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ELECTROCARDIOGRAPHIC FINDINGS IN PATIENTS WITH CHRONIC KIDNEY DISEASE BASED PRINCIPAL COMPONENTS ANALYSIS

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ABSTRACT

The purpose of this study was to investigate findings in electrocardiographic (ECG) parameters in patients with chronic kidney disease (CKD) based on Principal Component (PC) Analysis. This study was designed as a cross-sectional study of consisted of twenty-five men subjects 36 to 80 years with a diagnosis of stage 5 of CKD, selected at random from Nephrology Unit Hospital. All subjects were instructed to lie in the supine position for 3 min at rest while breathing normally with a ECG working at a sampling rate of 1200 Hz was used to record ECG parameters to obtain the classical parameters iPR, sPR, iQRS, sST, iRR and QTc and, subsequently, re-sampling procedure to bootstrapping based on 1000 samples. The PCs involve the calculation of the eigenvalue decomposition of the ECG parameters covariance matrix and use of the biplot graph, in order to understand the importance of each variable. CKD was associated with iRR (PC1: 0.998 and PC2: -0.040) ECG parameter showed greater contributions to PC1 and the QTc ECG parameter (PC1: -0.005 and PC2: 0.813) showed bigger contributions to PC2. In conclusion, the ECG findings in patients with CKD are particularly caused by reducing the RR interval and prolonged QT interval are particularly caused by an increase in the tone of the sympathetic nervous system.

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INTRODUCTION

The spectrum of infection induced kidney diseases is diverse and premature death (Prasad and Patel, 2018). Infections manifest in form of several renal clinical syndromes such as: acute kidney injury, acute and chronic glomerulonephritis syndrome, nephrotic syndrome, acute nephritic-nephrotic syndrome, acute or chronic tubulointerstitial nephritis, and rapidly progressive glomerulonephritis to levels less than 60 ml/min/1.73m² of body surface for more than three months, favoring the emergence of hydroelectrolytic, hormonal and metabolic disorders (Flores-Mireles *et al*., 2015; Glassock *et al*., 2015). This has been confirmed by multiple epidemiological studies wherein as compared with the general population, patients with chronic kidney disease (CKD) had more frequent and severe cardiovascular disease (Subbiah *et al*., 2016). The CKD per se is considered to be a coronary artery disease, inflammation, systemic arterial hypertension, left ventricular hypertrophy, early atherosclerosis (Varma *et al*., 2005) and, consequently, leading to an increase of the autonomic nervous system of sympathetic activity (Poulikakos *et al*., 2015) prevalent in CKD patients undergoing hemodialysis (Yamomoto; Kon, 2009) and in fact persons with early stages of CKD are more likely to die of cardiovascular disease than progress to end-stage renal disease (Subbiah *et al*., 2016).

The electrocardiogram (ECG) is a gold standard diagnostic tool for recording electrical phenomena of cardiac activity during renal therapy, because it is a mechanism widely used to detect cardiac pathologies and morphological problems (Pastore *et al*., 2016) in patients with CKD (Subbiah *et al.,* 2016; Green *et al*., 2011) and, mainly, the acquired prolonged QT interval syndrome that is a condition of high prevalence among patients with CKD on hemodialysis leading to left ventricular hypertrophy along with electrolyte changes developing coronary heart disease and heart failure (Yamomoto; Kon, 2009), consequently, sudden cardiac death (Shastri; Sarnak, 2010).

Previous studies have shown that patients with CKD on hemodialysis have a high frequency of ECG with pathological changes, including a high prevalence of patients with prolonged QT interval and a reduction in the RR interval (Bonoto *et al*., 2016; Green *et al*., 2011).

However, until the present study it has not been investigated which ECG parameters are associated with CKD using the principal component analysis after a biomedical literature review from Medline Pubmed, which makes this study justified.

Multivariate analysis is based on statistical techniques that have been studied in variables across multiple dimensions while taking into account the effects of all variables on the responses of interest (Rudd *et al*., 2019). The Principals Components Analysis (PCA) is a widely used statistical technique for unsupervised dimension reduction (Jolliffe; Cadima, 2016).

In the sense, PCA is an exploratory method because it investigates and confirms the previous hypotheses of collected data. The PCA has been used to project data onto a smaller subspace while preserving the maximum variance of the original data beyond the conventional noise-reduction explanation (Materko, 2018) and use of the biplot graph, in order to understand the importance of each variable ECG parameters in CKD. Thus, the purpose of the present paper was to describe the ECG parameters in patients with CKD using PCA.

METHODS AND MATERIALS

The study protocol was approved by a local Ethical Human Research Committee of Universidade Federal do Amapá (CAAE: 16335119.8.0000.0003), and an informed written consent was obtained from all subjects. This study was conducted in accordance with the instructions of the Helsinki Declaration of 2008 and in accordance with Resolution 466/2012 of the National Health Council.

Subjects: The sample consisted of twenty-five men subjects aged 36 to 80 years with a diagnosis of stage 5 of chronic kidney disease (CKD), nonsmokers and with no history of cardiopulmonary, metabolic and osteomioarticular diseases, selected at random from Nephrology Unit of Macapá of the Hospital of Clínics Dr. Alberto Lima (HCAL) located northwest of the North Region of Brazil, also known as the Amazon Region.

Anthropometric Measurements: During an orientation session, the testing procedures and time commitment required for participation in this study were verbally explained to the potential volunteers. The data collection and the anthropometric variables were performed by the same and experienced evaluator throughout the study. For measuring both body weight and height participants were kept barefoot, wearing light clothes and not carrying any object. The height was measured in centimeters and the body mass was measured in kilogram with certified and calibrated mechanics scale (Filizola, Brazil).

Acquisition of electrocardiographic data: The electrocardiogram was performed in the first hour of the hemodialysis session in all patients were instructed to remain quiet in the supine position for 3 min at rest with spontaneous breathing. A professional ECAFIX electrocardiograph, model 12S PC, of three channels, with 12 derivations with sampling frequency of 1200 Hz, with network and muscle filter, gain of 10 mm/mV and speed of 25 mm/s. The review of the recordings was conducted according to the Interpretation Guidelines for Electrocardiogram at Rest of the Brazilian Society of Cardiology (Pastore *et al.,* 2016). The electrocardiograms were reviewed through the creation of descriptive reports and determination of the following variables: (1) PR interval was measured from the beginning of the P wave to the beginning of the QRS complex, including the P wave and the PR segment (iPR); (2) the PR segment was measured between the end of the P wave and the beginning of the QRS complex (sPR); (3) the QRS interval was measured from the beginning of the Q wave to the end of the S wave (iQRS); (4) the ST segment was measured from the end of the QRS complex to the beginning of the T wave (sST); (5) RR interval was measured by the distance between two successive R waves (iRR) and, finally, (6) QT interval was measured from the beginning of the Q wave to the end of the T wave, time that represents ventricular depolarization and repolarization. The corrected QT interval (QTc) was used because it is considered more appropriate when taking heart rate into account (Kawataki *et al*., 1984). Thus, was used the QTc = QT/√RR, calculated using the Bazett equation (1920).

Data Processing: Descriptive statistical analyses of the data were expressed as mean ± standard deviation or standard error. The Kolmogorov-Smirnov test confirmed the normality of distributions. The bootstrap is a statistical procedure that resamples a single dataset to create many simulated samples. In the sense, the bootstrap was used to estimate statistics of the ECG parameters on a population based on 1000 samples defined in terms of bias and confidence intervals (Carpenter; Bithell, 2000). All the tests were assumed $\alpha = 0.05$. The PCA involves a mathematical procedure that transforms a number of possibly correlated variables into a smaller number of uncorrelated variables called principal components. It involves the calculation of the eigenvalue decomposition of the ECG parameters covariance matrix (SA_P) or singular value decomposition of the ECG parameters matrix and use of the biplot graph (Jolliffe; Cadima, 2016). The principal components (PCs) were obtained by the solutions of the linear system given by:

$$SA_P = \lambda_P A_p$$

where λ are the 6 eigenvalues ranked in decreasing order and A are the corresponding normalized eigenvectors.

The eigenvector with the highest eigenvalue is the first principal component. The second principal component corresponds to the second highest and so on (Zhang; Castelló, 2017). All procedures were processed in Matlab version 2020.b (Mathworks, USA).

RESULTS

Anthropometric and physical characteristics of the participants are presented in Table 1. Low standard deviation values confirmed the homogeneity of the sample.

Table 1. Anthropometric and physical characteristics of participants

Variables	Mean ± SD	CI95%	P-value
Age (years)	55,0 ± 12,4	49,8 – 60,1	0,22
Height (cm)	166,1 ± 7,1	163,1 – 169,1	0,91
Body mass (kg)	76,6 ± 13,6	70,9 – 82,3	0,09
BMI (kg/m2)	27,5 ± 3,4	26,1 – 28,9	0,33

Values are mean ± standard deviation (SD), CI 95% is the confidence interval around 95% the mean and P-value of Kolmogorov-Smirnov test.

The bootstrap was used to estimate statistics of the ECG parameters on a population based on 1000 samples defined low bias and confidence intervals within the sample mean for group are showed in Table 2.

Table 2. The bootstrap of ECG parameters of participants

Variables	Mean ± SE	Bootstrapping Bias	CI95%
iPR (ms)	163,2 ± 6,0	0,200	150,4 – 176,1
sPR (ms)	76,2 ± 3,5	0,120	68,4 – 83,2
iQRS (ms)	107,2 ± 4,4	-0,004	99,2 – 115,2
sST (ms)	204,0 ± 14,7	-0,006	176,0 – 232,0
iRR (ms)	766,4 ± 24,9	0,620	716,8 – 814,4
QTc (ms)	469,0 ±7,0	-0,08	456,1 – 484,0

Values are mean ± standard error (SE) and CI95% is confidence intervals 95%.

The results obtained by the technique of the principal components indicated that two first PCs were employed by 96.8% of the total variance explained of the original variables, in that PC1 corresponds to 92.3% and the PC2 for 4.5% of the variations of the data. Figure 1 illustrates the variable iRR (CP1: 0.998 and CP2: 0.040) showed bigger contributions to PC1 with higher weighting coefficient of all variables. The QTc parameter (CP1: -0.005 and CP2: 0.813) showed bigger contributions to PC2 with weighting coefficients than iQRS (CP1: 0.011 and CP2: 0.086), iPR (CP1: 0.062 and CP2: -0.562) and sPR (CP1: 0.011 and CP2: -0.109), finally, the variable sST showed a smaller contributions to PC1 and PC2 with weighting coefficients of 0.000 and -0.000, respectively.

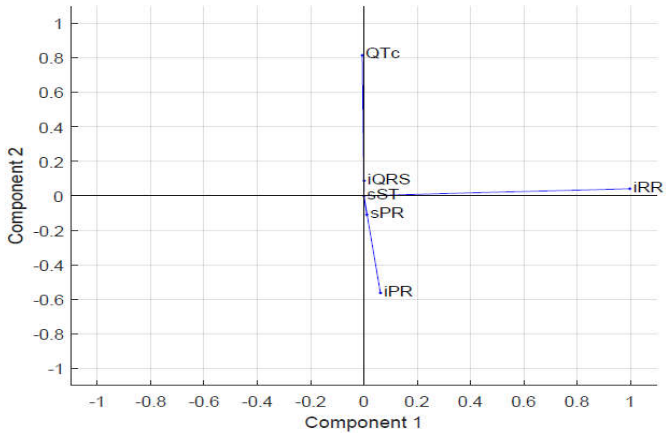

Figure 1. First and second principal component coefficients ECG parameters

DISCUSSION

The purpose of the present paper was to describe the impact of the ECG parameters in patients with CKD by PCA. Therefore, the patients with CKD were associated with iRR showed contributions to PC1 and the QTc parameter showed contribution to PC2. The bootstrap was used to estimate the statistics of the ECG parameters of patients with CKD in a population based on 1000 samples, defined as low bias and the average of the variables of the sample studied within the confidence intervals.

The ECG findings in patients with CKD are particularly caused by reducing the RR interval and prolonged QT interval, demonstrating the most important parameters in CKD. The findings regarding the QTc intervals durations use to be also a little bit controversial. Bignotto and co-works (2012) has detected in CDK patients QTc intervals prolongation explained by the occurrence of malignant ventricular arrhythmias (Kaye *et al*., 2013; Priori *et al*., 2013). Other studies have shown that hemodialysis is a factor that increases the dispersion of the QT interval (Bonato *et al*., 2016; Go *et al*., 2004).

The electrocardiographic QT interval is long, and this prolongation is clinically significant when it has a cut to a long QTc ≥ 450 ms for men and ≥ 470 ms for women, following the orientations of the Guideline of the Brazilian Society of Cardiology (Pastore *et al*., 2016). Similar to the QTc intervals found in our study at 469.0 ± 7.0 ms in patients men with CDK. The prolongation QTc interval increases the risk of ventricular tachyarrhythmia and can become a causative agent of sudden death (Skampardoni *et al*., 2019).

Cardiac disorders are the main causes of death in individuals with dialytic CKD, therefore, there are several studies pointing out that ventricular arrhythmias have a high prevalence in patients with CKD (Bonato; Canziani, 2017, Di Lullo *et al*., 2015). In this sense, the finding of the present study corroborates this hemodynamic instability with the presence of tachycardia in patient with CKD, with a decrease in heart rate variability by reducing the RR interval (Delgado *et al*., 2017), mainly in patients with CKD in the final stage (Poulikakos *et al*., 2015) to being responsible by the expressive rate of sudden death (Zoccali *et al*., 2004; Mitsnefes, 2008). Cardiac arrhythmias happen due to acute changes in serum electrolyte levels in the plasma and the significant removal of fluids during hemodialysis, such variations are common in patients with advanced CKD (Delgado *et al*., 2017). When the patient is hypertensive and dialyzed, the remove of fluids and electrolytes is explained by hydrosaline retention, leaving the individual more susceptible to hydroelectrolytic changes, contributing to the onset of arrhythmias (Agarwal; Light, 2009), resulting from the high prevalence of patients with CKD and arterial hypertension (Bucharles *et al*., 2019), as showed in the present study.

Future research should address the limitations of the present study by employing a sample from different age and both sexes, analyzing other renal replacement therapies, other nephrology centers and, mainly, identifying the predominance of inflammatory phenotype that requires monocytes to promote chronic inflammation by increasing IFN-γ, IL-6 and C-reactive protein produced by Th1 cells in patients with CKD and associating the ECG signal.

Conclusion

The electrocardiogram is a low-cost test that is accessible in all sectors of renal therapy and is an important diagnostic tool regarding cardiac electrical conduction. The ECG findings in patients with CKD are particularly caused by reducing the RR interval and prolonged QT interval are particularly caused by an increase in the tone of the sympathetic nervous system.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relations hips that could be construed as a potential conflict of interest.

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