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ABSTRACT:

Background: Autonomic modulation is finding an increasing role in the treatment of ventricular arrhythmias. Renal denervation (RDN) has been described as a treatment modality for refractory ventricular tachycardia (VT) in case series.

Objective: To evaluate RDN as an adjunctive therapy to cardiac sympathetic denervation (CSD) for ablation refractory VT.

Methods: Patients who underwent RDN after radiofrequency ablation and CSD procedures at our center from 2012 to 2019 were evaluated.

Results: Ten patients underwent RDN after CSD (9 bilateral, 1 left-sided only) with median follow-up of 23 months. Mean age was 59.9 ± 10.4 years and 90% were men. All had cardiomyopathy with average ejection fraction 33 ± 11% (20% ischemic). 4 (40%) underwent CSD during the same hospitalization as the RDN. Patients who underwent RDN as adjunctive therapy to CSD had a decrease in all ICD therapies (shocks + ATP) from 29.5 ± 25.2 to 7.1 ± 10.1 comparing 6 months prior to RDN to 6 months post-RDN (p=0.028). ICD shocks were significantly decreased from 7.0 ± 6.1 to 1.7 ± 2.5 comparing 6 months prior to RDN to 6 months post-RDN (p=0.026). This benefit was driven by a decrease in therapies for 6 patients that had a staged procedure, not performed during the same hospitalization (28.5 ± 24.3 to 1.0 ±1.2, p=0.043).

Conclusion: RDN demonstrates potential benefit when VT recurs after RFA and CSD. The benefit is seen in patients who undergo a staged procedure. The need for acute RDN after CSD portends a poor prognosis.

Keywords:

Autonomic modulation, autonomic nervous system, cardiac sympathetic denervation, monomorphic ventricular tachycardia, polymorphic ventricular tachycardia, radiofrequency catheter ablation, renal denervation

Introduction:

Autonomic modulation has become an important tool for the treatment of refractory ventricular arrhythmias. Cardiac sympathetic denervation (CSD) carries a class IIb indication for ventricular tachycardia (VT) in the setting of structural heart disease in the current guidelines.[1]

Management of refractory ventricular arrhythmias can be extremely challenging. While antiarrhythmic therapy and radiofrequency ablation (RFA) remain the first-line therapies for VT, success rates are modest, especially in non-ischemic cardiomyopathy (NICM), in large part because of the complexity and heterogeneity of the underlying substrates.[2] The need for additional treatment modalities for this complex patient population led to the use of autonomic modulation to treat refractory VT patients. CSD has been shown to decrease risk of recurrent implantable cardioverter-defibrillator (ICD) therapies in multicenter retrospective data.[3]

Renal artery denervation (RDN), originally developed for the management of refractory hypertension, has been shown in small retrospective studies to decrease frequency of VT both alone[4-6], and as an adjunctive therapy in combination with RFA[7].

However, there is no data available on the use of RDN in patients who have previously or concomitantly undergone CSD.

Methods:

Patients who underwent RDN after previous RFA and CSD with an indication of refractory VT at our center from 2012 to 2019 were evaluated. Retrospective data review was approved by the University of California, Los Angeles Institutional Review Board. Baseline characteristics, indication for RDN and available clinical follow-up were assessed (Table 1 and 2). ICD therapies were quantified before and after RDN (Figure 1 and 2). A RDN procedure was considered a success if the patient had no ICD therapies during the follow-up period, a partial success if ICD shock therapies decreased, and not a success if the patient had recurrent ventricular arrhythmias and ICD therapies leading to further clinical decompensation or requiring another procedure.

Renal artery denervation procedure

An abdominal aortogram was performed through a 5F pigtail catheter. Subsequent selective angiography of the renal arteries was performed using a 5F Cobra 2 catheter (Angiodynamics Inc, Lantham, NY, USA). Angiography confirmed the size, morphology and presence of any branches or atherosclerotic disease. An 8F Destination sheath (Terumo Inc., Tokyo, Japan) was then advanced into the distal renal artery just proximal to the bifurcation.

A 3.5 mm open irrigated ablation catheter was advanced through the sheath to this site. RFA lesions were delivered at 10W (max 42 degrees) for 60 seconds. Lesion sets were delivered by alternating superior and inferior deflection of the ablation catheter as it was pulled back from the renal artery bifurcation to the renal artery ostium, with attempts to avoid overlapping lesions. An electroanatomic map of the renal arteries (NavX, Abbott Medical, Minneapolis, MN) was obtained to monitor lesion location and avoid lesion overlap (Figure 3). After completion of the lesion set a repeat renal angiogram was performed to ensure no compromise of renal artery perfusion. High frequency stimulation was utilized in early cases to assess for blood pressure response pre- and post-RDN, similar to previous studies.[8, 9] However, due to unreliable effect in our patients, this technique was not utilized for the majority of cases.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared using the student t test. Categorical variables compared with the Fisher exact test. Variables measured before and after RDN procedure were compared using the Wilcoxon signed rank test. Data were analysed using SPSS version 25 (IBM, Armonk, NY, USA). A p-value of less than 0.05 was considered statistically significant.

Results:

Ten patients underwent RDN at our institution after previous CSD (9 BSG, 1 left-only) over a 6-year period with a median follow-up of 28 months. The mean age was

59.9 ± 10.4 years and 90% were men. All had cardiomyopathy with 80% non-ischemic, and the mean clinical VT cycle length was 395 ± 101ms (for monomorphic VT). All had undergone previous RFA for VT with an average of 2.2 ± 1.0 procedures. (supplementary table) The median time from CSD to RDN was 51 days (IQR 20, 434) and 40% underwent CSD during the same hospitalization as the RDN. (Table 1 and 2)

All patients had technically favorable renal artery anatomy to undergo RDN based on Okada classification. A mean of 5.8 ± 1.3 RF lesions were delivered per renal artery. (Table 2) Systemic blood pressure was not significantly decreased after RDN. There were no major acute complications and post-procedure GFR was unchanged (67.7 mL/min vs 66.3 mL/min). Patient 8 had transient slow flow in the left renal artery that resolved without sequelae. The antiarrhythmic drugs (AAD) were modified in the acute time period of RDN due to recurrent VT; there was no acute or intermediate-term decrease in the number of antiarrhythmic medications and doses. The total population of patients that underwent RDN as adjunctive therapy to CSD had a modest overall decrease in all ICD therapies (shocks + ATP) from 29.5 ± 25.2 to 7.1 ± 10.1 comparing 6 months prior to RDN to 6 months post-RDN (p=0.038). (Figure 1 and 2) ICD shocks were significantly decreased from 7.0 ± 6.1 to 1.7 ± 2.5 comparing 6 months prior to RDN to 6 months post-RDN (p=0.012).

Further analysis was undertaken evaluating patients who had RDN during the same hospitalization as CSD (acute) and those who underwent RDN after outpatient recurrence (staged). Median time from CSD to staged RDN was 395 days versus only 14 days for the acute in-hospital RDN procedures. Patients who had staged RDN had a marked reduction in VT/VF burden and associated ICD therapies. Five of the 6 patients

in this group were found to have freedom from VT at median follow-up of 16.9 months. Overall ICD therapy burden decreased from 28.5 ± 24.3 to 1.0 ±1.2 therapies in this group comparing 6 months prior to RND to 6 months post-RDN (p=0.042).

However, none of the four patients who underwent RDN during the same hospitalization had a clinically successful outcome. Two patients required repeat RFA at 2 and 6 months after RDN due to recurrent VT, one patient with a left ventricular assist device (LVAD) had recurrence of slow VT below the ICD detection zone, and one patient died within one month after RDN due to multiorgan failure and inability to wean off of extracorporeal membrane oxygenation support. In this group, ICD therapy burden was not significantly improved (31.0 ± 30.2 to 16.3 ± 10.8 therapies, p=0.46. There was a statistically significant difference in NYHA functional class in the patients who underwent staged versus acute RDN procedures (2.2 ± 0.4 versus 3.5 ± 0.6, p=0.003). There was no statistically significant difference in other baseline characteristics between the patients who underwent staged versus acute RDN in terms of age (65.0±5.9 vs. 55.3±12.8 years), ejection fraction (30.8±8.5% vs. 28.8±16.5%), kidney function (creatinine 1.2±0.2 vs. 1.3±0.5), number of failed AADs (3.0±1.1 vs. 3.3±0.5), number of prior ablation procedures (2.2±0.8 vs. 2.0±1.2), number of VTs (excluding polymorphic VT) (1.5±1.0 vs. 1.3±0.6), or VT cycle length (339±75ms vs. 449±121ms).

Discussion:

The key findings of this study are the following:

1) RDN may have additive benefit to RFA and CSD for refractory VT

2) RDN response appears to be driven by patients that had an initial response to CSD and underwent RDN in a staged fashion
3) Patients requiring emergent RDN during the same hospitalization as that for CSD do not appear to derive significant clinical benefit.

RDN has the potential to decrease circulating catecholamines and modulate the cardiac neuraxis, thereby secondarily decreasing the risk of recurrent VT.[10-13] Ukena and colleagues first described two patients with refractory VT treated with RDN.[6] Subsequent case series supported the potential benefit of RDN for refractory VT.[4, 5, 14] Everanos and colleagues assessed the adjunctive use of RDN with RFA in 16 patients compared to 56 RFA-only patients.[7] In their study there was a significant decrease in ICD therapies in the group that received RDN and RFA as compared to RFA-only. The current study is the first data demonstrating overall clinical benefit (decreased ICD therapies) for patients that had VT recurrence after both RFA and CSD.

Eighty percent of the patients in this series had a diagnosis of NICM. Given that NICM patients are known to have a lower VT ablation success rate then ischemic cardiomyopathy (ICM) patients, the need for further intervention in the NICM patients is not unexpected. A similar ratio of patients (71% NICM vs 27% ICM) requiring CSD after failed catheter ablation was reported by Vaseghi and colleagues.[3]

Our data suggests that a comprehensive autonomic approach targeting neuronal (CSD) and neuronlal/humoral (RDN) contributors to autonomic dysregulation may be clinically useful. Myocardial scar is associated with nerve sprouting along scar border zones and supersensitivity to circulating catecholamines which may explain the benefit

seen with RDN.[15-17] Given that all patients had previous CSD (9/10 bilateral), direct neural cardiac effects are unlikely to be driving the potential benefit and suggests the importance of additionally targeting circulating catecholamines.

However, there appears to be a clear differentiation between patients that had acute versus staged procedures. This may suggest that the staged patients had arrhythmias that were more adrenergically sensitive than those that underwent acute intervention. While not statistically significant, the staged patients had a VT cycle length that was on average >100ms shorter than the acutely treated patients. This difference is likely clinically significant and could explain the potential difference in adrenergic sensitivity. In prior data for patients undergoing CSD, patients with longer VT cycle length were less likely to benefit compared to those with faster VTs.[3] Our data also demonstrated that the acute patients had poorer NYHA functional class status, so it is possible that the slower VT cycle length could reflect worsening pump failure.

Further, the staged patients may have had a partial response to CSD allowing them to be discharged and then subsequently benefitted by RDN for more complete autonomic modulation. Whereas, the acute patients had no significant response to CSD and therefore were also unlikely to benefit from RDN. The interpretation is limited by an expected blanking period after CSD during which the response is not typically assessed. However, the severity of the recurrence in the acute treatment group required early (acute) intervention and therefore intermediate and chronic response to CSD could not be assessed.

An alternative explanation is that the acute patients comprised a sicker cohort overall, which is supported by the difference in baseline NYHA functional class between

patients who underwent staged versus acute RDN Procedures. However, patients that had acute procedures during the same hospitalization as their CSD had otherwise statistically similar baseline characteristics in terms of age, ventricular function, renal function, and number of ventricular arrhythmias, though analysis is limited by the small patient sample size. Given the severity of cardiac disease in combination with the failure of all available therapies (AAD, RFA, CSD and RDN) in the patient population studied, it may suggest that some patients reach a point where autonomic influences are no longer modifiable to a clinically significant degree. Whether earlier intervention would have benefitted the acute patients is not known.

Conclusion:

RDN when utilized as an adjunctive therapy with CSD may decrease risk of recurrent VT and associated ICD therapies in high risk patients. Targeting both direct and circulating adrenergic stimulation from autonomic dysregulation with this combination of interventions may have additive benefit. However, prospective data is needed.

Limitations:

This is a retrospective analysis of data from a single center. The decision to proceed with RDN was at the discretion the primary cardiologist and the cardiac electrophysiology team based on the acuity of the patient and therefore RDN timing was not based on a set protocol. Therefore, the time elapsed between CSD and RDN was

variable from days to months depending on evaluated clinical need. The overall clinical benefit of the entire cohort may be overestimated due to limitations of quantifying slow VT below the detection zone and on ECMO in the acute group. Current RDN techniques using standard ablation catheters do not have reliable parameters to monitor that signify a successful denervation. Therefore, failure in this setting could simply mean insufficient targeting of renal nerves due to technologic limitations.

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Figure Legend:

Figure 1: ICD therapies pre- and post-RDN (A) All ICD therapies delivered (ATP and shocks) in the 6 months prior and 6 months post-RDN (B) ICD shock therapies delivered in the 6 months prior and 6 months post-RDN

Figure 2: (A) All ICD therapies delivered pre- and post-RDN in patients undergoing staged procedures (B) All ICD therapies delivered pre and post-RDN in patients undergoing acute procedures. Follow-up in the acute group is limited by clinical outcomes: two patients required repeat RFA, one patient with an LVAD had recurrence of slow VT below the ICD detection zone, and one patient died after being unable to wean off of ECMO.

Figure 3: Representative anatomic geometry from a renal artery denervation procedure utilizing the Ensite (Abbott Medical, Minneapolis, MN) mapping system. Right anterior oblique view (RAO) is shown in panel A and left anterior oblique (LAO) image in panel B. Ablation lesions are represented as white dots.

Table 1: Baseline Patient Characteristics

CM = cardiomyopathy, NICM = non-ischemic cardiomyopathy, ICM = ischemic cardiomyopathy, CSD = cardiac sympathetic denervation, RDN = renal denervation

Patient #	Age (y)	Sex	CM Etiology	NYHA Class	EF (%)	VT Type	# of inducible VTs	Presentation	Failed Medications	Previous ablations	CSD	RDN Acute / Staged
1	54	Male	NICM	2	20-25	Monomorphic	1	VT Storm	Amiodarone Carvedilol	1	Bilateral	Staged
2	70	Male	NICM	2	35	Monomorphic	3	Recurrent	Metoprolol Amiodarone	2	Bilateral	Staged
3	69	Male	NICM	2	35	Monomorphic	1	VT Storm	Amiodarone Sotalol Metoprolol	2	Bilateral	Staged
4	64	Male	NICM	2	40-45	Polymorphic	-	Recurrent	Amiodarone Sotalol Dofetilide Mexiletine Metoprolol	2	Bilateral	Staged
5	68	Male	NICM	3	30	Polymorphic	-	Recurrent	Amiodarone Carvedilol Mexiletine	3	Bilateral	Staged
6	65	Male	NICM	2	20	Monomorphic	1	Recurrent	Amiodarone Metoprolol Mexiletine	3	Bilateral	Staged
7	63	Male	NICM	3	40	Polymorphic	-	Recurrent	Amiodarone Flecainide Sotalol Carvedilol	5	Bilateral	Acute

8	65	Female	ICM	4	<20	Monomorphic	1	Recurrent	Carvedilol Amiodarone Lidocaine	2	Left	Acute
9	37	Male	NICM	3	20	Monomorphic	1	Recurrent	Carvedilol Mexiletine Amiodarone	1	Bilateral	Acute
10	56	Male	NICM	4	45	Monomorphic	2	VT Storm	Amiodarone Esmolol Procainamide	3	Bilateral	Acute

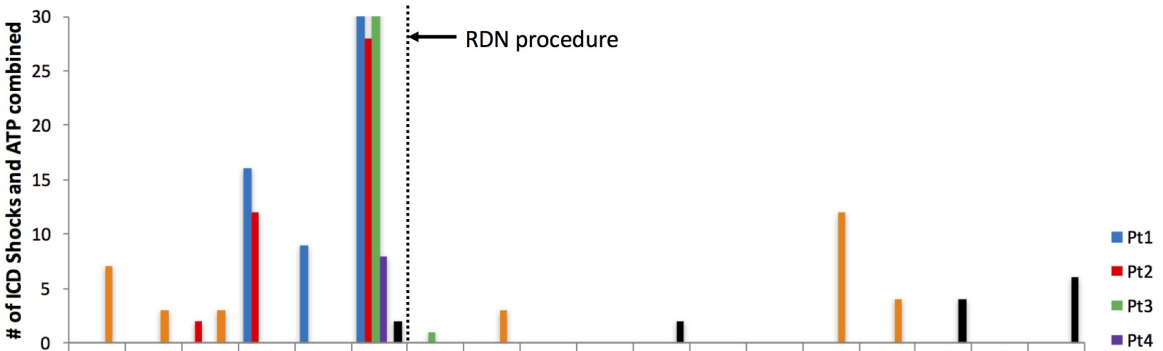
Table 2: Renal Denervation Procedural Characteristics

Medication dosages listed are in milligrams. RDN = renal denervation, CSD = cardiac sympathetic denervation

Patient #	Acute / Staged	Pre-RDN med regimen	# interim days CSD to RDN	Okada classification (R/L)	# of ablation lesions (R, L)	Complications	Immediate post-RDN med regimen	6-12 month post-RDN med regimen	Success/Partial/No success	Clinical outcome
1	Staged	Carvedilol 3.125 tid Sotalol 160 bid	472	A1/A1	7, 7	none	Carvedilol 3.125 tid Amiodarone 200 bid	Carvedilol 3.125 bid	Success	No ICD therapies at 18 months
2	Staged	Metoprolol 100 daily Amiodarone 200 daily	60	A1/A1	9, 6	none	Metoprolol 100 daily Amiodarone 200 bid	Metoprolol 100 daily	Success	No ICD therapies at 2 years
3	Staged	Metoprolol 25 bid	42	A1/A2	6, 5	none	Amiodarone 400 daily Mexiletine 150 tid Metoprolol 100 bid	Amiodarone 200 daily Mexiletine 150 tid Metoprolol 100 bid	Success	No ICD therapies at 15 months
4	Staged	Dofetilide 500 bid Mexiletine 150 bid Metoprolol 50 daily	1567	A1/A2	5, 6	none	Dofetilide 0.5 bid Mexiletine 150 bid Metoprolol 50 daily	Metoprolol 50 daily Amiodarone 200 daily	Success	No ICD therapies at 6 months
5	Staged	Amiodarone 200 daily Carvedilol 3.125 tid Mexiletine 200 bid	568	A1/A2	6, 5	none	Amiodarone 200 daily Carvedilol 3.125 tid Mexiletine 200 bid	Amiodarone 200 daily Carvedilol 3.125 tid Mexiletine 200 bid	No success	ICD shocks in the 9 months after RDN
6	Staged	Carvedilol 50 bid Mexiletine 150 tid	319	A2/A1	9, 5	none	Carvedilol 50 bid Mexiletine 150 tid	Carvedilol 50 bid Mexiletine 150 tid	Partial	ATP therapies in first year after

										RDN
7	Acute	Carvedilol 12.5 bid Flecainide 100 bid Sotalol 160 bid	10	A1/A1	7, 3	none	Amiodarone 400 daily Metoprolol 100 daily Ranolazine 500 bid	Amiodarone 400 daily Metoprolol 100 daily Ranolazine 500 bid	No success	ICD shocks leading to repeat RFA at 6 months
8	Acute	Amiodarone 400 bid Carvedilol 50 bid	7	A2/A2	3, 3	transient slow flow in left renal artery	Amiodarone 200 bid Carvedilol 50 bid	Amiodarone 200 bid Carvedilol 50 bid	No success	Slow VT below ICD detection zone at 6 months
9	Acute	Amiodarone IV Lidocaine IV Procainamide IV Metoprolol 25 bid	26	A1/A1	6, 5	none	Amiodarone IV Lidocaine IV Procainamide IV Metoprolol 25 bid	Metoprolol 25 bid Amiodarone 200 daily	No success	ICD shocks and repeat RFA at 2 months
10	Acute	Amiodarone IV Esmolol IV Procainamide IV	18	A1/A2	7, 6	none	Amiodarone IV Esmolol IV Procainamide IV	n/a	No success	Incessant VT and patient demise within 1 month

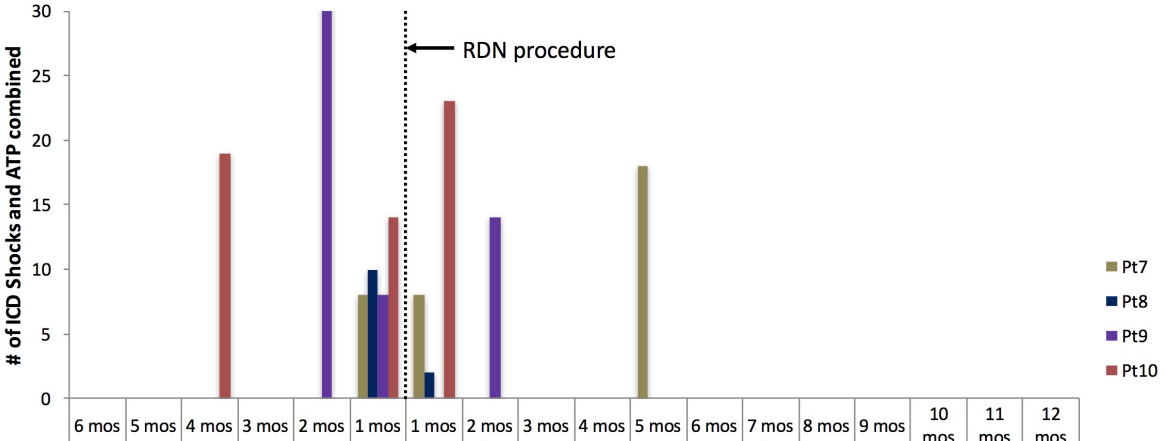
A



	6 mos prior	5 mos prior	4 mos prior	3 mos prior	2 mos prior	1 mos prior	1 mos after	2 mos after	3 mos after	4 mos after	5 mos after	6 mos after	7 mos after	8 mos after	9 mos after	10 mos after	11 mos after	12 mos after
Pt1	0	0	0	16	9	38	0	0	0	0	0	0	0	0	0	0	0	0
Pt2			2	12	0	28	0	0	0	0	0	0	0	0	0	0	0	0
Pt3	0	0	0	0	0	43	1	0	0	0	0	0	0	0	0	0	0	0
Pt4	0	0	0	0	0	8	0	0	0	0	0	0						
Pt5	7	3	3	0	0	0	0	3	0	0	0	0	0	12	4	0	0	0
Pt6		0	0	0	0	2	0	0	0	0	2	0	0	0	0	4	0	6

Time of ICD therapies with respect to RDN date

B



	6 mos prior	5 mos prior	4 mos prior	3 mos prior	2 mos prior	1 mos prior	1 mos after	2 mos after	3 mos after	4 mos after	5 mos after	6 mos after	7 mos after	8 mos after	9 mos after	10 mos after	11 mos after	12 mos after
Pt7	0	0	0	0	0	8	8	0	0	0	18*	0	0	0	0	0	0	0
Pt8	0	0	0	0	0	10	2	0	0	0	0	0△	0					
Pt9	0	0	0	0	65	8	0	14*	0	0	0	0	0	0	0	0	0	0
Pt10	0	0	19	0	0	14	23	⊗										

Time of ICD therapies with respect to RDN date

*Repeat catheter ablation

△VT recurrence below ICD detection zone

⊗Patient death