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IMPACT OF SERUM SODIUM ON HEART RATE VARIABILITY IN DIALYTIC CHRONIC RENAL PATIENTS

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ABSTRACT

Objective: to analyze the influence of serum sodium (sNa) on heart rate variability (HRV) in chronic dialytic renal patients. **Methods:** cross-sectional study with comparative approach with subjects undergoing maintenance hemodialysis and a control group. Resting HRV, in time (TD) and frequency domain (FD) analysis, and evaluation of biochemical markers of renal function were performed.The volunteers were allocated into three groups: normotremia dialysis group (NDG), hyponatremia dialysis group (HDG) and a control group (CG). **Results:** the sample consisted of 32 volunteers, being CG = 10, NDG = 14 and HDG = 8 participants. For the biochemical variables of renal function, there was a difference between CG vs NDG and HDG ($p = 0.001$). HRV analysis in TD showed that HDG presented a reduction in SDNN ($p = 0.002$) and rMSSD ($p = 0.005$) indices compared to CG. For the NN50 index, NDG and HDG presented significant differences in relation to the CG ($p = 0.010$ and $p = 0.001$ respectively).While in FD there was a reduction in the high frequency and low frequency band ($p = 0.037$ and $p = 0.007$ respectively) in HDG compared to CG. **Conclusion:** In dialysis patients there is a reduction in HRV, especially in those with hyponatremia.

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INTRODUCTION

Chronic renal patients in advanced stages may develop hyponatremia (ZHANG *et al*., 2016; GOLESTANEH *et al*, 2017), an electrolyte disorder commonly found in clinical practice, characterized by serum sodium (sNa) levels below 135 mmol/L. Moreover, hyponatremiais related to poor prognosis in severe disease and chronic diseases such as heart failure and liver cirrhosis (FERRARIO *et al*., 2015; KHAN *et al*, 2016).Recent studies have shown that chronic renal failure patients on maintenance hemodialysis (HD) have cardiac dysautonomia (HOYE *et al*., 2018) which can be verified by heart rate variability (HRV).In individuals without heart disease, HRV has a high degree of variability, in addition to indicating the body's ability to adapt to metabolic demands (TASK FORCE, 1996; VANDERLEI *et al*., 2009). Information on the impact of sNa levels on HRV of hemodialysis patients is scarce in the literature, as well as the operation of this machinery. Despite technological advances to improve the quality of uremic toxin removal and increased survival of chronic hemodialytic renal patients, there are numerous factors involved in morbidity and mortality in this population (FRANCZYK-SKÓRA *et al*., 2015). In recent decades, the number of adults requiring dialysis has increased, as well as the mortality rate (SESSO *et al*., 2017). It is necessary to understand the pathophysiology of hyponatremia in hemodialytic patients, as well as to use simple and inexpensive methods to stratify the risk of cardiovascular event and thus optimize clinical management. In the course of CKD in hemodialytic patients, changes in sNa and HRV levels are associated with unfavorable outcomes. We postulate that individuals with chronic renal failure undergoing maintenance HD with electrolyte disturbance presenting reduction in HRV will be more susceptible to cardiac dysautonomiathan individuals without electrolyte disturbance and renal disease.

MATERIALS AND METHODS

This is a cross-sectional, quantitative and comparative study. The sample consisted of 22 individuals aged 23 to 59 years of

both biological sexes, diagnosed with stage 5 chronic kidney disease with GFR <15 mL/min /1.73m² (NKF/KDOQI, 2002), registered at the Clínica de Doenças Renais in Rio Verde - Goiás.The control group (CG) consisted of 10 volunteers who belonged to the social life of dialytic patients aged 26 to 44 years old, for both sexes. All evaluations were performed only after the participant's knowledge through the informed consent form (ICF).The study included dialytic volunteers aged 18 to 60 years, with stable clinical and hemodynamic conditions, in maintenance HD three times a week for four hours, for at least three months, with the duly completed medical records containing the necessary data for biochemical research and analysis. While participants who presented hemodynamic instability, liver disease, active infection, heart failure, recent acute myocardial infarction, menopause, and total hysterectomy, as such situations may influence the reactions of the autonomic nervous system (ANS) (VON HOLZEN *et al*., 2016), transplanted patients, endocrine diseases, infectious diseases and pregnancy period, according to medical records, were excluded from the sample, as well as patients using any class of beta-blockers, as it interferes with ANS responses (SANDRONE *et al*., 1994).Regarding the control group, the sample was conceived for convenience, including volunteers who agreed through the ICF who had no history of heart disease, active infection, recent hospitalization, use of antihypertensive medication, and, besides that, presented normal renal function before the results of the biochemical tests and did not perform physical activity. The project was approved, according to Resolution No. 466/2012, by the Ethics and Research Committee of the Federal University of Goiás - Campus Jataí under opinion No. 3,166,511.

Analysis of dialytic patients' records: Health information was collected from the dialytic volunteers' medical records, such as: associated diseases, medication use, dialysis time, ultrafiltration rate (UFR) and biochemical markers of renal function, such as creatinine, urea, albumin, sodium, and index of Kt/V.

Anthropometricmeasures: All anthropometric measurements were performed using the World Health Organization standardization (WHO, 1995). Body mass was measured on a mechanical scale (model 110 CH, Welmy®, Brazil) with a capacity of up to 150 kg and a variation of 0.1 kg. Measurement was performed with the patient positioned in a bipedestation in the center of the platform, without support and without movement, with the arms extended at the side of the body. Height was measured using a stadiometer attached to the scale with a variation of 0.1 cm. Participants were instructed to stand barefoot in an upright position with legs extended, feet parallel, and heels together aligned with the stadiometer. Body mass index (BMI) was calculated as the ratio between the mass and the square of the participant's height (kg/m2).

Collection and analysis of heart rate variability: HRV analysis was performed in a room, with a temperature between 21ºC and 23ºC and humidity between 40 and 60%, between 5h and 16h to minimize the influences of circadian rhythm. The volunteers were instructed not to drink alcohol and/or ANS stimulants such as coffee and tea within 24 hours prior to the evaluation. For cardiac autonomic assessment, the resting heart rate (HR) was recorded using the Polar RS800CX heart rate monitor (Polar EletroOy, Kempele, Finland) for the acquisition of beat-to-beat signals corresponding to consecutive R-wave electrocardiogram (iR-R) intervals (WILLIAMS *et al*., 2017). This instrument consists of an elastic strap with a coupled pickup transmitter positioned on the volunteer's chest that captures information at a sampling rate of 1000 Hz, providing a temporal resolution of 1 millisecond (ms) for each iR-R. The data receiver, a watch, was placed on the subject's wrist. The dialytic volunteers were evaluated before the hemodialysis session, in the second or third weekly session. By decomposing the electrocardiographic signal, the iR-R tachogram and HRV analysis in the time (TD) and frequency (FD) domains were obtained, in accordance with standard procedures in the literature (TASK FORCE, 1996).Continuous 15 minutes of iR-R recording in supine position at rest were obtained. For the analysis, the first five minutes of recording were discarded and the next 10 minutes visually selected, the most stable five-minute stretch of stationary signal, representing the spontaneous breathing resting collection.

The electrocardiographic records were transferred to the computer and, with the aid of Polar ProTrainer 5™ software, encoded in text files and later analyzed in the Kubios HRV version 3.1 software, using the moderate-grade filter, obtaining the iR-R (MeanRR) values, in TD, the standard deviation indices of all normal iR-R (SDNN), the square root mean square of the differences between adjacent normal iR-R (rMSSD) expressed in ms, number absolute value of adjacent iR-Rs with duration difference greater than 50 ms (NN50) and percentage of adjacent iR-Rs with duration difference greater than 50 ms (pNN50), and in FD the high frequency (HF) components with variation 0.15 to 0.4Hz, which corresponds to respiratory modulation and is an indicator of the vagus nerve acting on the heart, a low frequency (LF) component with a variation between 0.04 and 0.15Hz, which is due to the action joint of the vagal and symptomatic components on the heart, with sympathetic predominance, very low frequency (VLF) component with a variation of 0.04Hz or less seems to be related to the renin angiotensin aldosterone system, thermoregulation and peripheral motor tone and the LF/HF ratio, reflects the absolute and relative changes between the sympathetic and parasympathetic components of the ANS, characterizing the sympathovagal balance over the heart (TASK FORCE, 1996).

Sodiummeasures: For plasma sodium analysis, the blood sample was collected at the pre-dialysis time and analyzed by the Ion-Selective Electrode method using the Electrolyte Analyzer Roche® equipment, according to technical specifications (AVL SCIENTIFIC CORPORATION, 1996). According to sNa levels, the dialytic volunteers were divided into two groups:hyponatremia dialysis group (HDG), which consisted of volunteers with sNa levels below normality, and normotremia dialysis group (NDG) with levels of sNa within the normal range parameters (KHAN *et al*., 2016).

Statistics

For data analysis, the Statiscal Package for Social Sciences version 20.0 software for Windows was used. Descriptive analysis of demographic and clinical data was performed. Data normality was assessed by the Shapiro Wilks test. All variables were checked for outlier presence. To compare the influence of sNa on HRV in the groups (CG, NDG, and HDG) we used the Kruskal-Wallis test and for multiple comparisons the Dunn post hoc was adopted. The Man-Whitney test was used to identify the differences between the variables obtained in each group. $P < 0.05$ were considered significant.

RESULTS

Of the 22 chronic renal failure patients undergoing maintenance HD, 14 had sNa levels within the normal range, constituting the dialysis group with normonatremia (NDG), while eight volunteers had sNA levels below the normal range characterizing the dialysis group with hyponatremia (HDG), the group without chronic kidney disease, ie, the control group (CG) was composed of 10 volunteers. The general characteristics of the participants, according to the groups, can be seen in Table 1. The drugs used by dialysis to control hypertension were: adrenergic inhibitors, calcium receptor inhibitors and angiotensin II receptor blockers. The biochemical variables related to renal function (urea, creatinine, and albumin) and sNa levels in the pre-dialysis groups, as well as in the CG, are shown in Table 2.

Statistical differences were observed between the groups (CG vs NDG and HDG), but there was no statistical difference between the NDG and HDG groups in relation to the biochemical data evaluated.The HRV analysis results from the TD analysis are shown in Table 3.The dialytic groups showed lower values when compared to the CG, especially the HDG.The SDNN index, which reflects the sympathetic component of the ANS, and the rMSSD index, which represents the parasympathetic component, are significantly reduced revealing impaired cardiac autonomic function.Analysis of HRV in TD on SDNN index showed that HDG was significantly reduced compared to CG ($p = 0.002$), as well as in rMSSD index where only HDG showed reduction when compared to CG ($p = 0.005$), demonstrating that in pairwise comparison HDG presented HRV reduction in addition to the predominance of parasympathetic modulation.

Table 1. Clinical and demographic characteristics of the study groups

Variable	CG (n=10)	NDG (n=14)	HDG (n=8)	p
Male gender (n)	3	7	5	0.85[a]
Age range (years)	31.80±5.49	38.35±10.24	43.87±13.55	0.07 [b]
Height (m)	1.67±0.40	1.62±0.72	1.61±0.07	0.15[b]
Bodymass (Kg)	74.21±7.12	67.41±11.46	64.33±17.51	0.08[b]
BMI (kg/m²)	26.48±2.05	26.39±4.69	25.58±6.47	0.57[b]
Ultrafiltration rate (ml)	-	2.61±1.23	2.81±1.05	0.73[c]
Dialysis time (months)	-	27.92±22.62	47.75±36.75	0.37[c]
Cause of CKD	-			0.79[a]
Hypertensivenephrosclerosis(n)	0	4	3	0.60[a]
Notclarified (n)	0	9	4	0.67[a]
Chronicglomerulonephritis(n)	0	1	1	0.70[a]

CG:control group; NDG = normotremiadialytic group; HDG = hyponatremiadialytic group; m = meters; BMI = body mass index; kg/m² = kilograms per square meter; kg = kilograms; ml = milliliters; Chi-square test, Kruskal-Wallis[b] test; Mann-Whitney[c] test.

Table 2. Biochemical data on renal function, electrolyte and dialysis adequacy according to study groups

Variable	CG (n=10)	NDG (n=14)	HDG (n=8)	p
Urea (mg/dL)	28.60±11.82	83.78±24.82	101.37±32.19	0.00 [ab]
Creatinine (mg/dL)	0.94±0.21	9.90±2.29	10.13±3.38	0.00 [ab]
Albumin (g/dL)	4.50±0.44	3.81±0.54	3.96±0.57	0.00 [ab]
Sodium (mmol/L)	140.74±1.12	137.64±1.15	133.50±1.51	0.00 [ab]
Kt/V	NA	1.48±0.39	1.48±0.45	0.91

CG:control group; NDG = normotremiadialytic group; HDG = hyponatremiadialytic group; mg/dL = milligrams per deciliter; g/dL = grams per deciliter; mmol/L = millimol per liter; Kt/V = dialysis adequacy index; NA = not applicable;Kruskal-Wallis test. [a] Difference between CG and NDG; [b] Difference between CG and HDG.

Table 3. Heart rate variability analysis data from time domain according to study groups

Variable	CG (n=10)	NDG (n=14)	HDG (n=8)	p
MeanRRms	837.20±126.22	807.08±118.54	772.54±102.59	0.70
SDNN ms	35.41±19.14	17.37±13.33	9.16±4.99	0.00 [a]
rMSSDms	39.50±24.79	18.13±18.30	9.97±6.96	0.01 [a]
NN50 ms	55.33±58.76*	12.21±36.01	2.25±6.36	0.00 [ab]
pNN50	16.66±18.21*	3.44±10.12	0.57±1.63	0.00 [ab]

CG:control group; NDG = normotremiadialytic group; HDG = hyponatremia dialysis group, MeanRR: mean of normal i-RR; SDNN = standard deviation between all adjacent i-RRs; rMSSD = square root of square mean of the differences between adjacent normal iR-R; NN50 = absolute number of adjacent iR-Rs with duration difference greater than 50 ms; pNN50 = percentage of adjacent iR-R with duration difference greater than 50 ms; ms = milliseconds. Kruskal-Wallis test; [a] Difference between CG and HDG groups; [b] Difference between CG and NDG groups, *outlier excluded.

Table 4. Heart rate variability analysis data from frequency domain according to study groups

Variable	CG (n=10)	NDG (n=14)	HDG (n=8)	p
VLF Hz	0.03±0.00	0.03±0.00	0.03±0.00	0.24
LF Hz	0.08±0.02	0.06±0.02	0.05±0.01	0.09
HF Hz	0.27±0.06	0.28±0.08	0.29±0.07	0.85
LF su	44.59±22.48	55.99±24.93	51.46±27.70	0.40
HF su	55.25±22.58	43.67±24.88	48.40±27.69	0.40
LF/HF	1.44±2.12	2.04±1.66	1.45±1.99*	0.30
VLFms²	25.22±22.92	38.69±51.08	9.41±13.65	0.08
LFms²	363.01±376.08*	183.22±249.23	29.06±25.65	0.01[a]
HFms²	798.25±1042.66*	155.21±308.59	40.66±47.28	0.03[a]

CG:control group; NDG:normotremiadialytic group; HDG:hyponatremiadialytic group; VLF: very low frequency; LF:low frequency; HF:high frequency; Hz:Hertz; su:standard units; LF/HF: low to high frequency ratio; ms²: absolute spectral; Kruskal-Wallis test; [a] Difference between CG and HDG groups, *excluded outlier

For the NN50 index, in pairwise comparison, the NDG and HDG presented significant differences in relation to the CG (p = 0.010 and p = 0.001 respectively), as well as for the pNN50 index revealing differences between the CG vs NDG (p = 0.014). and CG vs HDG (p = 0.001).Table 4 presents the results of the HRV analysis in the FD.As in TD, the groups with dialytic individuals showed a reduction in the absolute spectral low (LFms²) and high frequency (HFms²) components, especially in the HDG. The other indices were reduced in the dialysis groups, but without significance. These results reveal that hyponatremia had a negative impact on LFms² component in HDG compared to CG (p = 0.007), as well as HFms² component (p = 0.037). The other indexes of the FD did not present differences between the analyzed groups.

DISCUSSION

The results of the present study suggest that chronic renal patients undergoing maintenance HD present a reduction in cardiac autonomic modulation by HRV analysis when compared to individuals who do not undergo dialysis. In NDG, the autonomic imbalance found was the predominance of sympathetic modulation and impairment of parasympathetic modulation. In HDG, there was a predominance of parasympathetic modulation, but the values are lower compared to other groups, whose implication results in reduced cardiac autonomic function, predisposing to increased cardiovascular risk. The HRV analysis in the TD in the SDNN index, which represents the sympathetic activity of the ANS (TASK FORCE, 1996) showed significantly reduced values predominantly in the HDG (p = 0.002) compared to the other research groups.A previous study examined the association between HRV and cardiac and cerebrovascular events in patients with CKD undergoing HD, and found that SDNN values in the group that developed cardiac and cerebrovascular events were low compared to those who did not, and thus showed that the predominance of sympathetic modulation favors the development of cardiovascular disease (CVD) (KIDA *et al*., 2017). Although there are no established scores to define cardiac dysautonomia, a review by Hildreth (2012) on the prognostic indicators of HRV in CKD showed that individuals with SDNN values below 50ms had a higher risk of sudden cardiac death.In our study, the analyzed groups presented SDNN index with values below those reported in the literature (CG = 35.41 ± 19.14ms; NDG = 17.37 ± 13.33ms; HDG = 9.16 ± 4.99ms), in the CG. This fact is probably due to sedentary lifestyle. According to Maia (1997), under physiological conditions, the rMSSD and pNN50 indices represent the vagal activity. This author states that values lower than 30ms rMSSD and 4% pNN50 should be considered as a risk factor for triggering arrhythmias. In the present investigation, it was found that the volunteers of the dialysis groups presented rMSSD (NDG = 18.13 ± 18.30ms and HDG = 9.97 ± 6.96ms) and pNN50 (NDG = 3.44 ± 10.12 and HDG = 0.57 ± 1.63) below normality according to literature data.

The rMSSD, TD index reflecting parasympathetic activity (TASK FORCE, 1996) in HDG, showed significantly reduced values (p = 0.005) when compared to CG and NDG and, according to some studies, its reduction is associated with the independent risk of mortality in patients with CKD (DRAWZ *et al*., 2013). These results corroborate previous analyzes that found a reduction in SDNN and rMSSD indices in patients with chronic kidney disease undergoing HD (OIKAWA *et al*., 2009; SIPAHIOGLU *et al*., 2012; KIDA *et al*., 2017). The HRV analysis in the FD, in the NDG group presented with reduced values in the LFms² and HFms² component when compared to the CG, however, there was a predominance of sympathetic modulation since the LFms² component presented a higher score than the HFms² component. Similar relationship was reported in the study by Lerma *et al* (2014) in hemodialysis patients with a mean age of 32 ± 9 years of age in whom there was greater sympathetic influence at the pre-dialysis time. The LF component may reflect cardiac effects via the vagus-mediated baroreflex (SILVA *et al*., 2015; THOMAS *et al*., 2019).

The VLFms² index in FD was reduced in HDG (9.41 ± 13.65) compared to the other groups (CG = 25.22 ± 22.92 and NDG = 38.69 ± 51.08). This fact can be attributed to the dialysis time, which was longer in HDG than in NDG (47.75 ± 36.75 vs 27.92 ± 22.62 months respectively), which attenuated the activity of the renin angiotensin aldoterone system.In HDG hyponatremia accentuated cardiac dysautonomia when compared to the other study groups, however it is noted that in this group there was a slight parasympathetic modulation. Parasympathetic modulation, reflected by the HF component, in HDG is supposed to be a response due to prolonged dialysis time in which these patients have already experienced significant increase in sympathetic activity and changes in autonomic function contributed to changes in cardiovascular structure as a function of CKD. However, it is important to note that the relationship between changes in autonomic flow and cardiovascular remodeling is two-dimensional, and that altered cardiac and vascular morphology may influence parasympathetic tone during kidney disease (SALMAN, 2015). Hyponatremia in CKD in patients undergoing maintenance HD is not fully elucidated, it is assumed that it is a result of free fluid intake in the interdialytic period. Thus, hyponatremia may be an indicator of poor prognosis and inadequate water removal during dialysis (COMBS; BERL, 2013; GOLESTANEH *et al*., 2017; PEIXOTO; SANTOS, 2011; ZHANG *et al*., 2016) in addition to release excessive vasopressin due to non-osmotic stimuli, such as pain, anesthetics, hypoxemia, hypovolemia, and use of diuretics (RAMESH, 2012).A previous study by Serigar (2014) found that sNa levels can be used as predictors of extracellular fluid and volume in hemodialytic patients. For these individuals it is recommended that the intradialysis weight be between 2.5-2.9 Kg in order to avoid reduced sNa levels. In the present investigation it was observed that there was no strict control of the weight reflected by the ultrafiltration rate (NDG = 2540 ± 1250 and HDG = 27010 ± 1030 ml), although the study was cross-sectional. Importantly, proper control of fluid and sodium intake is crucial for this population, in order to avoid fluctuations in ultrafiltration and not to overload the cardiovascular system during HD (Chirakarnjanakorn *et al*., 2017). Although there are reports that uremic toxins can directly damage small nerve fibers by hydroelectrolytic changes producing expansion or shrinkage of the neural space, this mechanism is not completely elucidated (CHOU; TSAI, 2016). Previous trials report that CKD alters autonomic function indirectly through the following mechanism: the renin angiotensin aldosterone system is activated and angiotensin II modulates regional outflow and redefines the baroreflex toward a range of blood pressure. In addition, CKD also stimulates afferent fibers and impairs the inhibitory renal reflex, contributing to increased sympathetic activity. Other factors, such as salt retention, decreased nitric oxide

bioavailability, cardiovascular remodeling and increased endothelin and insulin production may also influence cardiovagal tone (CHOU; TSAI, 2016).To our knowledge, there are no studies in the literature that have investigated the influence of hyponatremia on HRV in chronic renal failure patients undergoing maintenance HD in adults and with prolonged dialysis duration, which shows our findings where individuals with sNa inferior to the normal range present a reduction in HRV, as well as a modest parasympathetic activation due to the course of renal disease and the morphofunctional adaptations imposed by hemodialysis therapy. Thus, due to the intermittent nature of HD, patients experience extreme changes in cell compartments, resulting in electrolyte changes, and hemodynamic instability, altering cardiac electrophysiology, which in turn accentuates autonomic dysfunction leaving this public susceptible to the risk of mortality from CVD.

Conclusion

Patients with end-stage CKD undergoing maintenance HD have reduced HRV, reflecting significant autonomic dysfunction, especially in those with hyponatremia. These conditions configure relevant risk factors for the development of a cardiovascular event. The study presented limitations regarding the sample size and that in the CG, only anamnesis about the health status was performed and there was no confirmation through specific exams that prove the absence of cardiovascular disease. As well, it was not possible to prove the sedentary lifestyle in the study groups, because no specific questionnaire was applied for this purpose, which was restricted to only one question in the evaluation form. Studies with a larger sample and tapered criteria for the control group are suggested to confirm the damage that changes in sNa levels may cause in the neurocardial axis of chronic renal patients.

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