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Acute effects of renal sympathetic denervation guided by renal nerve stimulation in CKD patients with ICD

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In the United States, statistics indicate that there are approximately one million annual deaths from cardiovascular disease, of which 330,000 are the result of sudden death [1,2]. It is well established in the literature the relationship between structural heart disease and the occurrence of SCD. In over 70% of cases, the underlying heart disease is the myocardial ischemia [3]. The importance of automatic implantable cardioverter-defibrillator (ICD) has been demonstrated in patients with previous myocardial infarction and severe systolic left ventricular dysfunction (secondary prevention) [4,5]. Survivors of cardiac arrest or those with sustained ventricular tachycardia at high risk of recurrence of such events [6]. The therapies used include antiarrhythmic drugs, surgical resection, endocardial catheter ablation and use of the implantable electronic cardiac device.

Sympathetic overactivity is well known to rise cardiovascular risk in patients with chronic kidney disease (CKD) [7-9]. In CKD, sympathetic overactivity seems to manifest at the earliest stage of clinical disease, showing a straight relationship with the severity of the illness of renal failure [10-13]. As the decrease in the glomerular filtration rate occurs, there is also an increase in cardiovascular events and mortality in patients with CKD [14], especially due to arrhythmic events and their consequences. We previously reported that in the presence of ventricular tachycardia, the anti-tachycardia pacing therapy (ATP) or synchronized cardioversion shock, and in cases of ventricular fibrillation detection, the ICD applies an unsynchronized shock of high energy defibrillation. These events are more common in CKD patients on stage 4 [15].

This study examined patients who underwent ICD implantation in patients with CKD on stage 4. We aim to compare the acute effect of renal sympathetic denervation (RSD) guided by renal nerve stimulation (RNS). This transversal study was piloted at the Department of Cardiac Artificial Stimulation and Cardiac Surgery of the Hospital e Clínica São Gonçalo, São Gonçalo, Rio de Janeiro, Brazil. A cohort of patients received standard therapy for primary or secondary prevention of sudden cardiac death (SCD) in patients with structural heart disease, subjected to the ICD-DR implant according to the "Guidelines for Implantable Electronic Cardiac Devices of the Brazilian Society of Cardiology" [16]. Inclusion criteria were as follows: (i) subjects with structural heart disease and ICD implantation indication for primary or secondary prevention of SCD; (ii) left ventricular ejection fraction ≤35%; (iii) patients who provided documentation not presenting cardiac ischemia before ICD implantation evidenced by myocardial scintigraphy at rest and during stress or coronary angiography; (iv) estimated glomerular filtration rate (eGFR) by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation, eGFR [17] between 15 and 29 mL/min/1.73 m^2. Exclusion criteria were: (i) ischemic heart disease; (ii) LVEF> 35%; (iii) absence of structural heart disease; (iv) valvar heart disease that might lead to arrhythmias; (v) the presence of previously documented atrial fibrillation. The recruitment of the patients began in January 2012 and ended in June 2015. We enrolled 40 patients with CKD on stage 4 identified in our offices. The study was conducted in agreement with the Declaration of Helsinki and was approved by the Ethics Committee of our hospital. All individuals provided written informed consent before inclusion in the study.

The 40 subjects with CKD on stage 4 were randomly divided into two groups (RNS, n=20, and RNS+RSD, n=20). The subjects underwent RSD were submitted to an acute subsequently RNS. The implantation and programming of the ICDs, twenty-four hour ABPM, and transthoracic echocardiography were previously reported in detail in our previously manuscript [15]. The 80 (40 lefft and 40 right) renal arteries from the 40 CKD patients on stage 4 were stimulated according to 16 pattern quadrant previously described by our group [18]. After the stimulation, we waited for the BP to return to baseline values and when ventricular tachycardia (VT) event occurred together we also waited for the rhythm return to the sinus rhythm, what happened spontaneously after stopping the RNS, and before proceeding to the next stimulation site. The patients remained hospitalized in the ward for 24 h after the procedure. Twenty CKD patients on stage 4 underwent RSD guided by RNS and submitted to to an acute subsequently RNS. The RSD was previously described in detail by our group [19].

All patients enrolled were included in the analysis. The results were expressed as the mean and standard deviation (mean ± SD) in the case of normal distribution and as median with interquartile range otherwise. Statistical tests were all of two sides. Comparisons between the two paired values were performed by paired t-test in case of Gaussian distribution or alternatively, by Wilcoxon test. The comparisons between more than two values paired values were performed by analysis of variance for repeated measures ANOVA or Kruskal-Wallis test, as appropriate, complemented by a post hoc test. Frequencies were compared with x^2 or Fisher's exact tests. P values <0.05 were considered significant. Correlations between two variables were performed by Pearson in the case of Gaussian distribution or,

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alternatively, with the Spearman correlation test. All statistical analyzes were performed using the program Graphpad Prism v 7.0 (Graphpad software, La Jolla, CA, USA).

The 40 patients who presented the inclusion criteria were included in the study. The baseline characteristics, like age, body mass index, gender, ethnicity and other features of the patients in the both groups are disposed of in detail in Table 1.

The correlation between the variation (Δ) in invasive systolic BP and VT occurrence in each quadrant of the left and right renal arteries by Pearson method during the RNS for CKD patients on stage 4 which

Table 1. Baseline features.

	CKD stage 4 RNS	CKD stage 4 RNS+RSD	Overall P value
N	20	20	---
Age, years	64.0 ± 15.5	70.0 ± 13.0	0.1899
Body mass index, kg/m²	27.3 ± 6.3	26.8 ± 6.8	0.8107
Male gender (%)	16 (80%)	13 (65%)	0.4801
White ethnicity (%)	15 (75%)	16 (80%)	>0.9999
Type 2 Diabetes *Mellitus* (%)	10 (50%)	12 (60%)	0.7512
Coronary artery disease	16 (80%)	17 (85%)	>0.9999
Ischemic etiology	16 (80%)	17 (85%)	>0.9999
Mean 24-hour ABPM, mmHg	123 ± 7/75 ± 4	122 ± 8/76 ± 2	0.6763/0.3236
Creatinine, mg/dL	2.62 ± 0.08	2.61 ± 0.10	0.7289
eGFR, mL/min/1.73 m²	25.0 ± 3.2	24.0 ± 2.6	0.2849
ACR, mg/g	74.8 ± 15.0	77.9 ± 12.7	0.4849
Antiarrhythmic agent			
Amiodarone	20 (100%)	20 (100%)	1.0000
Antihypertensive agents			
ACEI/ARB	20 (100%)	20 (100%)	1.0000
Spironolactone	20 (100%)	20 (100%)	1.0000
DHP Ca^{++} channel blockers	10 (50%)	11 (55%)	>0.9999
β-blockers	20 (100%)	20 (100%)	1.0000
Echocardiographic parameters			
LVMI, g/m²	155.7 ± 11.1	153.4 ± 7.8	0.4530
LVEF, %	28.4 ± 6.0	27.8 ± 5.3	0.7393
LVIDED, mm	68.3 ± 14.5	67.3 ± 11.4	0.8097
LVIDES, mm	54.0 ± 18.0	53.5 ± 15.6	0.9257

The values are presented as mean ± SD or %; ABPM: ambulatory blood pressure monitoring; ACEI: receptor inhibitor of angiotensin converting enzyme; ACR: albumin:creatinine ratio; ARB, angiotensin receptor blocker; CKD: chronic kidney disease; DHP: dihydropyridyne; eGFR: estimated glomerular filtration rate; LVMI: left ventricular mass index; LVEF: left ventricular ejection fraction measured by Simpson's method; LVIDED: left ventricle internal dimension at the end of diastole; LVIDES: left ventricle internal dimension at the end of systole; N: number of patients; RSD: renal sympathetic denervation; RNS: renal nerve stimulation.

Table 2. Sites where VT occurred during RNS, n (%) in CKD patients on stage 4 (n=40 patients).

Sites	20 patients = 40 renal arteries		20 patients = 40 renal arteries			
	RNS in the RNS group only		RNS before RSD in the RNS+RSD group		RNS after RSD in the RNS+RSD group, only in the sites where VT occurred	
RNS per quadrant (n=sites)	20 LRA (n=320)	20 RRA (n=320)	20 LRA (n=320)	20 RRA (n=320)	20 LRA (n=200)	20 RRA (n=140)
Quadrant1 - Ostium	14 (70%)	13 (65%)	12 (60%)	18 (90%)	1 (5%)***	3 (15%)***
Quadrant2 - Ostium	14 (70%)	9 (45%)	14 (70%)	18 (90%)	2 (10%)***	3 (15%)***
Quadrant3 - Ostium	11 (55%)	9 (45%)	15 (75%)	19 (95%)	4 (20%)*	3 (15%)**∗
Quadrant4 - Ostium	15 (75%)	0 (0%)	17 (85%)	0 (0%)	6 (30%)**	---
Quadrant1 - Proximal	17 (85%)	10 (50%)	20 (100%)	0 (0%)	1 (5%)***	---
Quadrant2 - Proximal	12 (60%)	12 (60%)	0 (0%)	20 (100%)	---	4 (20%)***
Quadrant3 - Proximal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	---	---
Quadrant4 - Proximal	0 (0%)	0 (0%)	0 (0%)	0 (0%)	---	---
Quadrant1 - Middle	0 (0%)	0 (0%)	0 (0%)	0 (0%)	---	---
Quadrant2 - Middle	0 (0%)	0 (0%)	0 (0%)	0 (0%)	---	---
Quadrant3 - Middle	15 (75%)	9 (45%)	20 (100%)	20 (100%)	4 (20%)***	2 (10%)***
Quadrant4 - Middle	0 (0%)	0 (0%)	0 (0%)	0 (0%)	---	---
Quadrant1 - Distal	0 (0%)	12 (60%)	0 (0%)	15 (75%)	---	4 (20%)**
Quadrant2 - Distal	0 (0%)	14 (70%)	20 (100%)	0 (0%)	4 (20%)***	---
Quadrant3 - Distal	14 (70%)	0 (0%)	14 (70%)	0 (0%)	6 (30%)*	---
Quadrant4 - Distal	12 (60%%)	0 (0%)	0 (0%)	16 (80%)	--–	4 (20%)***

CKD: chronic kidney disease; LRA: left renal artery; RNS: renal nerve stimulation; RRA: right renal artery; RSD: renal sympathetic denervation; VT: ventricular tachycardia; *P<0.05: **P<0.001, and ***P<0.0001 for comparisons between RNS after RSD in the RNS+RSD group *vs.* RNS in the RNS group only and RNS before RSD in the RNS+RSD group of renal arteries at the same side of the body.

Table 3. Δ mean invasive systolic BP during RNS, mmHg in CKD patients on stage 4 (n=40 patients).

Sites	20 patients = 40 renal arteries		20 patients = 40 renal arteries			
	RNS in the RNS group only		RNS before RSD in the RNS+RSD group		RNS after RSD in the RNS+RSD group, only in the sites where VT occurred	
RNS per quadrant (n=sites)	20 LRA (n=320)	20 RRA (n=320)	20 LRA (n=320)	20 RRA (n=320)	20 LRA (n=200)	20 RRA (n=140)
Quadrant1 - Ostium	27.6 ± 4.3	27.3 ± 4.4	26.3 ± 3.7	29.5 ± 4.1	16.4 ± 4.4$^{**/**}$	19.4 ± 5.3$^{**/**}$
Quadrant2 - Ostium	28.4 ± 5.4	26.8 ± 7.0	27.4 ± 4.3	30.2 ± 5.0	17.1 ± 5.1$^{**/**}$	19.9 ± 4.8$^{*/**}$
Quadrant3 - Ostium	26.3 ± 5.7	25.6 ± 6.4	28.4 ± 6.6	29.6 ± 3.5	18.1 ± 7.0$^{*/**}$	20.0 ± 4.5$^{*/**}$
Quadrant4 - Ostium	27.8 ± 3.8	6.8 ± 7.0	30.4 ± 3.4	6.5 ± 4.7	20.7 ± 5.5$^{**/**}$	---
Quadrant1 - Proximal	27.8 ± 3.3	28.9 ± 9.0	29.7 ± 2.7	8.2 ± 6.2	19.1 ± 3.0$^{**/**}$	---
Quadrant2 - Proximal	25.7 ± 2.8	28.8 ± 7.3	10.0 ± 8.5	31.5 ± 5.2	---	21.1 ± 6.0$^{*/**}$
Quadrant3 - Proximal	8.3 ± 5.1	6.0 ± 5.7	10.8 ± 4.1	4.3 ± 5.4	---	---
Quadrant4 - Proximal	7.3 ± 4.1	6.9 ± 5.5	9.2 ± 4.9	7.7 ± 7.3	---	---
Quadrant1 - Middle	5.8 ± 5.0	7.5 ± 4.6	8.7 ± 5.1	6.3 ± 3.8	---	---
Quadrant2 - Middle	7.1 ± 6.6	5.8 ± 5.2	7.1 ± 6.6	4.8 ± 4.8	---	---
Quadrant3 - Middle	28.2 ± 4.8	25.1 ± 5.1	30.4 ± 3.9	30.3 ± 2.2	21.9 ± 3.8$^{**/**}$	20.6 ± 3.4$^{*/**}$
Quadrant4 - Middle	4.2 ± 4.3	3.6 ± 4.0	3.0 ± 3.5	6.0 ± 5.0	---	---
Quadrant1 - Distal	4.9 ± 6.4	30.3 ± 8.1	4.6 ± 6.6	28.7 ± 6.4	---	18.0 ± 7.3$^{**/**}$
Quadrant2 - Distal	7.9 ± 6.6	29.8 ± 7.0	30.9 ± 3.6	7.5 ± 5.0	21.7 ± 3.9$^{**/**}$	---
Quadrant3 - Distal	29.6 ± 5.7	6.3 ± 5.1	28.3 ± 7.9	5.4 ± 5.0	19.1 ± 9.0$^{*/*}$	---
Quadrant4 - Distal	28.9 ± 5.4	6.4 ± 8.8	6.8 ± 5.4	28.8 ± 8.9	---	18.7 ± 8.5$^{**/*}$

were not submitted to RSD was: r=0.9809; 95% confidence interval (CI): 0.9445 – 0.9935; P<0.0001 for the left renal artery (LRA), and r=0.9825; 95%CI: 0.9489 – 0.9941; P<0.0001 for the right renal artery (RRA). To the subjects that underwent RSD, the same correlation, before the procedure, was: r=0.9726; 95%CI: 0.9209 –0.9907; P<0.0001 for the LRA, and r=0.9925; 95%CI: 0.9780 – 0.9455; P<0.0001 for the RRA. And after the RSD, this correlation was: r=0.8165; 95%CI: 0.5388 – 0.9341; P=0.0001 for the LRA, and r=0.9364; 95%CI: 0.8225 – 0.9781; P<0.0001 for the RRA. According to Tables 2 and 3 respectively, we can observe which areas are most susceptible to VT occurrence during RNS, and the changes of the invasive systolic BP in this population. The 20 CKD subjects on stage 4 which were not submitted to RSD presented area under the roc curve (AUC) = 0.9993/0.9985, 95% confidence interval (CI)=0.9965 to 0.9997/0.9958 to 0.9994, P value <0.0001/<0.0001, sensitivity= 95% / 98%, specificity= 99% / 100%, and the cutoff point of Δ invasive systolic blood pressure to trigger VT during RNS >25.5 mmHg/ >25.5 mmHg, from the LRA and RRA, respectively. The other 20 CKD subjects on stage 4 that underwent RSD subsequently showed before the procedure the AUC= 0.9980/0.9990, 95% CI=0.9956 to 0.9993/0.9986 to 0.9995, P value <0.0001/<0.0001, sensitivity = 96% / 99%, specificity= 100% / 100%, and the cutoff point of Δ invasive systolic blood pressure to trigger VT during RNS >25.5 mmHg/ >24.5 mmHg, from the LRA and RRA, respectively. After the RSD, the AUC= 1.0000, 95% CI=1.0000 to 1.0000, P value <0.0001, sensitivity= 100%, specificity= 100%, and the cutoff point of Δ invasive systolic blood pressure to trigger VT during RNS >25.5 mmHg, for both arteries.

In our study, after RSD a decline occurred in the incidence of ventricular arrhythmias and blood pressure rise provoked by RNS, even during new acute subsequently RNS in patients with CKD on stage 4. Our results suggest that RSD can control the higher incidence of malignant arrhythmias in advanced CKD stages.

Conflict of interests

The authors declare no conflict of interest.

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