

Renal Denervation for Ventricular Arrhythmia in Patients with Implantable Cardioverter Defibrillators

Experience in Asian Population

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Summary

To investigate the efficacy of renal denervation (RDN) on the recurrence of ventricular arrhythmia (VA) in Asian patients with implantable cardioverter defibrillators (ICDs).

Eight ICD patients with recurrent VA episodes underwent RDN using an off-the-shelf saline-irrigated catheter. The pre- and postprocedural VA episodes were counted via ICD interrogation. All patients underwent successful RDN without any complications related to radiofrequency catheter ablation. The median follow-up was 15 months (range 6-30), and the median VA episodes per month were significantly reduced from 3.17 (range 0.33-15.33) to 0.10 (range 0-5.83) after RDN ($P < 0.05$).

RDN is an effective suppressor of VA in Asian patients with ICDs.

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Key words: Renal sympathetic denervation, Ventricular tachycardia, Electrical storm, Ventricular fibrillation

The event of more than three separate episodes of ventricular arrhythmias (VAs) leading to implantable cardioverter defibrillator (ICD) therapies within 24 hours is referred to as an electrical storm (ES). ES represents a dramatic situation of acute electrical instability and correlates with a worsening prognosis.¹⁾ Treatment options for ES include intensive care unit admission, device reprogramming, correction of underlying problems, antiarrhythmic therapy and catheter ablation (CA).^{2,3)} Since none of these methods can effectively solve this problem, ES is among the most challenging therapeutic dilemmas for healthcare teams. The sympathetic nervous system plays a crucial role in the onset, maintenance and termination of VAs. A small change of autonomic tone can lead to dramatic effects on exacerbating or reducing VAs. Renal denervation (RDN) leads to a decrease of whole-body norepinephrine spillover and efferent muscle sympathetic nerve activity.⁴⁾ So far, a series of reports have demonstrated the benefits of RDN in patients with VAs.⁵⁻¹²⁾ However, no such experience has been reported in Asian population. We hypothesize that RDN could also reduce VAs as well as ES in Asian patients with ICDs.

Methods

Study design and population: This study was prospectively conducted in the First Affiliated Hospital of Nanjing Medical University in China. The study was conducted in

accordance with the ethical standards defined by local law and was approved by the local ethics committee. All patients provided written informed consent. ICD patients from our center were assessed for this study between April 2012 and February 2015. Criteria for inclusion were that patients be 18-75 years of age and present with ES or recurrent VAs during ICD interrogation. Exclusion criteria were that patients showed allergic reaction to contrast agent, active infection, systolic blood pressure ≤ 80 mmHg, renal artery stenoses, and declination of participation. Eligible patients then underwent RDN and were followed up for at least 6 months. Blood pressure and heart rate were measured using ambulatory blood pressure monitoring and 24-hour holter monitoring recording, respectively.

RDN procedure: The operation procedure of RDN was almost identical with that reported by Qiu, *et al.*¹³⁾ We chose an internally irrigated radiofrequency ablation catheter to complete this clinical research. After standard femoral vascular access, contrast renal angiography was performed to localize and assess the renal arteries for accessibility and appropriateness for RDN. Once the anatomy was deemed acceptable, the ablation catheter was introduced into each renal artery. About 4-10 ablations at 10 W for 60 s each were performed in both renal arteries. During ablation, the catheter system monitored tip temperature and impedance, adjusted the cold saline infusion speed according to tip temperature ($36^{\circ}\text{C} \leq T \leq 45^{\circ}\text{C}$) and

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Table I. Baseline Characteristics

Patient	Age (year)	Etiology	Ejection fraction (%)	Months of ICD	ES	Cardiac ablation	Antiarrhythmic medications	Hypertension	Diabetes	Smoking	NT-pro BNP (ng/L)	Creatinine (μmol/L)
1	19	DCM	34.5	5	No	No	BB	No	No	No	79	49.7
2	61	DCM	45.2	44	Yes	No	A, BB	Yes	No	Yes	193	85.4
3	50	DCM	36.2	17	Yes	No	BB	No	No	Yes	465	99.7
4	65	ICM	67	32	Yes	Yes	A, BB	Yes	Yes	Yes	220	63.9
5	52	DCM	25	15	No	No	BB	No	No	No	1045	59.4
6	52	HCM	68.5	4	Yes	No	A, BB	Yes	No	Yes	1083	120.5
7	61	iCM	62	28	Yes	Yes	BB, P	No	No	No	1076	68.9
8	51	DCM	29.1	3	No	No	BB	No	Yes	No	1130	80.8

HCM indicates hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; ICM, ischemic cardiomyopathy; iCM, idiopathic cardiomyopathy; ICD, implantable cardioverter defibrillator; ES, electrical storm; A, amiodarone; BB, beta blocker; P, propafenone; and NT-proBNP, N-terminal pro-brain natriuretic peptide.

Table II. Burdens of Ventricular Arrhythmia Pre- and Post-RDN (/month)

Patient	Pre-RDN				Post-RDN			
	VAs	ES	ATP	SHOCK	VAs	ES	ATP	SHOCK
1	1.33	0.00	1.33	0.00	0.11	0.00	0.17	0.00
2	1.67	1.67	5.67	1.33	0.17	0.00	0.33	0.08
3	4.67	3.33	5.33	1.00	0.06	0.00	0.06	0.00
4	15.33	12.67	2.67	9.00	2.13	2.00	2.23	0.33
5	0.33	0.00	0.00	0.33	0.10	0.00	0.05	0.10
6	7.33	6.00	14.33	11.67	0.00	0.00	0.00	0.00
7	13.67	7.67	28.00	8.00	5.83	5.00	10.50	3.33
8	0.67	0.00	0.67	0.00	0.00	0.00	0.00	0.00

VAs indicate ventricular arrhythmias; ES, electrical storm; and ATP, antitachycardia pacing.

adjusted the radiofrequency energy delivery in response to pain tolerance. Radiofrequency energy delivery was stopped immediately if the tip impedance suddenly increased.

Statistical analysis: Continuous variables were reported as mean \pm SD or median and range. Dichotomous variables were described as numbers and percentages. Comparison of VAs burden, antitachycardia pacing (ATP), shock, creatinine, heart rate, blood pressure, and n-terminal pro-brain natriuretic peptide before and after RDN was made using the nonparametric Wilcoxon signed rank test. All tests were two tailed, and statistical significance was accepted at *P* value of 0.05. All statistical analyses were performed using SPSS 13.0.

Results

Baseline characteristics: Between April 2012 and February 2015, 72 patients implanted with ICDs for primary or secondary prevention were assessed for this study. Among them, 28 did not have ES or recurrent VAs, one showed allergic reaction to contrast agent, 6 had systolic blood pressure \leq 80 mmHg, 5 had renal arteries stenosis, and 24 declined to participate. Finally, eight patients (seven males, 51.4 ± 14.3 years) were enrolled. Seven of these patients had nonischemic cardiomyopathy, and one patient had ischemic cardiomyopathy. Among seven patients with nonischemic cardiomyopathy, one was hypertrophic cardiomyopathy, five were dilated cardiomyopathy and one was idiopathic cardiomyopathy with left ventricular aneurysm. The mean ejection fraction was $48.3 \pm 17.1\%$, and

ES occurred in five cases. Two patients underwent a previous unsuccessful CA. The rest six patients did not perform CA because of polymorphic ventricular tachycardia. All patients were on long-term use of beta-blockers (metoprolol, bisoprolol or carvedilol); one patient was on long-term use of propafenone; and three patients were on long-term use of amiodarone. Medications were used at least 3 months before RDN and were not changed after RDN. Patient baseline characteristics are summarized in Table I.

Burdens of VA: ICD interrogation after RDN was available in all patients for at least 6 months. Among them we had six patients at 12 months, four patients at 21 months, and one patient at 31 months. The median VAs/month before RDN was 3.17 (range 0.33-15.33) and significantly reduced to 0.10 (range 0-5.83) after RDN (*P* < 0.05). During the first 3 months after RDN, one patient had an onset of ES with 60 episodes of ventricular tachycardia/fibrillation, while another patient had an onset of ES with 30 episodes of ventricular tachycardia/fibrillation. Three months after RDN, all patients were free from ES. The median ATP/month and Shock/month before RDN were 4 (range 0-28) and 1.17 (range 0-11.67) and were significantly reduced to 0.11 (range 0-10.5) and 0.04 (range 0-3.33) after RDN, respectively (*P* < 0.05; see details in Table II).

Procedure characteristics: Mean lengths of the left and right renal arteries were 36.2 ± 12.4 and 43.3 ± 12.1 mm, while mean diameters of them were 5.3 ± 1.1 and 5.1 ± 0.8 mm. In one patient, one accessory artery was identified. According to Okada classification,¹⁴⁾ 10 renal arteries

Table III. Characteristics of RDN Procedure

Patient	Energy (W)	Temperature (°C)	Duration (S)	Impedance Pre (Ω)	Impedance during (Ω)	Lesion
1	5.8	38.9	120.4	217.4	208	18
2	9.5	38.9	71.3	188.8	175.3	19
3	7.1	38.2	84.1	208.9	199.4	15
4	10	38.9	70.9	182.6	176	19
5	8.5	38	76.8	216.3	200.8	18
6	9.9	39.3	65.6	178.1	161.3	15
7	8.9	36.9	69	167.7	157.4	20
8	7.9	36.3	80.1	180.9	166	16
Mean ± SD	8.5 ± 1.5	38.2 ± 1.1	79.8 ± 17.5	192.6 ± 19	180.5 ± 19.6	17.5 ± 1.92

Table IV. Comparison of Variables between Pre- and Post-RDN (6 Months after RDN)

	Pre-RDN	Post-RDN	P
NT-proBNP (ng/L)	661.4 ± 464.2	461.9 ± 324.3	0.012
Creatinine (μmol/L)	78.5 ± 23.2	69.5 ± 13.1	0.161
Heart rate (bpm)	69.3 ± 13.9	70.6 ± 14	0.395
SBP (mmHg)	111.5 ± 8.9	103.8 ± 12.4	0.262
DBP (mmHg)	70.6 ± 7.7	67.9 ± 7.1	0.482

NT-proBNP indicates N-terminal pro-brain natriuretic peptide; SBP, systolic blood pressure; and DBP, diastolic blood pressure.

were A1 type, and 6 were A2 type. The actual ablation power was 8.5 ± 1.5 W, temperature was $38.2^\circ\text{C} \pm 1.1^\circ\text{C}$, time duration was 79.8 ± 17.5 S, and ablation lesions were 17.5 ± 1.9 . Renal artery impedance was reduced from 192.6 ± 19 to 180.5 ± 19.6 Ω during RDN. Detailed parameters of RDN procedure are shown in Table III. No procedure complications were observed.

Follow-up: The median follow-up was 15 months (range 6-30), and there was no death or loss to follow-up. Creatinine, heart rate, and blood pressure were not different before and 6 months after RDN. N-terminal pro-brain natriuretic peptide was reduced from 661.37 to 461.86 ng/L ($P = 0.012$; see Table IV).

Discussion

Main findings: With this sample, we find that RDN also inhibits VAs in Asian patients with ICDs, and the efficiency lasts for more than 1 year. Our result is in line with other reports. In 2013, Ukena, *et al.*⁵⁾ reported the first in-man experience of RDN in two patients with refractory ES. In both cases, a significant reduction of VAs was documented. From then on, a series of case reports have demonstrated the advantage of RDN on VAs.^{6,7,9)} Among them, the longest duration of follow-up is 14 months,⁸⁾ and the largest number of patients is 16.¹¹⁾ Furthermore, most of our patients were nonischemic cardiomyopathy, which existed more in Asian population.

Safety of RDN: Risks of RDN include vascular access complications and direct renal artery damage such as femoral artery pseudoaneurysm and dissection, renal artery dissection, and stenosis with the potential for associated renal failure. To date, renal failure as a complication has been exceedingly uncommon. A meta-analysis by Davis, *et al.*¹⁵⁾ demonstrated an overall procedure complication rate of < 1% (including 1 renal artery dissection

and 4 pseudoaneurysms). In our study, RDN was well tolerated acutely and demonstrated no clinically significant complications during a median follow-up of 15 months.

Mechanism of RDN for VAs: Schlaich, *et al.*⁴⁾ reported that RDN resulted in a reduction of whole-body norepinephrine spillover as well as efferent muscle sympathetic nerve activity. By reducing circulating catecholamines, RDN has the potential to reduce VAs immediately. Furthermore, RDN suppresses atrial ectopy and reentrant circuits.¹⁶⁻¹⁸⁾ Effects of RDN on trigger arrhythmias are also available from animal experiments.^{7,19)} RDN can even directly increase the ventricular effective refractory period^{20,21)} and action potential duration.²⁰⁾

Aside from immediate antiarrhythmic properties, RDN ameliorates the symptoms of chronic heart failure and therefore eliminates VAs during a long-term follow up.^{22,23)} Two patients in our study had ES recurrence during a short- rather than long-term follow-up, which may be related to this mechanism. And this phenomenon was also reported by other researchers.^{5,7,8)} More recently, we demonstrated another probable long-term protective mechanism that RDN could reduce cardiac fibrosis.²⁴⁾ Thirty-one survival isoproterenol-induced cardiomyopathy rats were randomized into the RDN ($n = 15$) and Sham group ($n = 16$). After 10 weeks, collagen volume fraction of left atrio-ventricular and kidney tissues reduced significantly in RDN group compared with the Sham group.²⁴⁾

In our study, four patients had ejection fraction < 37%, which was comparable with other researches. Among the other four patients with normal or near normal ejection fraction, one was coronary artery disease, one was dilated cardiomyopathy, one was hypertrophic cardiomyopathy, and one was idiopathic cardiomyopathy with left ventricular aneurysm. In the research of Remo, *et al.*,⁸⁾ they also reported good efficiency of RDN in this kind of patients with normal or near normal. Armaganijan, *et al.*⁹⁾ even reported RDN efficiency on patients with Chagas disease, which usually had fibrosis in the epicardium. With all of these results, we may suspect that RDN suppresses VAs in different myocardium substrate with or without low ejection fraction.

RDN and CA: CA can be life saving in patients with incessant VAs or ES,²⁵⁾ but only a moderate long-term efficacy has been reported.²⁶⁾ Furthermore, the arrhythmia substrate of nonischemic cardiomyopathy is more variable and more aggressive ablation strategies targeting all inducible ventricular tachycardia are needed to improve long-term freedom from VAs.²⁷⁻²⁹⁾ Most of our patients were

nonischemic cardiomyopathy, which suggested that RDN could be another choice for VA treatment in this kind of patients. As a simple percutaneous procedure, RDN reduces sympathetic tone and suppress VAs. However, even with experienced experts, RDN alone is not always effective. In the research of Armaganijan, *et al.*,⁹⁾ two patients showed no reduction of VAs because of incomplete ablation of renal sympathetic nerves and lack of sympathetic trigger for the persistent idioventricular rhythm.

In fact, CA ablates the cardiac substrate and RDN triggers to autonomic modulation; the two methods can complement each other. Early clinical evidence has suggested a possible benefit of RDN as an adjunct treatment option not just for VAs but for atrial fibrillation as well.^{30,31)}

Study limitations: There are certain limitations in this study. First, norepinephrine spillover was not measured. In prior animal researches, we had already found that RDN could suppress norepinephrine spillover.^{24,32)} However, many researchers used the term “renal denervation” instead of “intra-renal artery ablation.” Scientifically, as long as denervation is not examined in the individuals, the intravascular procedure cannot be called the “denervation.” Second, the present study enrolls a relatively small number of patients. However, this is the first report of such researches in Asian population, and the most underlying disease is nonischemic cardiomyopathy. Our study shows that this specific kind of population can benefit from RDN. Third, this is an observation research. Multiple factors, such as nature history of VAs could interrupt the results. Further identification is expected by randomized and controlled studies.

Conclusions

RDN can effectively suppress VA episodes in Asian population, and it can be an adjunct treatment option for CA.

Disclosures

Conflicts of interest: The authors have no conflicts of interest to disclose.

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