



Renal Denervation in CKD Hypertensive Patients: Would it be Possible to Prevent the Development of Risk Factors Responsible for Sudden Cardiac Death in this Population?

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Kidney disease induces cardiac remodeling including left ventricular hypertrophy (LVH), and heart fibrosis. Several clinical studies, including those who recruited participants with mild to moderate reduction in estimated glomerular filtration rate (eGFR) showed an independent association between chronic kidney disease (CKD) and LVH.¹⁻⁴ Specifically, there is a progressive increase in the prevalence of LVH and left ventricular mass increased when the eGFR decreases. In addition, among participants with more advanced kidney disease on dialysis, magnetic resonance image (MRI) with contrast demonstrates a diffuse pattern image with gadolinium uptake suggestive of fibrosis and non-ischemic cardiomyopathy.⁵ The pathogenesis of these conditions is considered multifactorial, and the presence of commonly associated comorbidities, such as hypertension, diabetes mellitus and anemia, explain only part of the left ventricular remodeling.⁶⁻⁸ The molecular basis for these changes includes activation of growth factors, proto-oncogenes, plasma norepinephrine, cytokines, and angiotensin II.

These factors regulate intracellular processes that accelerate cardiac hypertrophy, myocardial fibrosis, and apoptosis.^{9,10} Any LVH and cardiac fibrosis has been linked to increased risk of sustained ventricular arrhythmias and predisposition to sudden cardiac death (SCD).¹¹⁻¹⁵ In hypertensive patients with elevated E/e' ratio (non-invasive method to allow early assessment of left ventricular filling pressure, estimated by tissue Doppler) the annual mortality rate is 10% and the ratio is considered to be a prognostic factor for the development of cardiovascular disease (CVD).¹⁶ Diastolic heart failure is

an important factor that increases mortality related to the cardiovascular system in patients with CKD whose extent of kidney function deterioration differs.¹⁷ Recently, renal dysfunction was assessed as an independent risk factor for SCD, which has been considered as a distinct endpoint in several cohort studies and clinical trials.

The current study evaluated 10 patients with CKD and without LVH who were selected according to a previously published protocol.¹⁸ The Committee of Ethics in Research of the Medical School of Universidade Federal Fluminense approved the study and written informed consent was obtained from every patient. In the period from June 2011 to December 2012, these patients underwent renal sympathetic denervation (RSD). All of them had resistant hypertension and CKD (stages 2, 3 and 4), as shown in table 1. They underwent laboratory tests and assessment of renal function at baseline and 24 hours post procedure, before discharge.

The procedures were performed in the catheterization laboratory with direct visualization using fluoroscopy and radiopaque contrast. In several cases, we also used three-dimensional mapping system EnSite Velocity (St. Jude Medical, St. Paul, Minnesota, USA) for construction of renal arteries and aorta anatomy, as well as for radiofrequency application in the selected sites. All patients remained under unconscious sedation. Patients were discharged after 24 hour hospitalization, clinically stable, walking without difficulty. Bruising or aneurismal formation was not seen at the puncture site. According to the protocol,¹⁸ in the follow-up period,

Table 1. General features of patients at baseline

N	10
Age (years)	48 ± 12 ^a
Female sex (%)	7 (70%)
Ethnicity (white) (%)	8 (80%)
Body mass index, kg/m ²	31.8 ± 4.9
Coronary artery disease (%)	3 (30%)
Atrial fibrillation (%)	0 (0%)
Stroke (%)	0 (0%)
Type 2 diabetes (%)	2 (20%)
Number of antihypertensives	4.2 ± 1.6
eGFR, mL/min/1.73m ² (CKD-EPI)	70.9±21.4
Stages of CKD	
2	8 (80%)
3	1 (10%)
4	1 (10%)
Office blood pressure, mmHg	185±18/112±16

^aMean±SD; eGFR, estimated glomerular filtration rate.

Doppler ultrasound of the renal arteries was performed one and 6 months after the procedure in all patients and did not show any complication or change in blood flow. Left ventricular mass (LVM) assessed by echocardiography at baseline and 6 months post procedure was calculated from LV linear dimensions using the equation of Devereux.^{19,20} The left ventricular mass was indexed to body surface area (g/m²), as described.^{19,21} LVH was considered present when LV mass exceeding 115 g/m² for men and 95 g/m² for women was observed.¹⁹

The changes at the 6th month after RSD in mean office systolic/diastolic blood pressure, mean systolic/diastolic ambulatory blood pressure measurements (ABPM), average number of antihypertensive drugs, mean creatinine values, mean eGFR,

and albumin:creatinine ratio (ACR) are shown in table 2. The LVM indexed to body surface area decreased substantially during the follow-up, from 88.0±12.0 g/m² at baseline to 74.9±9.8 g/m² at 6 months (P<0.0001), as shown in figure 1A. At baseline the end-diastolic left ventricular internal dimension (LVIDd) was 50.5±2.7 mm with a reduction to 48.4 ± 3.2 mm at 6 months (P=0.0009) (figure 1B). The left ventricular end-diastolic posterior wall thickness (PWTd) was reduced from 9.5±1.1 mm at baseline to 9.0±0.8 mm at 6 months (P=0.0150) (figure 1C). The same phenomenon was observed in the end-diastolic interventricular septum thickness (IVSTd), occurring reduction from 9.7±.2 mm at baseline to 8.9±0.9 mm at 6 months (P=0.0002), as shown in figure 1D. The patients underwent to RSD did not show improvement in LV ejection fraction (62.9±6.3% at baseline vs. 66.2±7.4% at 6 months, P=0.0931). The isovolumic relaxation time reduced from 116.5±32.2 ms at baseline to 100.0±26.7 ms at the 6th month after RSD, P=0.0036 (Figure 2A). The mitral valve lateral E/e' decreased from 8.6±2.2 at baseline to 6.5±1.4 at the 6th month post procedure, P=0.0021 (Figure 2B). The mitral valve E deceleration time also reduced from 239.3±52.5 ms to 207.1±34.9 ms, 6 months post RSD, P=0.0030 (Figure 2C). We also observed a reduction in the left atrial diameter, from 36.8±5.2 mm at baseline to 34.1±5.8 mm, 6 months after de procedure, P=0.0281 (Figure 2D).

In this study, we reported for the first time the reduction in left ventricular mass and diameter, and the improvement on diastolic function, as well as, the reduction in left atrium diameter in CKD hypertensive patients that do not have LVH. Our results suggest that the RSD in this kind of patients seems to be effective in reducing lesions of target organs such as the heart and kidneys. Furthermore, these results suggest that would be possible to prevent the development of risk factors (LVH and augmented left ventricular filling pressure) responsible for sudden cardiac death in this population.

Declarations of Interest

The authors declare no conflicts of interest.

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The authors state that they abide by the statement of ethical publishing of the Journal of Advanced Therapies and Medical Innovation Sciences.²²

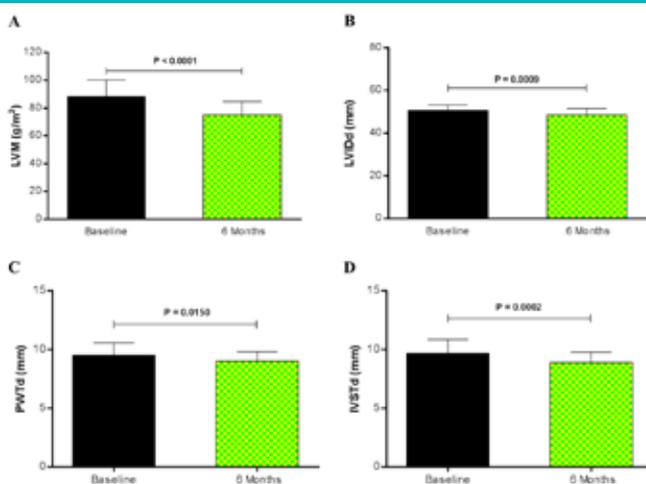


Figure 1: (A) Left ventricular mass (LVM) g/m², (B) end-diastolic left ventricular internal dimension (LVIDd) measured in mm, (C) left ventricular end-diastolic posterior wall thickness (PWTd) measured in mm, and (D) end-diastolic interventricular septum thickness (IVSTd) measured in mm, at baseline and 6 months after renal sympathetic denervation (n=10). Values are presented as mean±SD.

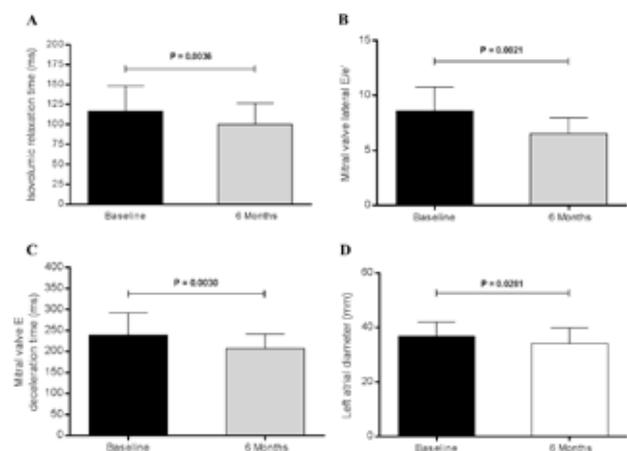


Figure 2. (A) Isovolumic relaxation time measured in ms, (B) mitral valve lateral E/e', (C) mitral valve E deceleration time measured in ms, and (D) left atrial diameter measured in mm, at baseline and 6 months after renal sympathetic denervation (n=10). Values are presented as mean±SD.



Table 2. Parameters at baseline and 6 months after renal sympathetic denervation

Variable	Baseline	6th month	P value
Office Systolic BP, mmHg	185±18 ^a	199±9	<0.0001
Office Diastolic BP, mmHg	112±16 ^a	88±4	0.0012
Systolic ABPM, mmHg	148±19 ^a	127±10	0.0014
Diastolic ABPM, mmHg	94±14 ^a	83±9	0.0045
Number of AH drugs	4.2±1.6 ^a	2.9±0.9	0.0224
Creatinine values, mg/dl	1.22±0.78 ^a	0.92±0.9	0.0001
eGFR, ml/min/1.73m ²	70.9±21.4 ^a	98.7±30.8	0.0002
Albumin: creatinine ratio, mg/g	42.6 ^b (35.9 - 109.0)	11.6 (8.3 - 30.8)	0.0011

^aMean±SD; ^bMedian (Interquartile range); eGFR, estimated glomerular filtration rate.

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