Study of Ventricular Electrical Systole in Patients with End-Stage Kidney Disease on Hemodialysis

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Abstract

Background: Patients with end-stage kidney disease (ESKD) experience elevated cardiac stress because of the repetitive and intermittent character of dialysis. Changes in ventricular electrical systole induced by necessary dialysis significantly contribute to predict sudden death due to arrhythmia in ESKD.

Objective: The major objective of this study was to assess the behavior of ventricular repolarization in dialysis by analyzing QTc interval and QTc dispersion.

Methods: This study sample consisted of 47 patients undergoing hemodialysis (61.7% males and 38.3% females), whose mean age was 66.79 ± 13.16 years. All of them underwent three electrocardiograms performed before, during and after one dialysis session. Ventricular electrical systole was analyzed later.

Results: An increase in maximum QTc interval and QTc dispersion associated with dialysis was observed. In addition, an increase in the number of individuals meeting the electrocardiographic criteria for left ventricular hypertrophy (LVH) was observed. After dialysis, higher means of the maximum QTc interval (473 ± 27.63 mseg) and of the QTc dispersion (58.95 ± 18.87 mseg) were observed in individuals with LVH as compared with those in individuals without LVH (455.21 ± 26.85 mseg and 44 ± 16.41 mseg, respectively).

Conclusion: This study confirmed an increase in the QTc interval and QTc dispersion associated with dialysis. That emphasizes the dependence of ventricular repolarization on fluid and electrolyte balance, and suggests a profile of higher vulnerability to arrhythmia associated with dialysis (Arq Bras Cardiol. 2013;100(3):261-268).

Keywords: Renal Insufficiency, Chronic; Renal Dialysis; Mortality; Arrhythmias, Cardiac.

Introduction

The National Kidney Foundation (NKF) has defined two major outcomes for chronic kidney disease (CKD): progressive loss of kidney function and presence of complications, especially the cardiovascular ones[1-3]. To better characterize disease progression, five stages of CKD have been established, stage 5 requiring kidney replacement therapy[2,3].

Hemodialysis is the most frequently used kidney replacement therapy worldwide, indicated when the kidneys can no longer perform their multiple homeostatic functions[4].

Patients with end-stage renal disease (ESRD) undergoing hemodialysis have a high mortality rate, which is correlated with the occurrence of cardiovascular disorders, such as ventricular arrhythmias and sudden cardiac death[5,6].

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Hemodialysis therapy is intermittent, causing significant changes in blood volume, in acid-base balance, and in serum potassium concentrations, which contribute to the occurrence of those complications[5,7,8]. Electrocardiographic changes are frequently found in individuals undergoing hemodialysis, and the dialytic therapy itself potentiates the occurrence of a large number of changes[5,6].

The changes in ventricular electrical systole during the dialytic therapy are associated with an increased risk of potentially malignant ventricular arrhythmias due to QT interval prolongation and dispersion. Such changes translate heterogeneity in ventricular depolarization and repolarization in individuals with ESRD, and can predict ventricular arrhythmias and sudden cardiac death[5,6,9,10].

Thus, studying the duration of ventricular electrical systole on surface electrocardiography (ECG) and myocardial repolarization heterogeneity in different ventricular areas potentiated by dialytic therapy is the major objective of this study. The importance of this study lies in the fact that those changes in ventricular electrical systole seem to provide important information about the substrate for potentially malignant tachyarrhythmias in ESRD.

Methods

Initially, this study's project was submitted to the Beira Interior Dialysis Center (CDBI) for approval. After that, patients with ESRD on hemodialysis at that center were instructed about this study and, of the 120 patients undergoing hemodialysis at CDBI, 70 provided written informed consent to participate in this study. On a second phase, ECG was performed at three defined time points of the dialytic therapy. Of those 70 patients, only 47 met the inclusion criteria.

The inclusion criteria were as follows: patients with ESRD undergoing hemodialysis; patients accepting their participation in the study; and sinus rhythm on ECG. The exclusion criteria were as follows: chronic atrial fibrillation; bundle branch block; impossibility to define the end of the T wave on more than three electrocardiographic leads; and refusal to participate in the study. The exclusion criteria were applied based on ECGs previously performed, their reports, and clinical information.

Three 12-lead ECG were performed at rest in all individuals at the following three different times: before hemodialysis; during hemodialysis (between two and two and a half hours into the dialysis session); and after hemodialysis (up to 30 minutes after the session). A BTL-08 SD® ECG device was used with 3M® electrodes (ten electrodes used per every three ECG performed in the same individual), and the recording was analyzed by using the BTL-08 WIN® software.

The QT interval (measure of the time between the start of the QRS and the end of the T wave) was calculated on the three ECGs at all leads at which that interval could be measured and in two consecutive cardiac cycles; it was corrected for heart rate according to the Bazzet formula ($QTc = QT/\sqrt{RR}$)[11]. The end of the T wave was defined as the return to the baseline on ECG; in the presence of U waves, the end of the T wave was defined as the point between the T and U waves[11]. The maximum QTc interval was defined as the longest QTc interval on ECG. Then, the QT dispersion (difference between the maximum and the minimum QT intervals) and QTc dispersion (difference between the maximum and the minimum QTc intervals) were analyzed. The QTc interval was considered increased as follows: in men, > 450 mseg; and in women, > 460 mseg[11].

Left ventricular hypertrophy (LVH) was assessed by using the Sokolow-Lyon index (SL) and Cornell index (CI) at the following three time points: before the hemodialysis session; during the hemodialysis session; and after the hemodialysis session. Individuals under the age of 35 years and those with extensive anterior necrosis did not undergo LVH assessment.

Frequency of the following ventricular arrhythmias on ECG was assessed: isolated ventricular ectopic beats; paired ventricular ectopic beats; and self-limited tachycardia.

Patients were weighed twice, before and after the dialysis session, and the weight lost during session was calculated.

Statistical analysis

Data were analyzed with the SPSS 17.0® program for Windows®. Simple descriptive statistics was used for the characterization of the sample and respective distribution of the variables.

Means were compared by use of Student *t* test. Generalized linear model was used for simple repeated measures and for mixed repeated measures with post-hoc Bonferroni test, and the models' assumptions were validated. The following nonparametric tests were also used: Friedman test; Cochran Q test; and chi-square of independence.

The significance level of 5% was adopted for a 95% confidence interval.

Results

Description of the sample

The duration of the dialytic therapy ranged from three to 126 months (mean, 43.49 ± 26.66 months). All individuals underwent three dialysis sessions per week. Twenty-eight individuals underwent hemodialysis on Mondays or Thursdays (59.6%), corresponding to their first session of the week, while 19 individuals underwent hemodialysis on Fridays or Saturdays (40.4%), corresponding to their third and last session of the week.

The duration of each dialysis session ranged from 245 and 270 minutes. Most individuals (n = 32; 68.1%) underwent 250 minutes.

The patients' ages ranged from 30 to 87 years (mean age, 66.79 ± 13.16 years), and, of the 47 patients studied, 29 (61.7%) were males.

The major cause of ESRD was diabetes mellitus (DM) (44.7%, n = 21), followed by unknown etiology, with an equally elevated frequency (23.4%, n = 11).

The cardiovascular risk factors associated with ESRD observed in the sample were as follows: arterial hypertension (AH), 87.2% (n = 41); DM, 46.8% (n = 22); and dyslipidemia, 29.8% (n = 14).

The following cardiovascular disorders frequently associated with ESRD: angina pectoris (38.3%, n = 18); acute myocardial infarction (AMI - 12.8%, n = 6); and cerebrovascular accident (CVA - 10.6%, n = 5).

Study of LVH

The frequency of LVH was assessed by use of the SL and CI at the three time points in the study. An increased frequency of LVH was observed throughout the session ($p < 0.001$), considering the increase in the QRS complex amplitude associated with dialysis and calculating the LVH by use of those indices (Chart 1).

To better characterize LVH, the increase in the QRS complex amplitude throughout therapy was analyzed at the three time points in the study by calculating the SL and CI. The statistically significant differences are shown in chart 2.

The mean decrease in patients' weight was 2.30 ± 0.86 kg from the pre-dialysis period to the post-dialysis (69.34 ± 11.31 kg and 67.03 ± 11.19 kg, respetively), and that difference was significant ($p < 0.001$).

Considering the weight reduction, two models were adjusted relating weight and the SL and CI to the pre- and post-dialysis periods; a significant interaction between weight and the two indices was observed ($p < 0.001$), confirming that the increase in the QRS complex amplitude is associated with weight loss in those patients (Chart 3).

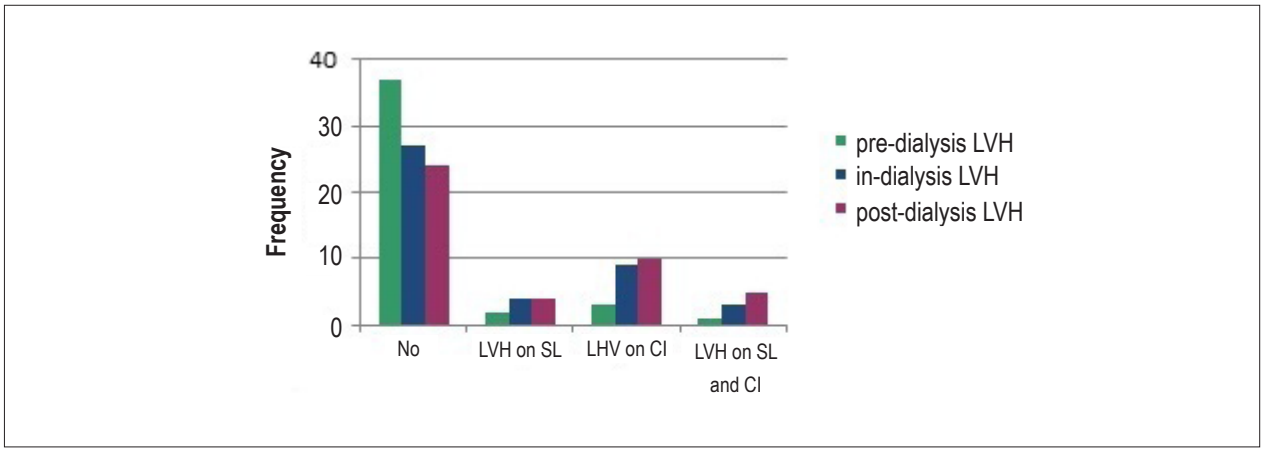

Chart 1 – *Sample distribution according to LVH before, during and after dialysis. LVH: left ventricular hypertrophy; SL: Sokolow-Lyon index; CI: Cornell index.*

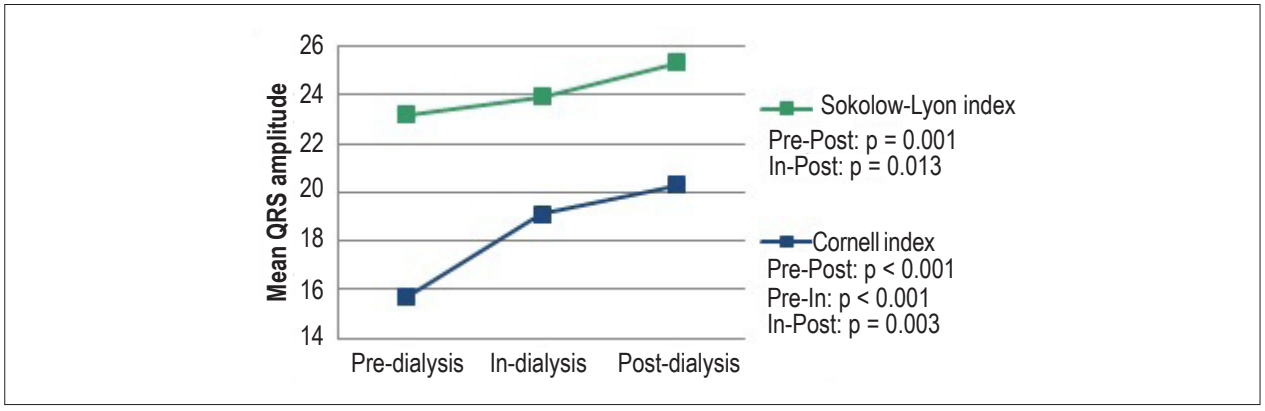

Chart 2 – *Mean of the Sokolow-Lyon and Cornell indices before, during and after dialysis.*

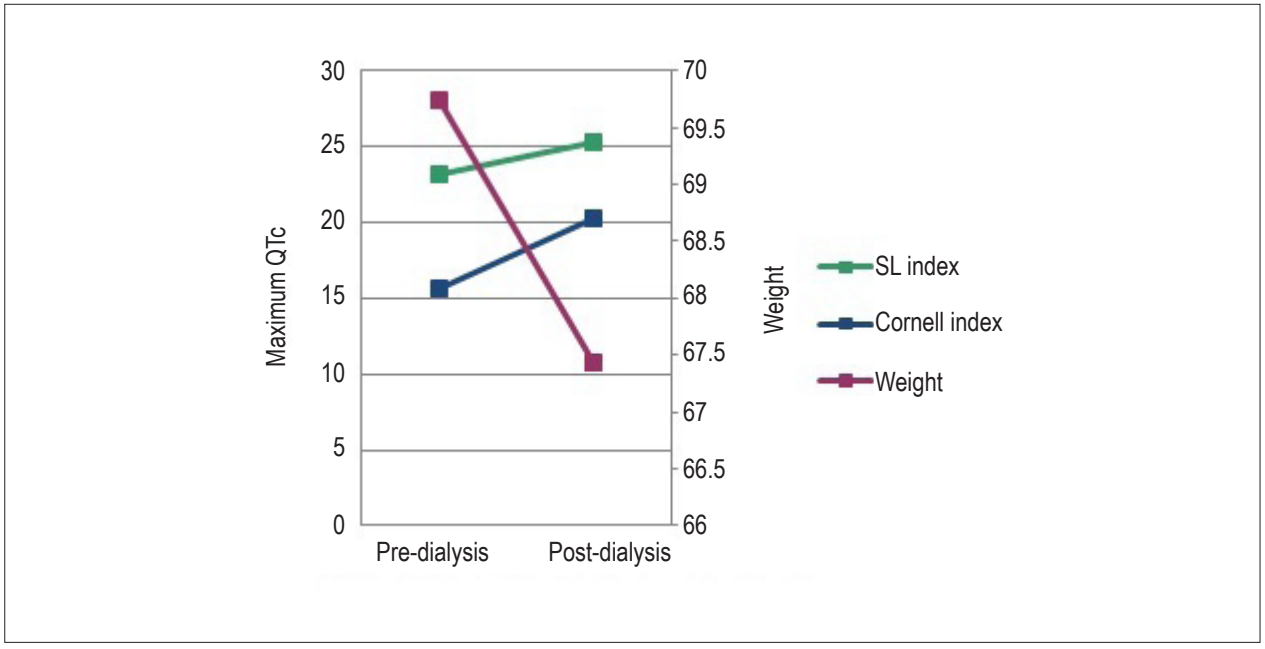

Chart 3 - *Variation of the Sokolow-Lyon and Cornell indices and weight before and after dialysis. SL: Sokolow-Lyon index.*

Study of the ventricular electrical systole

The mean maximum QTc interval was as follows: before dialysis, 452.91 ± 21.84 mseg; during dialysis, 459.23 ± 26.77 mseg; and after dialysis, 460.89 ± 29.44 mseg (Chart 4). Thus, the mean maximum QTc interval increased throughout the dialytic therapy, and the differences were significant between the first and third measurements (p = 0.028), and marginally significant between the first and second measurements (p = 0.079).

The frequency of patients with maximum QTc intervals above the normal limit increased from the pre-dialysis measurement to the following two measurements [pre-dialysis, 38.3% (n = 18); during dialysis, 57.4% (n = 27); and post-dialysis, 51.1% (n = 24), p = 0.043].

The mean QTc interval dispersion decreased from the first to the second measurement, and increased from the second to the third measurement, and the differences were statistically significant (p = 0.013) [pre-dialysis, 46.83 ± 12.87 mseg; during dialysis, 43.47 ± 13.36 mseg; post-dialysis, 51.3 ± 18.52 mseg] (Chart 5).

The frequency of patients with QTc dispersion > 65 mseg on every measurement behaved similarly to the mean QTc dispersion, and was as follows: before dialysis, 8.5% (n = 4); during dialysis, 4.3% (n = 2); and after dialysis, 23.4% (n = 11). It also showed significant differences throughout dialysis (p = 0.011).

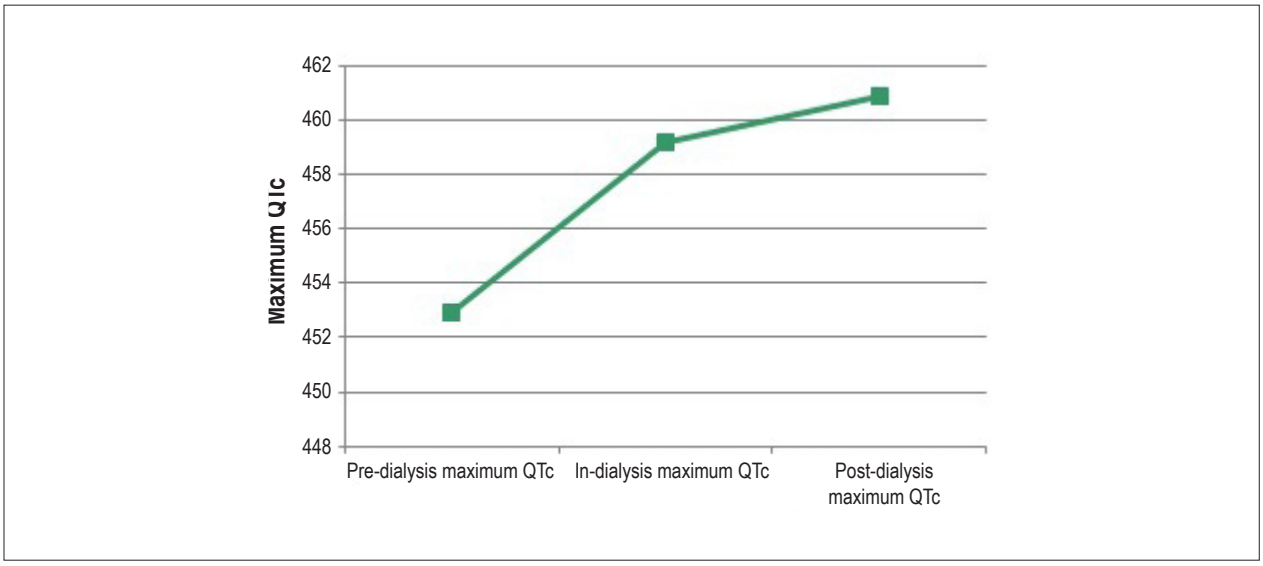

Chart 4 - *Maximum QTc interval before, during and after dialysis.*

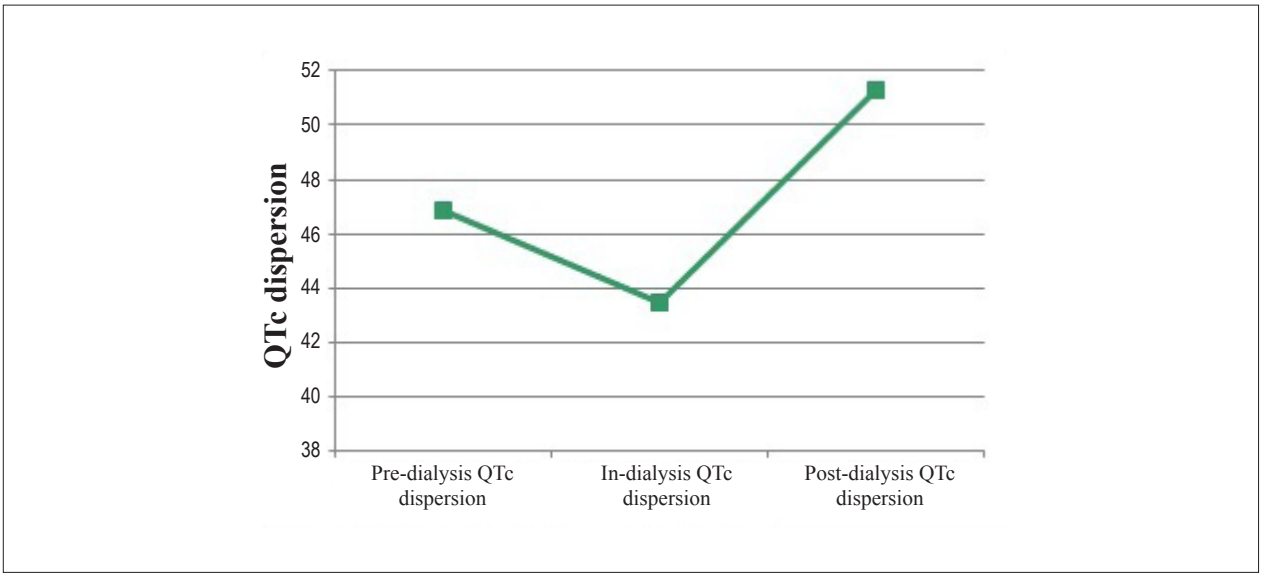

Chart 5 - *QTc dispersion before, during and after dialysis.*

Of those 11 patients with QTc dispersion > 65 mseg (23.4%), eight had QTc dispersion > 74 mseg (17%) after dialysis (Chart 6).

Study of the ventricular electrical systole in individuals with LVH

The mean maximum QTc interval after dialysis and mean QTc dispersion after dialysis in individuals with LVH were higher than those in individuals without LVH, and the differences were statistically significant for both (Table 1). Thus, the increase in the frequency of LVH is associated with an increase in the maximum QTc interval and in QTc dispersion after dialysis.

Study of ventricular electrical systole in individuals with ventricular arrhythmias

The only ventricular arrhythmia observed was isolated extrasystole, which occurred in 2.1% of the patients before dialysis (n = 1), in 14.9%, during dialysis (n = 7), and in 8.5%, after dialysis (n = 4). Ventricular arrhythmias were more prevalent during dialysis, and the differences in their prevalence were statistically significant throughout the dialytic therapy (p = 0.034).

A possible relationship between the occurrence of ventricular extrasystole and increased maximum QTc intervals and QTc dispersion on any of the three measurements was not found.

Study of the ventricular electrical systole regarding the time elapsed since the beginning of treatment and the weekly session

No significant difference was observed in the maximum QTc interval and QTc dispersion related to the time elapsed since the beginning of treatment and the weekly session, at any time point of the session.

Discussion and Conclusions

The dialytic therapy has been frequently described as a potentiator of changes in ventricular electrical systole, and such changes can act as predictors of ventricular arrhythmias or sudden cardiac death caused by arrhythmia[5,6]. Individuals with ESRD undergoing hemodialysis experience elevated cardiac stress caused by the attempt to replace 168 hours of kidney function per week with 12 hours corresponding to the usual three weekly dialysis sessions, compounded by the intermittent and repetitive character of the dialysis[5,7,8]. The chronicity and indispensability of the therapy, only replaced by kidney transplantation, in addition to the fact that the changes in ventricular electrical systole during dialysis can provide essential information to predict arrhythmias potentially malignant, motivated this study. Analysis of QTc interval and QTc dispersion can be obtained in a simple, non-invasive and inexpensive way, but should be carefully performed. The difficulty in clearly defining the end of the T wave and the exact point between the T and U waves for better characterizing the duration of ventricular electrical systole is one of the difficulties of their use in clinical practice, and one of the limitations of this study.

Chronic kidney disease and DM are interrelated, DM being the major cause of CKD. Approximately 20% to 40% of diabetic patients develop diabetic nephropathy during the progression of disease[2,3]. In this sample studied, that prevalence was even higher, and 44.7% of the patients (n = 21) had DM as the etiology of their ESRD, confirming the increased risk of ESRD in individuals with CKD and DM associated.

In addition to its progressive character, patients with CKD have a strong prevalence of cardiovascular risk factors and history of cardiovascular disorders, being prone to die rather from cardiovascular causes than from kidney failure. Thus, the

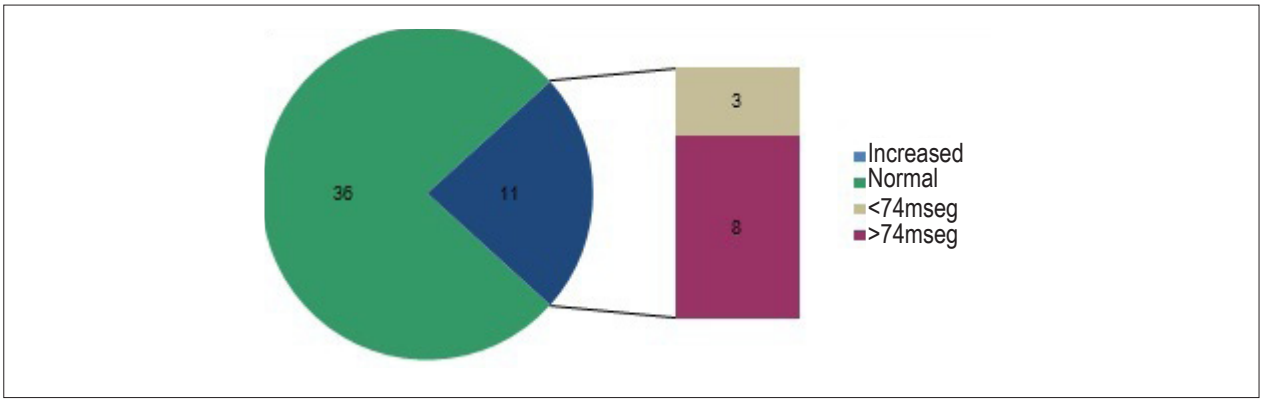

Chart 6 - *QTc dispersion after dialysis (n).*

Table 1 – Maximum QTc interval and QTc dispersion after dialysis in individuals with LVH and without LVH

	LVH after dialysis	N	Mean (mseg)	Standard deviation	p (value)
Maximum QTc interval after dialysis	No	24	455.21	26.854	0.039
	Yes	19	473.00	27.633	
QTc dispersion after dialysis	No	24	44.00	16.413	0.008
	Yes	19	58.95	18.869	

early management of cardiovascular risk factors and associated comorbidities is extremely important to delay disease progression[12,13]. However, despite the strong prevalence of cardiovascular risk factors, other factors may play a relevant role in CKD, and their detection could improve the adverse cardiovascular outcomes of CKD patients[12].

Chronic kidney disease has an irreversible character and progresses to ESRD. In our sample, cardiovascular risk factors were highly prevalent, especially AH and DM, and history of angina was the most prevalent cardiovascular disorder. Although less prevalent, other cardiovascular diseases, such as AMI and CVA, were also found.

Another cardiovascular disorder invariably present in ESRD is uremic cardiomyopathy in the form of LVH[6,9,12]. The abnormalities in left ventricular structure are an important trigger of arrhythmias and a strong independent indicator of mortality[9,12]. In addition to this predisposition to malignant arrhythmias in LVH, QTc interval prolongation and increased arrhythmogenesis occur[6,14].

This study confirmed the predisposition to arrhythmia in the post-dialysis measurement of individuals with LVH, who have a superior mean of the maximum QTc interval and QTc dispersion as compared with individuals without LVH.

The number of individuals with electrocardiographic criteria for LVH increased throughout therapy, because an increase in QRS amplitude was registered. That has been described by several authors, although the cause of the phenomenon has not been completely defined, and can be associated especially with volume changes and myocardial ischemia[15-17].

According to some authors, the major factor accounting for that increase is extracellular fluid volume reduction[15,17]. Weight loss during dialysis is associated with that extracellular fluid volume reduction. In our sample, the mean weight loss of 2.30 ± 0.86 kg was observed. Weight loss during hemodialysis has been associated with an increase in QRS complexes, which is in accordance with that reported by Madias and Narayan[16]. Those authors, in addition to reporting a correlation between the percentage change in the sum of QRS complexes of all 12 electrocardiographic leads and weight loss ($p = 0.038$), have also reported a correlation between net fluid removed and weight loss ($p = 0.005$)[16].

Studying the duration of ventricular depolarization and repolarization on surface ECG by use of maximum QTc interval and myocardial repolarization heterogeneity by use of QTc dispersion, an increase in those parameters was observed after dialysis. Thus, those individuals have a greater arrhythmic predisposition associated with dialysis sessions, and those results might help us predict and explain the sudden death caused by arrhythmia of individuals with ESRD undergoing hemodialysis. We observed an increase in the prevalence of increased maximum QTc intervals from the pre-dialysis measurement to the two following measurements, and, in more than half of the individuals, that happened in the post-dialysis measurement. However, it is worth noting that in the pre-dialysis measurement, 38.3% of the individuals already had that interval enlarged. QTc dispersion greater than 65 mseg and consequent greater risk of arrhythmia[11] were observed in 23.4% of the individuals ($n = 11$) in the post-dialysis measurement and in only 8.5% of the individuals ($n = 4$) in the pre-dialysis measurement. Of the 11 individuals with QTc dispersion > 65 mseg, eight had QTc dispersion > 74 mseg, representing, thus, an independent risk factor for all-cause mortality, cardiovascular mortality, and mortality due to arrhythmia[6,18].

The increases in maximum QTc interval and in QTc dispersion from pre-dialysis to post-dialysis measurements observed in our results are in accordance with those of a study with 94 patients undergoing ECG before and after a hemodialysis session. The maximum QTc interval and QTc dispersion increased, and the difference was significant for both[19]. Similarly, the effect of hemodialysis on ventricular electrical systole (QT interval, QTc interval, QT dispersion, and QTc dispersion) was studied by performing ECG 10 minutes before and after the hemodialysis session. In 34 patients, a pre-hemodialysis increase in those intervals was observed, with consequent significant increase in the post-hemodialysis measurement. The increased duration of the intervals studied was independent of age, sex, AH, duration of the dialysis program, secondary hyperparathyroidism, and concomitant cardiovascular disorders[20].

The prevalence of ventricular arrhythmias during dialysis therapy was low, occurring only in the form of isolated extrasystole, and no relationship was found between them and increased maximum QTc interval and QTc dispersion. According to the literature, other mechanisms than changes in ventricular electrical systole might be involved in the origin of ventricular arrhythmias during hemodialysis, such as ischemic heart disease (silent ischemia) and electrolytic changes, and might also influence ventricular electrical systole[21,22]. The high prevalence of ventricular arrhythmias during hemodialysis was confirmed, especially in the last hour of therapy, by use of continuous electrocardiographic analysis[22]. Thus, for better characterizing prevalence, complexity and prediction of ventricular arrhythmias during hemodialysis, analysis of the ventricular electrical systole is important, as well as the continuous electrocardiographic analysis of the session and other factors that contribute to arrhythmogenesis. Thus, the lack of arrhythmias was one limitation of our study.

Sudden cardiac death caused by arrhythmia has been reported as accounting for approximately 60% of the deaths of patients on hemodialysis. That frequency increases with the duration of the session and the time since the previous dialysis session, increasing substantially when that time exceeds 36 hours[6]. In this study sample, although the time interval between the first dialysis session in the week and the previous dialysis session was longer, statistically significant difference was observed in neither the maximum QTc interval nor the QTc dispersion at any time point of the therapy. Thus, we can state that the changes observed in the QTc interval and QTc dispersion in our results occur independently of the week session. Regarding the time elapsed since the beginning of the dialytic therapy, no significant differences in the maximum QTc interval and QTc dispersion were found.

The risk of an arrhythmia associated with the increase in the QTc interval and QTc dispersion during dialysis has been reported and should be carefuly considered by researchers and health professionals. Those changes in ventricular electrical systole can associate with several factors, and many of such factors can be combined in ESRD.

The objectives of our study were fully met, confirming an increase in the QTc interval and QTc dispersion associated with hemodialysis, based on a single dialysis session. This suggests an elevated predisposition to arrhythmia in those individuals.

Further studies are required to approach the variations in ventricular electrical systole during hemodialysis in the same individual over a longer period of time and in different dialysis sessions, to assess its behavior considering the chronic and repetitive character of the therapy. In addition, continuous electrocardiographic study in a session and between sessions could provide data on the occurrence and prevalence of arrhythmias, and their possible association with increased QTc intervals and QTc dispersions immediately after the dialysis session. This could be relevant information for the study and prediction of malignant ventricular arrhythmias in individuals with ESRD.

Studying ventricular electrical systole in ESRD is an important challenge in clinical practice, because there is an increasing number of individuals requiring dialysis worldwide. In addition, current scientific evidence indicates sudden death caused by arrhythmia as the major contributor to mortality in those individuals, who should be considered at high risk for arrhythmia.

Prophylatic cardioverter-defibrillator implantation has been extremely important in primary or secondary prevention of sudden death in high-risk groups, such as individuals with long QT syndrome. Although individuals with ESRD on dialysis are not at high risk, cardioverter-defibrillator implantation can be a solution to reduce sudden death in ESRD.

Clear knowledge about all factors conditioning sudden death in those individuals should be pursued, and that information might be useful not only to predict malignant ventricular arrhythmias, but also to consider individuals with ESRD as a group at high risk for cardioverter-defibrillator implantation.

Longitudinal studies with survival analysis of individuals with ESKD are suggested, as well as the correlation of the results found.

Author contributions

Conception and design of the research: Valentim B, Pereira A, Coelho P; Acquisition of data: Valentim B, Pereira A; Analysis and interpretation of the data: Valentim B, Pereira A, Coelho P, Pereira T; Statistical analysis and Writing of the manuscript: Valentim B, Pereira A, Pereira T; Wwriting of the manuscript: Valentim B, Coelho P, Pereira T; Critical revision of the manuscript for intellectual content: Valentim B, Pereira A, Coelho P, Pereira T.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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