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Ventricular arrhythmia in incident kidney transplant recipients: prevalence and associated factors

Aline P. Marcassi,[1] Daniel C. Yasbek,[1] Jose Osmar Medina Pestana,[1] Fernando Carlos Fachini,[2] Edgar Bezerra de Lira Filho,[2] José Luiz Cassiolato[3] and Maria Eugênia F. Canziani[1]

1 Nephrology Division, Federal University of São Paulo, São Paulo, Brazil
2 Cardiology Laboratory, Department of Psychobiology, Federal University of São Paulo, São Paulo, Brazil
3 Cardios Research Institute, São Paulo, Brazil

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Correspondence
Maria Eugênia F. Canziani, Rua Pedro de Toledo 282, CEP 04039-000, São Paulo – SP, Brazil. Tel.: 55 11 5904 8499; fax: 55 11 5572 1862; e-mail: dialisefor@uol.com.br

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Summary

Cardiovascular mortality in kidney transplant recipients has shown to be substantially elevated particularly in the first year of transplantation. Complex ventricular arrhythmia (VA) has been pointed as one of the etiologies of sudden death. The aim of this study was to evaluate the prevalence of VA and to investigate the factors associated with their occurrence in incident kidney transplant recipients. A total of 100 incident kidney transplant recipients were included in the study (39.7 ± 10.1 years, 55% male, 43.6 ± 10.1 days of transplantation, 66% living donors). All the patients underwent 24 h electrocardiogram, echocardiogram and multi-slice computed tomography. Thirty percent of the patients had VA. Left ventricular hypertrophy was observed in 57% of the patients while heart failure was found in 5%. Coronary artery calcification (CAC) was observed in 26 patients, from which 31% had severe calcification. The group of patients with VA was predominantly male, had been on dialysis therapy for a longer time and had more coronary calcification. In the multiple logistic regression analysis, male gender and CAC score were independently associated with the presence of VA. In conclusion, kidney transplant recipients exhibited a high prevalence of VA and the factors associated with its occurrence were the male gender and the presence of CAC.

Introduction

Renal transplantation is the preeminent treatment for end-stage renal disease patients. A number of reports have demonstrated that kidney transplanted recipients have less comorbidities, improved quality of life and better survival in relation to patients on long-term dialysis therapy [1–3]. Nevertheless, compared with the general population, kidney transplant recipients have a fourfold higher risk of cardiovascular disease and a twofold higher risk of cardiovascular death [4]. In fact, cardiovascular disease is incontestably the leading cause of death in chronic kidney disease even after transplantation [5,6]. Of note, the cardiovascular mortality in kidney transplant recipients has shown to be substantially elevated particularly in the first year of transplantation [5].

Complex ventricular arrhythmia has been pointed as one of the etiologies of sudden death, which is responsible for 15% of the mortality among kidney transplant recipients with functioning grafts [7,8]. In view of the lack of information on the occurrence of arrhythmias in kidney transplant recipients, we aimed to evaluate the prevalence of ventricular arrhythmia and to investigate the factors associated with ventricular arrhythmia in these patients.

Materials and methods

Subjects and study design

This is a cross-sectional study with 100 incident kidney transplant recipients from the outpatient transplant unit of the Federal University of São Paulo, Brazil. All patients

who had undergone kidney transplantation within 2 months were invited to participate in the study satisfying the following the exclusion criteria: age below 18 years, creatinine clearance lower than 30 ml/min, clinical evidence of cardiac congestive failure, hepatic failure, neoplasic or infectious diseases. Patients who had experienced any cardiovascular events 3 months prior to transplantation were excluded. The majority of the patients were on regular use of antihypertensive drugs (88%). Patients were receiving β-blockers (45%), calcium channel blockers (43%), diuretics (32%), α blockers (7%) and angiotensin receptor blockers or angiotensin-converting enzyme inhibitors (3%). No patient received digitalis.

According to local protocol, all patients were using initial immunosuppression with prednisone. Living donors HLA I (totally matched) also received cyclosporine and azathioprine, HLA II (partially matched) and III (fully mismatched) used tacrolimus and azathioprine. Deceased donors were induced with basiliximab, and received tacrolimus and micophenolic acid. Thymoglobulin was used when patients had higher panel response assay (>20%).

The study was reviewed and approved by the Ethics Advisory Committee of the Federal University of São Paulo, and each patient signed the informed consent form.

All laboratory tests, echocardiogram and coronary computed tomography were performed within 2 months after transplantation.

Laboratory data

Blood samples were drawn in a fasting state for the following laboratory tests: lipid profile, creatinine, blood count, bicarbonate, intact parathyroid hormone (iPTH – Immulite Assay; reference range 10–65 pg/ml), alkaline phosphatase (references: 40–129 U/l for male, 35–104 U/l for female), ionized calcium, phosphorus, blood glucose and C-reactive protein (CRP) levels determined using chemiluminescence immunoassay. Proteinuria was measured by obtaining 24 h urine samples. Abnormal proteinuria was defined as urinary protein excretion >3 g/24 h. Creatinine clearance was estimated by Cockcroft and Gault's equation [9]. Anemia was defined as hemoglobin <11 g dl [10]. Hyperparathyroidism, hyperphosphatemia, and hypercalcemia were defined according to bone metabolism K/DOQI guidelines [11].

24-h electrocardiogram

Cardiac arrhythmia was evaluated by a 3-channel 24-h electrocardiogram monitoring (Cardios-Light®; Cardios, São Paulo, Brazil). The mean of recording time was 23.7 h. Ventricular arrhythmia was classified according to Lown and Wolf [12]: Lown grade 0 (absence of ventricular extrasystoles); grade 1 (up to 30 unifocal ventricular extrasystoles/h); grade 2 (more than 30 unifocal ventricular extrasystoles/h); grade 3 (multifocal ventricular extrasystoles); grade 4 (paired ventricular extrasystoles or nonsustained ventricular tachycardia) and grade 5 (R wave over T). Heart rate variability was assessed based on the standard deviation of the mean of the R-R intervals (SDNN) and on the number of instances per hour in which two consecutive R-R intervals differ by more than 50 ms over 24 h (pNN50). Then, abnormalities in heart rate variability were defined as SDNN <60 ms or pNN50 <5%.

Echocardiogram

Two-dimensional color Doppler echocardiogram (Philips® HDI 5000; Royal Philips Electronics, Amsterdam, Netherlands) was performed in 82 patients according to the recommendations of the American Society of Echocardiography [13]. Presence of left ventricular hypertrophy was considered for a left ventricular mass index >134 g/m^2 among men and >110 g/m^2 among women. Systolic dysfunction was defined as the ejection fraction ≤55%.

Coronary computed tomography

All patients underwent coronary calcium quantification by a multi-slice computed tomography scanner (LightSpeed® Pro16 – GE Healthcare, Milwaukee, WI, USA) using a gantry rotation of 0.4 s; collimation of 2.5 mm (slice thickness); and reconstruction time of 6 frames/s. A calcium threshold of ≥130 Hounsfield Units (HU) was used. The images were scored by a single radiologist blinded to all clinical and biochemical aspects of the patient. As described by Agatston, 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 [14]. The sum of each lesion of all coronary arteries was used for analysis. Presence of coronary artery calcification (CAC) was defined as calcium score >10 AU, and severe CAC as calcium score ≥400 AU.

Statistical analysis

Mean and standard deviation, median and interquartile range values or frequencies (proportions) were calculated for all variables. Comparisons of continuous variables were performed using Student's *t*-test and the Mann–Whitney *U*-test for normal and skewed data, respectively. Comparisons of proportions were performed using chi-square analysis or using Fischer's exact test, as appropriate. Multiple logistic regression analysis was applied to

assess the variables associated with the presence of ventricular arrhythmia including the variables that showed significance at the 0.10 level in the univariate analysis. A *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows (SPSS Inc, Chicago, IL, USA).

Results

The characteristics of the studied patients ($n = 100$) are shown in Table 1. As can be seen, patients were relatively young and had been previously on dialysis therapy for 2 years. All patients were within 60 days on transplant, and most of them (66%) were living donors (HLA I 24%, HLA II 34%, and HLA III 8%). Based on the chronic kidney disease classification proposed by the National Kidney Foundation (K-DOQI), the majority of the patients (89%) were on stages II and III. Overweight (BMI ≥25 kg/m^2) and obesity (BMI ≥30 kg/m^2) were found in 25% and 6% of the patients, respectively.

Proteinúria was observed in 19 patients [0.7 (0.5–1.3) g/day]. Although the mean value of hemoglobin was within the normal range, anemia was detected in 17% of the patients. Fasting serum glucose above 100 mg/dl was observed in 19% of the patients. Total cholesterol levels were >200 mg/dl in 51% of the patients, HDL cholesterol <40 mg/dl in 17%, LDL cholesterol >100 mg/dl in 57%, and triglycerides >150 mg/dl in 53%. Regarding bone metabolism, hypophosphatemia was observed in 48%, hypercalcemia in 39% and hyperparathyroidism in 43% of the patients. Levels of CRP were >0.1 mg/dl in 43% of the patients and >0.5 mg/l in 16%.

Table 1. Characteristics of the patients ($n = 100$).

Gender (male)	55
Age (years)	39.7 ± 10.1
Caucasians	41
Diabetes	6
Hypertension	89
Sedentary inactivity	79
Body mass index (kg/m^2)	23.6 ± 4.0
Duration of dialysis (months)	24 (11–60)
Previous transplantation	8
Time of transplantation (days)	43.6 ± 10.1
Creatinine (mg/dl)	1.3 (1.1–1.6)
eGFR (ml/min)	65.6 ± 18.9
Potassium (mEq/l)	4.9 ± 0.6
Bicarbonate (mEq/l)	24.5 ± 4.2
Hemoglobin (g/dl)	12.9 ± 1.9
Serum glucose (mg/dl)	87.5 (79.2–96.7)
LDL cholesterol (mg/dl)	109.5 ± 31.6
HDL cholesterol (mg/dl)	55.5 ± 16.0
Triglycerides (mg/dl)	154 (112.2–218.2)
iPTH (pg/ml)*	66.5 (46–124.7)
Alkaline phosphatase (U/l)	85.5 (71.7–134.7)
Ionized calcium (mmol/l)	1.41 (1.35–1.45)
Phosphorus (mg/dl)	2.7 ± 0.8
C-reactive protein (mg/l)*	0.09 (0.03–0.38)
Left ventricular mass index (g/m^2)	133 ± 48.8
Ejection fraction (%)	67.2 ± 8.1
Calcium score in calcified patients (AU)	238.5 (66.5–844)

Mean ± SD, median (interquartiles).
eGFR, estimated glomerular filtration rate; iPTH, intact parathyroid hormone.
*$n = 68$.

Forty-four patients had cardiac arrhythmias, from which 30 had ventricular arrhythmia and 22 supraventricular arrhythmia. Eight patients had both ventricular and supraventricular arrhythmia. Among patients with ventricular arrhythmia, 14 patients were on grade I, two were on grade II, four were on grade III, and 10 patients were on grade IV, as determined by Lown and Wolf [12]. The median of ventricular extra-systoles in patients with cardiac arrhythmias was 125 (13.5–359.5) events/24 h and of supraventricular extra-systoles was 73.5 (20–187.2) events/24 h. Considering heart rate variability, the proportion of patients with abnormal pNN50 reached 90% and with abnormal SDNN was considerably lower (13%). Left ventricular hypertrophy was observed in 57% of the patients while heart failure was found in 5% of the patients. Regarding coronary calcium quantification, the presence of CAC was observed in 26 patients, from which 31% had severe CAC. Their median calcification score was 238.5 (66.5–844) AU.

Considering all patients, the number of ventricular extrasystoles tended to be associated with ventricular mass index ($r = 0.21$, $P = 0.058$) and was significantly correlated with calcium score ($r = 0.23$, $P = 0.022$). The comparisons between patients according to the presence of ventricular arrhythmia are shown in Table 2. As shown, patients with arrhythmias were predominantly male, had longer vintage on previous dialysis treatment, and had more coronary calcification. A lower level of triglycerides was observed in such patients when compared with those without ventricular arrhythmia. Of note men had a trend to have lower levels of triglycerides compared with women [141 (106–206) vs. 175 (122–234) mg/dl, $P = 0.072$]. There was no significant difference between the groups regarding immunosuppression therapy; however, the three patients who received thymoglobulin during the hospitalization had ventricular arrhythmia. Sixty percent of the patients with arrhythmia were on regular use of β blockers comparing with 40% of those with out arrhythmia ($P = 0.048$). In the multiple logistic regression analysis, male gender and coronary calcium score were the factors independently associated with the presence of ventricular arrhythmia in these kidney transplant recipients (Table 3).

Table 2. Comparison between patients according to the presence of ventricular arrhythmia.

	With ventricular arrhythmia (n = 30)	Without ventricular arrhythmia (n = 70)	P value
Male [n (%)]	23 (77)	32 (46)	0.004
Age (years)	42.4 ± 11.5	38.6 ± 9.2	0.11
Caucasians [n (%)]	11 (37)	30 (43)	0.56
Hypertension [n (%)]	29 (97)	60 (86)	0.17
Sedentary [n (%)]	24 (80)	55 (79)	0.87
Body mass index (kg/m^2)	23.0 ± 3.9	23.9 ± 4.1	0.29
Duration of dialysis (months)	38 (17.5–75)	19.5 (9–43.2)	0.003
Deceased donors [n (%)]	13 (43)	21 (30)	0.20
Creatinine (mg/dl)	1.33 (1.09–1.91)	1.30 (1.06–1.53)	0.15
Potassium (mEq/l)	4.9 ± 0.6	4.9 ± 0.6	0.98
Bicarbonate (mEq/l)	23.93 ± 5.36	24.74 ± 3.58	0.45
Ionized calcium (mmol/l)	1.38 (1.33–1.47)	1.41 (1.38–1.45)	0.32
Phosphorus (mg/dl)	2.64 ± 0.94	2.73 ± 0.69	0.61
Hemoglobin (g/dl)	12.99 ± 1.70	12.88 ± 1.96	0.79
Blood glucose (mg/dl)	89.5 (79.7–101.2)	87.5 (79–96)	0.62
LDL cholesterol (mg/dl)	108.73 ± 37.45	109.79 ± 28.99	0.88
HDL cholesterol (mg/dl)	52.37 ± 16.97	56.83 ± 15.55	0.20
Triglycerides (mg/dl)	139.5 (105.7–179.5)	154 (122.5–234.2)	0.04
Left ventricular mass index (g/m^2)	144.5 ± 56.0	127.4 ± 44.3	0.14
Left ventricular hypertrophy	16 (61)	29 (55)	0.56
Ejection fraction (%)	67.2 ± 9.7	67.2 ± 7.3	0.98
Calcium score (AU)	2 (0–242)	0 (0–3)	0.019
CAC >10 AU [n (%)]	13 (45)	13(19)	0.007
CAC ≥400 [n (%)]	6 (21)	2 (3)	0.007
pNN50	0.67 (0.25–2.44)	1.17 (0.31–2.68)	0.52
SDNN	84 (68–104.5)	88 (70.2–109.5)	0.44

Mean ± SD, median (interquartiles).

Table 3. Multiple logistic regression for the presence of ventricular arrhythmia.

	β coefficient	P value	OR	95% CI
Male	1.419	0.015	4.131	1.318–12.946
Calcium score (AU)	0.002	0.042	1.002	1.000–1.004
Duration of dialysis (months)	0.012	0.072	1.012	0.999–1.026
Triglycerides (mg/dl)	−0.006	0.079	0.994	0.987–1.001

Discussion

The rate of sudden cardiac death is elevated in kidney transplant recipients, particularly during the first year [5,7]. Although complex ventricular arrhythmia has been suggested as the primary cause of sudden death, the occurrence of ventricular arrhythmia and its risk factors had not been so far described post-transplantation. This study demonstrated that ventricular arrhythmia is highly prevalent among incident kidney transplant recipients, and the male gender and the presence of CAC were the strongest factors associated with the occurrence of ventricular arrhythmia in these patients.

A number of studies have consistently shown that complex ventricular arrhythmia is frequent and are closely associated with high mortality among patients undergoing long-term dialysis therapy [15–18]. According to the United States Renal Data System (USRDS), arrhythmic alterations are responsible for 58–64% of the cardiac deaths and 25–27% of all deaths among dialysis population [15]. The electrolytic disturbances and abnormalities in the myocardial structure and function attributed to the long-term exposure to the disease and dialysis treatment are thought to be the important contributors for the high prevalence of ventricular arrhythmia observed in this population [15–17,19].

Available literature describes gender as an important factor associated with the occurrence of ventricular arrhythmia. Thus, it is likely that the known difference in the sudden cardiac death rate between men and women may be a consequence of differences in the susceptibility to arrhythmia triggering. In fact, there are evidences that men may have a greater propensity to ventricular arrhythmia than women [20,21]. In patients with coronary artery disease and implantable cardioverter-defibrillators, it has been shown that women were less likely to experience

ventricular tachycardia or ventricular fibrillation recurrences than men [20]. Accordingly, in this study almost 80% of the patients with arrhythmia were men. The physiologic mechanism that triggers this phenomenon is not clear. It has been suggested that some differences in electrophysiologic proprieties related to sex hormones may, at least in part, explain the gender-specific propensity to ventricular arrhythmia [22]. In addition, some studies advocate that gender differences in autonomic nervous system function, evaluated by variability in heart rate, could influence ventricular tachyarrhythmia [23,24]. Actually, decreased heart rate variability frequently observed among men [25] has been established as a significant risk factor for higher mortality in general population and dialysis patients [26,27]. However, in this study the heart rate variability did not differ between men and women, as well as between patients with and without arrhythmia. Therefore, it is unlikely that the ventricular arrhythmia in these patients was mediated by the autonomic nervous system.

Coronary artery calcification was also a common finding among our incident kidney transplant recipients. The previous studies have demonstrated that this cardiovascular injury is highly prevalent in all stages of chronic kidney disease [28–31], including kidney transplant recipients [32]. There are some evidences that the presence and extension of the vascular calcification have prognostic value on mortality in dialysis population [33]. Very recently, the association of artery calcification score with cardiovascular events, hospitalization, and mortality has been demonstrated in nondialyzed chronic kidney disease patients [31]. Of note, vascular calcification, especially in the median wall of arteries, has been associated with cardiac arrhythmia in dialysis patients [32]. In agreement, the CAC score was independently related to the occurrence of ventricular arrhythmia in our kidney transplant recipients.

A relationship of left ventricular hypertrophy with cardiac arrhythmia has also been observed in patients on hemodialysis [17,19]. In this study, the number of ventricular extrasystoles tended to be associated with ventricular mass index, however, the left ventricular mass index of the patients with ventricular arrhythmia was not different when compared with the patients without arrhythmia. Another contrasting aspect from the literature was the effect of age on the occurrence of ventricular arrhythmia. The association of aging with the episodes of ventricular arrhythmia has been well recognized in the general population [21]. However, we did not find differences in age between the group of patients with and without ventricular arrhythmia. Probably, the effect of age on the occurrence of arrhythmia was not a prominent fact since the studied patients were young.

This study has some limitations such as the cross-sectional model of the study and the relatively small sample of patients. In addition, we have to consider that, as elsewhere, the kidney transplant recipients are derived from a highly selected group of dialysis patients who are deemed suitable for transplantation. However, to the best of our knowledge, this is the first study to demonstrate the prevalence as well as the factors associated with the occurrence of ventricular arrhythmia in incident kidney transplant recipients.

In conclusion, the prevalence of ventricular arrhythmia in incident kidney transplant recipients was elevated. The male gender and the CAC were the factors associated with the occurrence of ventricular arrhythmia in these patients. The prognostic value of this cardiovascular injury in kidney transplant recipients remains to be investigated. This finding, however, calls attention to the need for early diagnosis of ventricular arrhythmia. Further examinations focusing on the interventions to prevent and treat ventricular arrhythmias are needed in attempt to contribute in reducing the rate of sudden death in chronic kidney disease and kidney transplantation.

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