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ORIGINAL PAPER

Renal denervation for treatment of ventricular arrhythmias: data from an International Multicenter Registry

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Abstract
Introduction Ventricular arrhythmias (VAs) in patients with chronic heart failure (CHF) are sometimes refractory to antiarrhythmic drugs and cardiac ablation. This study aimed to investigate catheter-based renal sympathetic denervation (RDN) as antiarrhythmic strategy in refractory VA.
Methods These are the first data from a pooled analysis of 13 cases from five large international centers (age 59.2 ± 14.4 years, all male) with CHF (ejection fraction 25.8 ± 10.1 %, NYHA class 2.6 ± 1) presented with refractory VA who underwent RDN. Ventricular arrhythmias, ICD therapies, clinical status, and blood pressure (BP) were evaluated before and 1–12 months after RDN.
Results Within 4 weeks prior RDN, a median of 21 (interquartile range 10–30) ventricular tachycardia (VT) or fibrillation (VF) episodes occurred despite antiarrhythmic drugs and prior cardiac ablation. RDN was performed bilaterally with a total number of 12.5 ± 3.5 ablations and without peri-procedural complications. One and 3 months after RDN, VT/VF episodes were reduced to 2 (0–7) ($p = 0.004$) and 0 ($p = 0.006$), respectively. Four (31 %) and 11 (85 %) patients of these 13 patients were free from VA at 1 and 3 months. Although BP was low at baseline (116 ± 18/73 ± 13 mmHg), no significant changes of BP or NYHA class were observed after RDN. During follow-up, three patients died from non-rhythm-related causes.
Conclusions In patients with CHF and refractory VA, RDN appears to be safe concerning peri-procedural complications and blood pressure changes, and is associated with a reduced arrhythmic burden.

Keywords Heart failure · Ventricular fibrillation · Electrical storm · Renal denervation

Introduction

Implantable cardioverter-defibrillators (ICDs) are well established for the primary and secondary prevention of sudden cardiac death in patients with cardiomyopathy and chronic heart failure (CHF) [1–3]. However, recurrent ventricular arrhythmias (VAs) with subsequent ICD shocks are associated with increased mortality and deterioration of ventricular function [4], as well as psychological trauma. In addition to beta-blockers, the use of antiarrhythmic agents such as amiodarone may reduce VA further, but its use is often limited by serious side effects [5]. Cardiac catheter ablation of VA has been shown to be an effective treatment option for VA with a reasonable safety profile, in particular in scar-related heart disease [1]. However, even in experienced centres, a significant proportion of patients with CHF experience recurrent VA episodes despite catheter ablation and treatment with antiarrhythmic agents. In

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particular in non-ischemic dilated cardiomyopathy (NIDCM), up to 50 % of patients will suffer from recurrent VA [6, 7]. Given the involvement of the sympathetic nervous system (SNS) in the initiation and maintenance of VA, sympathomodulatory treatments, such as left cardiac sympathetic denervation, have been proposed as adjunctive or rescue treatment options [8, 9].

Catheter-based RDN has been shown to reduce sympathetic activity and blood pressure (BP) in certain hypertensive patients in open, non-controlled studies [10–14], in a real-life registry on 1000 patients [15] and in sham-controlled studies [16, 17]. Also, potentially beneficial electrophysiological effects, such as reduction in heart rate [18], alterations in ventricular refractoriness [19], reduction of ventricular premature beats [20], occurrence of VA during acute myocardial ischemia [21], and atrial arrhythmias [22], have been described following RDN in both experimental and clinical settings. Case reports and some smaller series have reported the first experiences of RDN as treatment of VA [18, 23–28]. The present multicenter international registry was designed to evaluate the safety and efficacy of RDN for treatment of refractory VA in patients with CHF using the largest published experience to date.

Methods

Study design and patient selection

The present analysis represents first data from a pooled analysis of 13 cases from five large international centers undergoing RDN for treatment of VA. Patients with CHF were included if recurrent VA occurred when medical antiarrhythmic treatment and cardiac ablation were ineffective or not technically feasible. Patients were excluded if VA occurred in the setting of acute myocardial infarction, sepsis, or any reversible cause, such as electrolyte disturbances. Also, patients with hemodynamically relevant renal artery stenosis or patients in whom RDN could not be performed due to other reasons were excluded. Patients were informed of the experimental approach and provided written consent. Review of the clinical data accords with the guidelines of the local ethic committees.

Renal denervation procedure

The RDN procedure was performed as previously described [18]. An ICD interrogation was performed to assess the number of VT/VF-episodes in the 4 weeks prior to the procedure. The choice of the RDN catheter was left to the discretion of the treating physicians. Renal angiograms were performed via femoral access to confirm anatomic eligibility. Peri-procedural complications and the number of ablations on each side were documented. Heparin was given to achieve an activated clotting time during the procedure of more than 250 s.

Follow-up

Follow-up examinations were performed at 1, 3, 6, and 12 months after RDN, which included an assessment of the clinical status, review of current medication, office BP measurements, 12-lead electrocardiogram, and an ICD interrogation. Programming of the ICD, in particular detection criteria and treatment of ventricular arrhythmias, was not changed during follow-up. Short-term follow-up of 3 of the 13 patients has been reported previously as case reports [9, 24, 25].

Statistical analysis

Data are presented as mean ± standard deviation (SD) or number (percentage) unless otherwise specified. Comparisons within groups were performed using the Pearson Chi-square test for categorical variables and the paired *t* test or the Wilcoxon rang sum test for continuous variables where appropriate. A two-tailed p value of <0.05 was regarded as statistically significant. All statistical analyses were performed with SPSS statistical software (version 23.0, SPSS Inc., Chicago, IL).

Results

Baseline characteristics of the 13 patients are shown in Table 1. All patients were male with a mean age of 59.2 ± 14.4 years. Cardiovascular comorbidities were highly prevalent with 85 % of the patients having a history of hypertension, 54 % diabetes, and 46 % chronic kidney disease with an estimated glomerular filtration rate ≤60 ml/min. Etiology of heart failure was ischemic in 7 (54 %) and IDCM in 6 (46 %) patients. The ejection fraction was 25.8 ± 10.1 % (range 15–44 %), and NYHA functional class was 2.6 ± 1.0. Beta-blockers and sotalol were prescribed in 11 (85 %) and 2 (15 %) patients, respectively. Amiodarone was used in 8 (62 %) patients with a daily dose of 394 ± 343 mg at the time of RDN. Another 2 (15 %) patients were treated with class-I antiarrhythmics. In total, the mean number of current antiarrhythmic agents was 1.8 ± 0.7.

Arrhythmic burden and procedural details

Data on the arrhythmic burden, previous cardiac ablations, as well as details on the RDN procedure are summarized in

Table 1 Baseline characteristics

Characteristic	Value
Age (years)	59.2 ± 14.4
Male gender	13 of 13 (100 %)
Body mass index (kg/m^2)	30.2 ± 7.7
Hypertension	11 of 13 (85 %)
Diabetes	7 of 13 (54 %)
GFR (ml/min)	62.8 ± 20.9[a]
Coronary artery disease	7 of 13 (54 %)
Ischemic etiology of heart failure	7 of 13 (54 %)
NYHA class	
I–II	5 of 13 (38 %)
III–IV	8 of 13 (62 %)
Ejection fraction (%)	25.8 ± 10.1
LVEDD (mm)	67.8 ± 11.6[b]
SBP (mmHg)	115.9 ± 18
DBP (mmHg)	73.2 ± 12.9
Heart rate (bpm)	66.5 ± 13
ICD/CRT-D	10 (77 %)/3 (23 %) of 13
Medications	
ACEI/ARB	13 of 13 (100 %)
Beta-blocker	11 of 13 (85 %)
Aldosterone antagonists	10 of 13 (77 %)
Diuretic	10 of 13 (77 %)
Amiodarone	8 of 13 (62 %)
Daily dose >200-mg amiodarone	4 of 13 (31 %)
Other antiarrhythmics	4 of 13 (31 %)

Values are mean ± SD or numbers (%). GFR: glomerular filtration rate

SBP systolic blood pressure, *DBP* diastolic blood pressure, *ICD* implantable cardioverter-defibrillator, *CRT-D* cardiac resynchronization therapy-defibrillator, *ACE-I* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers

[a] Value available in 12 of 13 patients

[b] Value available in 11 of 13 patients

Table 2 Arrhythmic burden and procedural details

Characteristic	Value
Monomorphic VT	7 of 13 (54 %)
Polymorphic VT	6 of 13 (46 %)
VF	8 of 13 (62 %)
≥3 VT/VF episodes within the last 24 h	5 of 13 (38 %)
Previous cardiac ablation	9 of 13 (69 %)
Endocardial	8 of 13 (62 %)
Epicardial	5 of 13 (38 %)
RDN procedure	
Procedure duration (mins)	80.0 ± 28.9[a]
Contrast medium (ml)	97.7 ± 55.6[a]
Fluoroscopy time (min)	14.1 ± 10.8[a]
Unilateral treatment	1 of 13 (8 %)
Bilateral treatment	12 of 13 (92 %)
Single electrode RDN catheter	6 of 13 (46 %)
Multielectrode RDN catheter	2 of 13 (15 %)
Non-irrigated cardiac ablation catheter	0 of 13 (0 %)
Irrigated cardiac ablation catheter	5 of 13 (38 %)
Number of ablation points	
Total	12.5 ± 3.5
Left	6.6 ± 2.1
Right	6.3 ± 2.1
Peri-procedural complications	0 of 13 (0 %)

Values are mean ± SD or numbers (%)

VT ventricular tachycardia, *VF* ventricular fibrillation, *RDN* renal denervation

[a] Value available in 11 of 13 patients

Table 2. A median number of 21 (10–30) VA occurred with the need for 14 (9–30) ICD shocks and 5 (0–12) anti-tachycardia pacing (ATP). Monomorphic VTs were prevalent in 7 (54 %) patients, polymorphic VTs in 6 (46 %), whereas VF episodes occurred in 8 (62 %) patients. Previous cardiac ablations were performed in 9 (85 %) patients; in 2 (15 %) patients with ICM and 2 (15 %) patients with NIDCM, cardiac ablation was not performed due to polymorphic arrhythmias or according to patient's request. In 5 (38 %) patients, RDN was performed as an acute treatment of electrical storm.

RDN was performed without any peri-procedural complications. Unilateral RDN was performed in one patient with a single-sided kidney. In 8 (62 %) patients, the procedure was done with a single electrode (Medtronic, Symplicity Flex catheter) or multielectrode RDN catheter (St. Jude EnligHTN), whereas in the remaining 5 (38 %), an irrigated cardiac ablation catheter was used. A total of 12.5 ± 3.5 ablations points were generated, which were equally distributed between both sides. An accessory renal artery was present in one patient, which was also treated.

Follow-up

At 1, 3, 6, and 12 months after RDN, 13, 10, 9, 8 patients presented for follow-up, respectively. Three patients died within the first year after the procedure. Causes of death were progressive heart failure in two patients (6 and 7 months after RDN) and septic shock with respiratory failure in one patient (2 months after RDN).

The number of sustained VA and ICD shocks 1 month before RDN and during follow-up is shown in Fig. 1. The median number of VT/VF episodes decreased from 21 (10–30) to 2 (0–7) at 1 month ($p = 0.004$) and 0 at 3 months ($p = 0.006$). Likewise, the numbers of ICD interventions were reduced: ATP from 5 (0–12) to 0

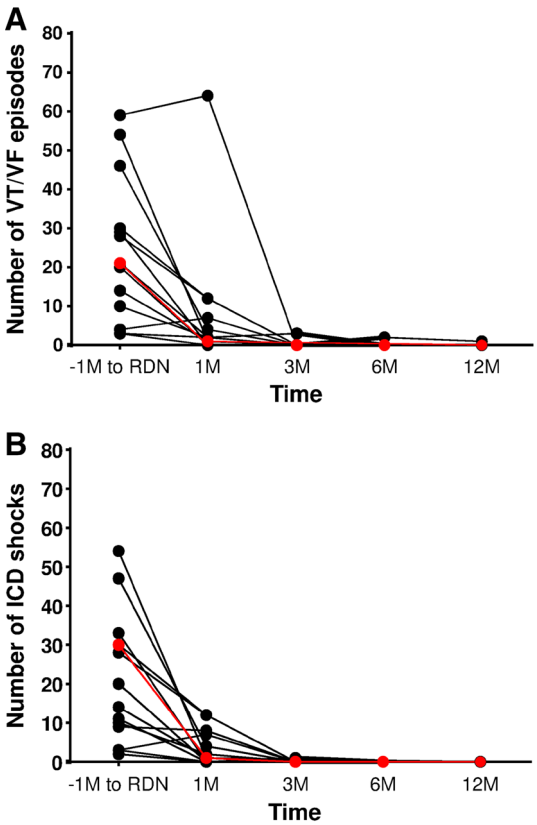

Fig. 1 Number of ventricular arrhythmias (**a**) and ICD shocks (**b**) before and after renal denervation in each patient and median number of all patients (*red line*). *VT* ventricular tachycardia, *VF* ventricular fibrillation, *M* month

($p = 0.157$) and ICD shocks from 14 (9–30) to 1 (0–7) at 1 month ($p = 0.004$). In the first month after RDN, 4 (31 %) patients were completely free from any VA. After the first month, 11 (85 %) patients were completely free from any further VT/VF episodes. Changes of antiarrhythmic drugs were documented in 3 (23 %, two patients with recurrent VA) and 1 (8 %) patients at 1- and 3-month follow-up and, thereafter, in none of the remaining patients.

Safety issues and complications

No acute peri-procedural complications occurred. BP and heart rate were not significantly altered after RDN (Fig. 2), and more importantly, no symptomatic hypotension was reported during follow-up. Furthermore, NYHA functional class remained unchanged with a mean of 2.5 ± 0.8 ($p = 0.501$), while 3 (23 %) patients had a worsening by one class and 2 (15 %) patients had an improvement by one class (Fig. 3). At 3-month follow-up, ejection fraction assessed by echocardiography was available in 8 (62 %) patients, and remained unchanged compared with baseline measurements (24.9 ± 12.1 %; $p = 0.8$).

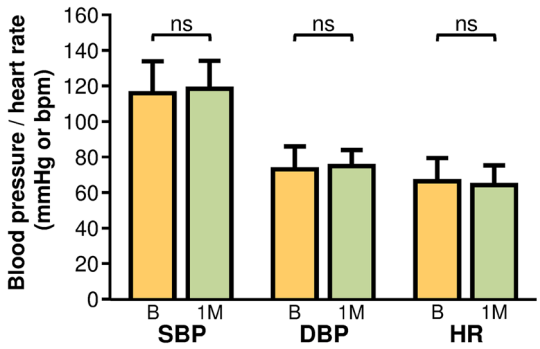

Fig. 2 Mean blood pressure at baseline and 1 month after renal denervation. *B* baseline, *1M* 1-month follow-up, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *bpm* beats per minute, *ns* non-significant ($p > 0.05$)

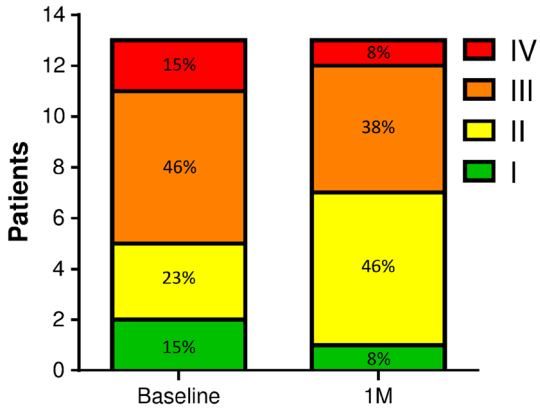

Fig. 3 Proportion of NYHA-class at baseline and after 1 month after renal denervation. *1M* 1-month follow-up

Discussion

Herein, we report the largest cohort of patients with severe CHF undergoing RDN for treatment of recurrent VA. RDN appeared to be safe with respect to the procedure and functional parameters, such as NYHA class and BP, during follow-up. Moreover, in patients resistant to cardiac ablation and antiarrhythmic drugs, arrhythmic burden was significantly reduced by RDN in the setting of VT storm or unstable and frequent VA with frequent ICD shocks and interventions.

Most patients suffering from VA have underlying structural heart disease. Cardiac ablation and antiarrhythmic drug therapy may not sufficiently suppress VA in certain patients. The involvement of the SNS in the development and progression of CHF as well as its detrimental role in the onset and maintenance of VA has been well described [29, 30]. The electrophysiological effects of SNS activity in the ventricle include a reduction of the effective refractory period, increased automaticity, and a higher susceptibility to VA [30]. Surgical cardiac denervation or cervical sympathectomy has been considered in

patients with refractory VA, but this approach is limited by its invasive nature and adverse effects [8, 31].

Renal sympathetic afferent and efferent nerves are important mediators of renal and whole-body sympathetic activity and contribute to the development and progression of hypertension [32]. Catheter-based RDN has been shown to reduce BP in several observational studies and in three randomized, controlled trials (Symplicity HTN-2, Prague 15 and DENERHTN) [16, 33, 34]. In the Symplicity HTN-3 trial, RDN was safe but not superior to drug therapy in reducing office or ambulatory BP [17]. Inappropriate patient selection and performance of an ineffective procedure have been suggested by some authors as possible causes for this negative result [35–38]. Sham-controlled trials in patients with hypertension are ongoing (NCT02439775, NCT02439749, NCT02392351).

In patients with CHF, cardiac but also renal sympathetic activity is elevated [39], which, in turn, can be modulated by RDN [10, 12]. Based on these considerations, the rationale for treating VA with a sympathomodulatory approach such as RDN is sound [40, 41]. Since the first-in-man report in 20 [9, 12], several other case reports and case series documented the ability of RDN to significantly improve arrhythmic burden in patients with different entities of chronic heart failure [25–28]. A recent study included ten patients undergoing RDN for treatment of refractory VA [26]. Six of these patients had Chagas disease, two had NIDCM, and two ICM. In these patients with previous failed or contraindicated cardiac ablation on amiodarone, RDN was safely performed with an irrigated-tip cardiac ablation catheter without deleterious effects on BP or HR during follow-up. After RDN, the median number of VA was reduced from 28.5 to 1 and 0 at 1- and 6-month follow-up [26].

In this report, patients with mainly ischemic cardiomyopathy (54 %) or non-ischemic dilated cardiomyopathy were included. Medical treatment of CHF was maximally tolerated doses and guideline-recommended with patients receiving renin–angiotensin system blocking agents, beta-blockers, and aldosterone antagonists. Despite antiarrhythmic agents and previous cardiac ablation, patients in the present registry had recurrent VA, mainly polymorphic VT or VF. In line with a recent study [26], the number of VA was significantly reduced after RDN without any deterioration of BP or functional status during follow-up. Thereby, our data provide further evidence on probable antiarrhythmic effects of RDN in patients with CHF.

Three prospective, randomized multicenter studies investigating RDN as treatment for VA were initiated. The ARDEVAT trial (NCT02071511) and the RESET-VT trial (NCT01858194) investigate the value of RDN as adjunctive treatment to VT ablation alone. While the RESET-VT trial enrolls all patients with structural heart disease planned for cardiac ablation, the ARDEVAT trial was focused on patients with ischemic cardiomyopathy and an ejection fraction $\geq$30 %. The ARDEVAT trial has been terminated earlier following the results of Symplicity HTN-3. The RESCUE-VT trial (NCT01747837), which is currently enrolling patients, aims to investigate the effects of RDN as adjunctive treatment in patients receiving an ICD for either secondary prevention or primary prevention with inducible VT. More studies are needed to further investigate the safety and efficacy of this therapy.

The role of the present international multicenter experience is to provide data of VA reduction by RDN, when the procedure is performed under real-life conditions in patients with a few or no therapeutic options. The registry in being expanded and will continue to enroll international patients with VA who have undergone RDN.

Limitations

Based on the design and size, the study has some potential limitations. Although it represents the largest cohort of patients published so far, the overall number of patients is relatively small, and the follow-up period is rather short. Given the uncontrolled nature of the collected data, a possible placebo or Hawthorne effect or a change of adherence to medication cannot be ruled out. Moreover, the patient cohort is heterogeneous (different etiologies of heart failure), and the RDN procedure was not strictly standardized. Eight patients were treated with a dedicated RDN catheter and five with conventional cardiac ablation catheters. Although these catheters are not intended to be used in renal arteries, data on safety and effectiveness in patients with hypertension or atrial fibrillation have been published [42, 43]. The use of cardiac ablation catheter in the present registry reflects the real-life condition of this analysis. Furthermore, no measurements of sympathetic tone were conducted. In hypertensive patients, reduction of blood pressure is regarded as parameter of successful treatment. This criterion cannot be applied to CHF, as these patients typically have normal or low blood pressure, which remains unchanged after the procedure. Identification of parameters of successful RDN treatment is of utmost importance, in particular in patient with VA. Considering these limitations, the presented registry offers only limited conclusions on the efficacy and safety of RDN as antiarrhythmic treatment, and further controlled trials are needed.

Conclusions

RDN for treatment of recurrent VA was not associated with adverse events in patients with CHF. Furthermore, the number of VA was significantly reduced following RDN

possibly mediated by a decreased sympathetic activity after the procedure. Further randomized, prospective clinical trials studies are urgently needed to scrutinize the efficacy of RDN as adjunct to or as a replacement of standard therapy of VA. Until then, RDN remains a rescue therapy in patients with recurrent VA despite conventional therapies, such as antiarrhythmic drugs and cardiac ablation.

Compliance with ethical standards

Conflict of interest CU, FM, and MB are supported by the Ministry of Science and Economy of the Saarland. FM and DL are supported by the Deutsche Hochdruckliga. CU and MB are supported by the Deutsche Forschungsgemeinschaft (KFO 196). FM, DL and MB are supported by Deutsche Gesellschaft für Kardiologie. CU, FM, and MB received scientific support and speaker honorarium from Medtronic Inc. and St. Jude Medical. DT was supported by the DZHK (Deutsches Zentrum für Herz-Kreislauf-Forschung—German Center for Cardiovascular Research) and the BMBF (German Ministry of Education and Research). JSS has served as consultant to Medtronic, Boston Scientific and Biosense Webster, and has received research support from Medtronic and Biosense Webster.

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