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Original Paper

Asymptomatic Ventricular Arrhythmia and Clinical Outcomes in Chronic Kidney Disease: A Pilot Study

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Key Words
Ventricular arrhythmia · Cardiac arrhythmia · Cardiovascular disease · Chronic kidney disease

Abstract
Background/Aims: Ventricular arrhythmia is associated with increased risk of cardiovascular events and death in the general population. Sudden death is a leading cause of death in end-stage renal disease. We aimed at evaluating the effects of ventricular arrhythmia on clinical outcomes in patients with earlier stages of chronic kidney disease (CKD). ***Methods:*** In a prospective study of 109 nondialyzed CKD patients (estimated glomerular filtration rate 34.8 ± 16.1 ml/min/1.73 m^2, 57 ± 11.4 years, 61% male, 24% diabetics), we tested the hypothesis that the presence of subclinical complex ventricular arrhythmia, assessed by 24-hour electrocardiogram, is associated with increased risks of cardiovascular events, hospitalization, and death and with their composite outcome during 24 months of follow-up. Complex ventricular arrhythmia was defined as the presence of multifocal ventricular extrasystoles, paired ventricular extrasystoles, nonsustained ventricular tachycardia, or R wave over T wave. ***Results:*** We identified complex ventricular arrhythmia in 14% of participants at baseline. During follow-up, 11 cardiovascular events, 15 hospitalizations, and 4 deaths occurred. The presence of complex ventricular arrhythmia was associated with cardiovascular events ($p < 0.001$), hospitalization ($p = 0.018$), mortality ($p < 0.001$), and the composite outcome ($p < 0.001$). In multivariate Cox regression analysis, adjusting for demographic characteristics, complex ventricular arrhythmia was associated with increased risk of the composite outcome (HR 4.40; 95% CI 1.60–12.12; $p = 0.004$). ***Conclusion:*** In this pilot study, the presence of asymptomatic complex ventricular arrhythmia was associated with poor clinical outcomes in nondialyzed CKD patients.

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Introduction

Asymptomatic ventricular arrhythmias are associated with a substantially increased risk of sudden and all-cause cardiac death in the general population [1]. Accounting for 26% of all-cause mortality, cardiac arrest or arrhythmia is also the most common cause of death among patients with end-stage renal disease (ESRD) undergoing dialysis treatment [2]. Factors that predispose to malignant ventricular arrhythmias in ESRD include coronary ischemia due to atherosclerosis and arterial calcification, left ventricular hypertrophy, impaired left ventricular function, and rapid electrolyte shifts related to the dialysis procedure itself [3].

Asymptomatic complex ventricular arrhythmias that predispose to malignant ventricular arrhythmias were detected in 13–50% of ESRD patients undergoing dialysis [4–8] and in 14–16% of patients with earlier stages of chronic kidney disease (CKD) [5, 9]. Subclinical ventricular arrhythmias were associated with increased risk of mortality among patients with ESRD [4], but there are little data on subclinical ventricular arrhythmias and clinical outcomes in patients in earlier stages of CKD. We performed a prospective pilot study of nondialysis CKD patients to test the hypothesis that the presence of subclinical complex ventricular arrhythmia, as assessed by 24-hour electrocardiogram at baseline, is associated with increased future risks of cardiovascular events, hospitalization, death, and with their composite outcome.

Methods

Population

We recruited 109 consecutive nondialysis patients with CKD stage 2–5, who were free of cardiac symptoms, from the outpatient CKD clinic of the Federal University of São Paulo, São Paulo, Brazil. Exclusion criteria included symptoms of coronary ischemia or heart failure, age less than 18 years, presence of autoimmune disease, active malignancy, human immunodeficiency virus, viral hepatitis, or chronic use of steroids.

Study Design and Protocol

This was a pilot prospective observational study of 24 months. All patients underwent an assessment of their clinical history, physical examination, laboratory tests and cardiac evaluation, including the 24-hour electrocardiogram, within 1 month of enrollment in the study. The occurrence of cardiovascular events (acute myocardial infarction, angina, stroke, and heart failure), hospitalization, and death was recorded during a period of 24 months. Two independent physicians adjudicated all cardiovascular events. Follow-up time was censored at dialysis initiation or upon kidney transplantation; only events that occurred before dialysis initiation were included in the analysis.

24-Hour Electrocardiogram

All participants underwent 3-channel 24-hour electrocardiogram monitoring (CardioLight®, Cardios, São Paulo, Brazil), which was read by a single cardiologist blinded to the clinical and biochemical characteristics of the participants. Presence of complex ventricular arrhythmia was defined as multifocal ventricular extrasystoles, paired ventricular extrasystoles, nonsustained ventricular tachycardia, or R wave over T wave. Results of the 24-hour electrocardiogram were not used in our clinical practice, and no treatment was implemented after detection of complex ventricular arrhythmia.

Echocardiogram

Two-dimensional color Doppler echocardiography (Philips® HDI 5000, Royal Philips Electronics, The Netherlands) was performed by a single cardiologist blinded to the clinical and biochemical characteristics of the participants according to the recommendations of the American Society of Echocardiography [10]. Presence of left ventricular hypertrophy was defined as left ventricular mass index >50 g/m$^{2.71}$ among men and >47 g/m$^{2.71}$ among women [11]. Systolic dysfunction was defined as ejection fraction <55%.

24-Hour Ambulatory Blood Pressure Monitoring

The 24-hour blood pressure monitoring was performed using Dyna equipment (Cardios). The oscillometers were adjusted to systolic blood pressure varying between 290 and 70 mm Hg and diastolic blood pressure varying between 180 and 45 mm Hg, as well as memory of up to 300 measurements. Blood pressure measurements were obtained at intervals of 20 min during the day and at intervals of 30 min during sleep. Participants were instructed to keep their habitual routine during the 24-hour period and to pause momentarily during each blood pressure measurement. Uncontrolled hypertension was defined as average 24-hour blood pressure >130/80 mm Hg.

Coronary Computed Tomography

Patients underwent coronary artery calcification (CAC) quantification by a multislice computed tomography scanner (LightSpeed® Pro 16; GE Healthcare, Milwaukee, Wis., USA) using a gantry rotation of 0.4 s, collimation of 2.5 mm (slice thickness), and reconstruction time of 6 frames per second. A calcium threshold of 130 or more Hounsfield units was used. A single radiologist blinded to the clinical and biochemical aspects of the patient scored the images. As described by Agatston et al. [12], the calcium score was determined by multiplying the area of each calcified lesion by a weighting factor corresponding to the peak pixel intensity for each lesion. The sum of each lesion of all coronary arteries was used for analysis. Presence of calcification was defined as a CAC score >10 Agatston units and severe calcification as a CAC score >400 Agatston units.

Laboratory Tests

Blood samples were drawn after an overnight fast of at least 12 h. Biochemical and hematological parameters included serum creatinine, hemoglobin, potassium, magnesium, lipid profile, ionized calcium, phosphate, intact parathyroid hormone (chemiluminescence immunoassay; Immulite, DPC-Biermann, Bad Nauheim, Germany; reference values 10–65 pg/ml), and intact fibroblast growth factor 23 (ELISA; Kainos Laboratories, Tokyo, Japan; reference values 18–108 pg/ml). High-sensitivity C-reactive protein was determined by immunochemiluminescence (immunometric assay; CRP Immulite, Los Angeles, Calif., USA) and interleukin-6 was measured using a commercially available ELISA (BD Biosciences, Pharmingen, Calif., USA). Proteinuria was quantified in 24-hour urine samples, and abnormal proteinuria was defined as urinary protein excretion >150 mg/24 h. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [13].

Statistical Analysis

We compared clinical characteristics according to presence or absence of complex ventricular arrhythmia using Student's t test, Mann-Whitney U test, χ^2 test, or Fisher's exact test as appropriate. The cardiac structural variables were examined on a continuous scale. We compared event-free survival curves according to presence or absence of complex ventricular arrhythmia using the Kaplan-Meier method and log-rank test. Since we had a limited number of events, we also analyzed time to the first cardiovascular event, hospitalization, or death as a composite outcome. To adjust for potential confounding, we performed multivariable Cox regression analyses of time to the composite outcome in which complex ventricular arrhythmia was the primary predictor and considering demographic variables (age and sex). In order to determine the impact of left ventricular mass index, ejection fraction, and CAC score on the relationship between complex ventricular arrhythmia and the composite outcome, these variables were sequentially incorporated individually in the adjusted model.

p values <0.05 were considered statistically significant. All analyses were performed using a standard statistical package (SPSS for Windows, version 19; SPSS, Chicago, Ill., USA).

Results

Baseline Characteristics

The study population of 109 individuals included mainly CKD patients of stage 3a (16%), stage 3b (30%), and stage 4 (41%). Complex ventricular arrhythmia was found in 15 patients (14%), of whom 6 had nonsustained ventricular tachycardia. The median number of extrasystoles in the group with complex ventricular arrhythmia was 169 (38–620) beats/24 h.

Table 1. Baseline characteristics of the 109 nondialyzed CKD patients according to the presence of complex ventricular arrhythmia

	All	Without complex VA	With complex VA	p value
Subjects	109	94	15	–
Male	66 (61)	55 (58)	11 (73)	0.27
Age, years	57±11	55±11	64±11.5	0.006
White	55 (50)	50 (53)	5 (33)	0.11
Diabetes	26 (24)	25 (27)	1 (7)	0.11
Tobacco use	57 (52)	46 (49)	11 (73)	0.08
Body mass index	26.9 ± 5.3	27.1±5.4	26.8±4.3	0.39
Atherosclerotic disease	17 (16)	13 (14)	4 (29)	0.23
Creatinine, mg/dl	2.26±0.85	2.32±0.86	1.9±0.67	0.74
eGFR, ml/min/1.73 m^2	34.8±16.1	33.8±15.4	40.9±19.8	0.11
Proteinuria, g/24 h	0.24 (0.00–0.79)	0.25 (0–0.8)	0.04 (0–0.42)	0.19
Hemoglobin, g/dl	12.7±1.8	12.6±1.8	13.8±1.7	0.01
Potassium, mEq/l	4.7 (4.3–5.1)	4.7 (4.3–5.1)	4.7 (4.4–5.2)	0.9
Magnesium, mEq/l	1.9 (1.72–2.1)	1.9 (1.75–2.1)	1.9 (1.7–2.0)	0.57
Ionized calcium, mmol/l	1.28±0.05	1.28±0.05	1.28±0.06	0.9
Phosphorus, mg/dl	3.78±0.72	3.81±0.75	3.63±0.52	0.39
iPTH, pg/ml	113 (63–193)	118 (72.5–200.2)	63.5 (48.5–146)	0.09
FGF23, pg/ml	47.3 (23.3–102.8)	45.5 (24.1–103.9)	67.6 (12.49–101.5)	0.9
C-reactive protein, mg/dl	0.28 (0.12–0.77)	0.27 (0.09–0.76)	0.39 (0.24–0.93)	0.14
Interleukin-6, pg/ml	4.6 (2.7–8.4)	4.5 (2.5–8.4)	6.7 (3.6–13.8)	0.14
Total cholesterol, mg/dl	184±37.8	186.2±39.2	169.8±24.1	0.13
LDL cholesterol, mg/dl	100.9±28.4	102.2±29.2	92.9±21.5	0.26
HDL cholesterol, mg/dl	51.6±14.4	50.6±14.7	58±10.2	0.07
Triglycerides, mg/dl	125 (98–201)	139 (105–211)	99 (67–111)	0.001
Median systolic BP, mm Hg	125 (116–137)	125 (116–138)	128 (114–134)	0.82
Mean diastolic BP, mm Hg	79±11	79±11	77±14	0.68
Left ventricular mass index, $g/m^{2.71}$	52±1	50±16	61±11	0.016
Ejection fraction, %	67 (62–70)	67 (63–71)	58 (44–65)	0.001
Calcium score, Agatston unit	9 (0–334)	1 (0–250)	354 (39–1,417)	0.003

Values are means ± SD, medians (interquartile ranges), or n (%). VA = Ventricular arrhythmia; eGFR = estimated glomerular filtration rate; iPTH = intact parathyroid hormone; FGF23 = fibroblast growth factor 23; LDL = low-density lipoprotein; HDL = high-density lipoprotein; BP = blood pressure.

Demographic, laboratory, and cardiovascular data are summarized in table 1 overall and according to presence or absence of complex ventricular arrhythmia.

When compared to patients without complex ventricular arrhythmia, those with complex ventricular arrhythmia were older, had lower triglycerides and ejection fraction, and higher hemoglobin, left ventricular mass index, and coronary calcium score. They also exhibited a higher frequency of systolic dysfunction (40 vs. 5%; p = 0.001), left ventricular hypertrophy (87 vs. 46%; p = 0.003), and CAC (86 vs. 43%; p = 0.003).

Clinical Events

By the end of the 24-month follow-up period, 20 patients had initiated dialysis treatment, and 1 patient had received a kidney transplant. During the follow-up, there were 11 cardiovascular events (angina, n = 4; stroke, n = 3; acute myocardial infarction, n = 3; and heart failure, n = 1), 15 hospitalizations (cardiovascular events, n = 8; other n = 7), and 4 deaths (2 due to cardiovascular causes).

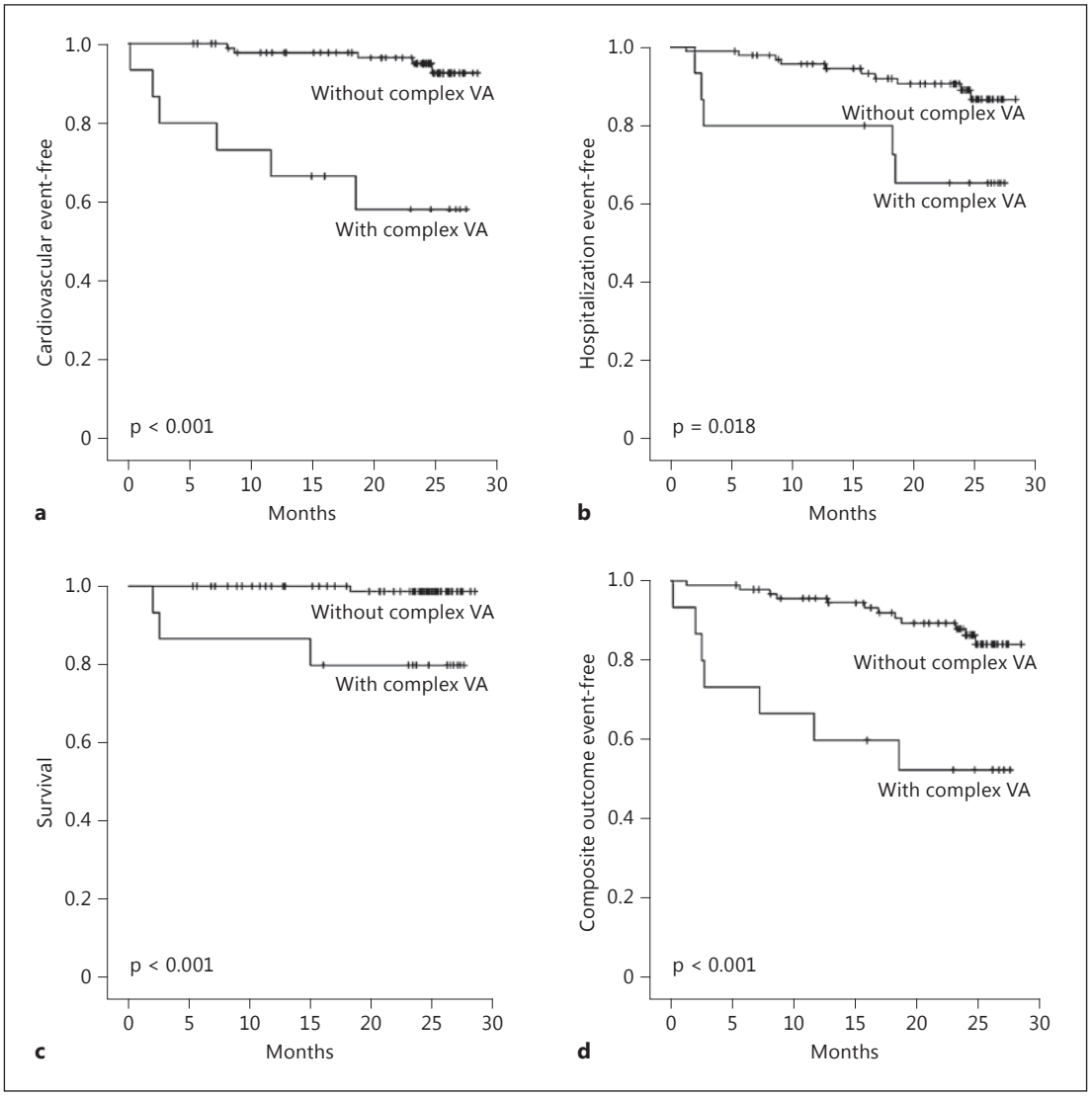

Fig. 1. Cardiovascular event-free time (**a**), hospitalization event-free time (**b**), survival (**c**), and composite outcome event-free time (**d**) of 109 nondialyzed CKD patients, according to the presence of complex ventricular arrhythmia. VA = Ventricular arrhythmia.

Compared to the group without complex ventricular arrhythmia, the group with complex ventricular arrhythmia was at significantly higher risk of cardiovascular events ($p < 0.001$), hospitalization ($p = 0.018$), death ($p < 0.001$), and their composite ($p < 0.001$) (fig. 1).

In the multivariate Cox model that was adjusted for sex and age, presence of complex ventricular arrhythmia was independently associated with increased risk of the composite outcome (HR 4.40; 95% CI 1.60–12.12; $p = 0.004$) (table 2). When we adjusted the multivariable time to the composite event analysis further for left ventricular mass index, ejection fraction, and CAC score, presence of complex ventricular arrhythmia remained independently associated with increased risk of the composite outcome (table 2). There was also no change when the first model was adjusted for hemoglobin levels, estimated glomerular filtration rate, presence of hypertension, and diabetes.

Table 2. Unadjusted and adjusted associations of complex ventricular arrhythmia with the composite outcome of cardiovascular events, hospitalizations, and death

	HR	95% CI	p
Unadjusted model	4.82	1.89–12.26	0.001
Adjusted models			
Adjusted for sex and age (model 1)	4.40	1.60–12.13	0.004
Mediation analyses			
Model 1 + adjustment for LVMI	4.15	1.5–11.44	0.006
Model 1 + adjustment for EF	3.09	1.08–8.79	0.035
Model 1 + adjustment for CAC	4.83	1.67–13.99	0.004

LVMI = Left ventricular mass index; EF = ejection fraction.

Discussion

The present pilot study demonstrated a high prevalence of complex ventricular arrhythmia in nondialyzed CKD patients, which was associated with worse clinical outcomes. To the best of our knowledge, this is the first study to illustrate the impact of complex ventricular arrhythmia on clinical outcomes in nondialyzed CKD patients.

Due to its complexity, ventricular arrhythmia has been considered a potentially life-threatening condition in the general population. Among dialysis patients, prevalence rates of complex ventricular arrhythmia varying from 13 to 50% have been reported [4–8]. Such wide variability could be partially explained by the different criteria used across studies to classify complex arrhythmia. To our knowledge, only one previous study investigated complex ventricular arrhythmia in nondialysis CKD patients and found a prevalence of 17% [5], which is similar to our data. Considering that the prevalence of simple ventricular premature complexes is only 3.8–5.4% in general populations with a similar age distribution as our cohort [14, 15], these results suggest that complex arrhythmias are approximately 3- to 5-fold more common in CKD stage 2–5 patients not undergoing dialysis.

In the general population, complex ventricular arrhythmias have been proposed as the best predictors of mortality after myocardial infarction [1] and in nonischemic dilated cardiomyopathy [16]. In CKD patients on dialysis, complex ventricular arrhythmias have been recognized shortly before sudden cardiac death, suggesting that the arrhythmias may increase susceptibility to fatal events [4]. In the present study, we confirmed these results and extended them to patients with earlier CKD stages, in whom complex ventricular arrhythmias were associated with higher mortality and greater frequency of cardiovascular events and hospitalizations.

The basis for ventricular arrhythmia usually encompasses a vulnerable diseased myocardium with a transient arrhythmic trigger [17]. In the overall population, the underlying process is frequently coronary artery disease or heart failure [18, 19]. In contrast, recent evidence suggests different pathophysiological mechanisms in patients undergoing dialysis, including left ventricular hypertrophy and vascular calcification [4, 7, 20, 21]. In nondialyzed CKD patients, we previously demonstrated that systolic dysfunction, left ventricular hypertrophy, and CAC were associated with the presence of ventricular arrhythmia [3]. In addition, we also demonstrated that presence of CAC in kidney transplant recipients was related to complex ventricular arrhythmia [9]. Similarly, in the current study of nondialyzed CKD patients, the presence of complex ventricular arrhythmia was related to lower ejection fraction, higher left ventricular mass index, and increased coronary calcium score. While these observations support the conclusion that complex ventricular arrhythmia may be an indicator of underlying structural cardiac disease in CKD patients, interestingly, only

adjustment for ejection fraction partially attenuated the association between complex ventricular arrhythmia and the composite outcome. Larger follow-up studies are needed to further examine the interrelationships between structural cardiovascular disease, complex ventricular arrhythmia, and clinical outcomes in CKD.

We acknowledge several limitations of our study. Due to the relatively small sample size and short follow-up, the number of clinical events was limited. Consequently, it was not possible to apply the Cox modeling analysis for each specific set of events separately. Therefore, the models for the composite outcome were markedly constrained and should be interpreted cautiously. Our study, however, has also unique strengths. To date, this is the only prospective study relating complex ventricular arrhythmia to increased mortality, hospitalization, and cardiovascular events in earlier stages of CKD. Perhaps, ambulatory electrocardiographic monitoring to identify subclinical complex ventricular arrhythmias should be considered as a novel instrument to stratify risk in CKD.

Statement of Ethics

The study was reviewed and approved by the Ethics Advisory Committee of the Federal University of São Paulo (approval No. 569.458). All patients gave written informed consent.

Disclosure Statement

The authors declare no conflicts of interest.

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