms vs. 180.77±119.85 ms) (p=0.002), respectively.

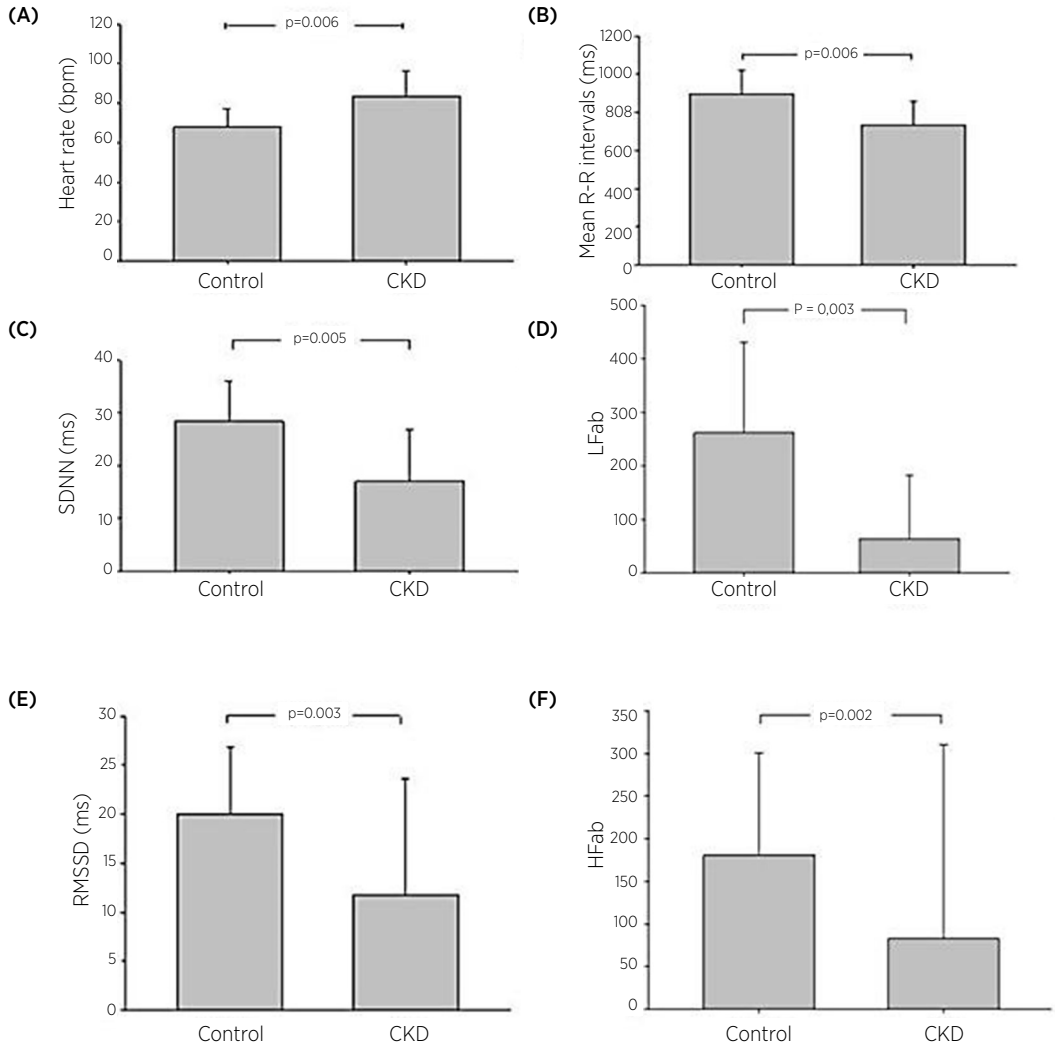

Figure 2. Results of the global linear (A, B, C and D) and parasympathetic (E and F) indices of the HRV in the time and frequency domains: (A) Heart rate (bpm); (B) Mean R-R intervals (ms); (C) SDNN: standard deviation of all R-R intervals (ms); (D) LFab: absolute low frequency (ms); (E) RMSSD: square root of the mean of the differences between the R-R intervals (ms); (F) HFab: absolute high frequency (ms).

DISCUSSION

The results of this study showed that individuals with CKD in HD have impaired HRV with impaired vagal modulation when compared with healthy individuals. In this context, chronic end-stage nephropaths present impaired autonomic adjustment and, consequently, worse global variability through lower values in the iR-R, SDNN and LFab indices, as well as the mean HR.

Vita et al.[13] corroborate our findings of a reduction in LFab in comparison with healthy individuals, which indicates a reduction in the sympatovagal balance, i.e., low HRV. The study by Chandra et al.[14], involving 305 chronic renal patients of moderate to late stage (stages 3 to 5), observed that chronic nephropaths on hemodialysis have lower SDNN values, like in our study. However, they observed this reduction when compared with chronic renal patients in stage 3 of the disease, suggesting there is a progressive worsening of the overall HRV during the course of the disease stages. Added to this, lower SDNN values in CKD patients are related to lower glomerular filtration rates[9]. The same study also showed that chronic renal patients, from stage 3, already have lower values of the frequency domain indexes (HF, LF, LF/HF) and SDNN compared with healthy individuals[13]. Thio et al.[9] also studied the SDNN, RMSSD, HF, LF and LF/HF indices through the PREVEND study and found that the prevalence of low HRV is significantly higher in individuals with CKD.

According to available evidence, the reduction of such indices predicts cardiovascular adverse events, including cardiovascular death from all causes[8,12,15,16]. Also, in a 2.7-year follow-up, the frequency domain indices (HF, LF, LF/HF) were the best predictors of outcomes in this population, such as cardiovascular events (15%), renal failure (22%) and death (8%)[13].

According to authors, HRV is more suppressed in CKD patients with ischemic heart disease, with systemic diseases such as diabetes mellitus or amyloidosis, and in those with a history of intradialytic hypotensive episodes[17-21]. HRV can also be directly affected by factors related to the dialysis procedure, such as composition[22] and dialysate temperature[23], PTH levels[24] and the duration of maintenance dialysis[25].

In autonomic modulation, both vagal withdrawal and sympathetic hyperactivity may contribute to the reduction of HRV[8]. The pathogenesis of autonomic dysfunction in this population may be multifactorial, caused by increased sympathetic activity and/or reduced vagal activity due to hyperactivity of RAAS and afferent signs released due to renal ischemia that stimulate sympathetic flow[26-28]. In the latter condition, the kidneys' activation with increased sodium resorption results in fluid overload, which exacerbates kidney and heart diseases[29]. In patients with renal failure combined with heart disease, low HRV may also be related to the presence of myocardial structural abnormalities[30]. In addition, Salman[31] found that mental stress also contributes to the decrease in HRV in these patients, since it interferes with CKD risk factors, such as changes in the ANS and the neuroendocrine system activity[32].

The small number of subjects from both groups should be considered a limitation in this study. However, we emphasize the difficulty of recruiting fully healthy elderly subjects and also the severity of chronic renal patients, who have a high frequency of complications and hospitalizations.

We conclude that patients with CKD undergoing outpatient hemodialysis treatment presented a reduction in parasympathetic modulation when compared with healthy individuals, suggesting impairment of the sympathovagal balance and, consequently, cardiac autonomic dysfunction.

Clinical applicability

Considering the importance of physical therapy in patients with CKD in dialysis, this study sees the HRV evaluation as a promising tool, since it represents an efficient, safe and low-cost alternative for the implementation of interventions aimed at improving cardiovascular health and quality of life of these individuals.

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