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ORIGINAL PAPER

Effects of renal denervation on 24-h heart rate and heart rate variability in resistant hypertension

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Abstract

Background Catheter-based renal sympathetic denervation (RDN) can reduce sympathetic activity and blood pressure (BP) in patients with hypertension. The present study aimed at investigating the effects of RDN on heart rate (HR), number of premature captions, and heart rate variability (HRV).

Methods A total of 105 patients (67% male, age 63.5 ± 10 years) with resistant hypertension (BP 169 ± 22/89 ± 14 mmHg) underwent bilateral RDN using a radiofrequency catheter (Symplicity Flex, Medtronic). 24-h Holter monitoring was performed at baseline and after 6 months. Besides HR profile, the number of premature atrial (PAC) and ventricular captions (PVC), time and frequency domain-based HRV were analyzed. Data are presented as mean ± standard deviation or median (interquartile range).

Results Office systolic and diastolic BP were reduced after RDN by 21.8 ± 25.2 mmHg and 8 ± 18.7 mmHg ($p < 0.001$ for both), respectively. Twenty-eight (27%) patients had a reduction of < 10 mmHg in systolic BP. At baseline, mean 24-h HR was 65.7 ± 9.9 bpm. The prevalence of PAC [median 1.2 (0.3–6.2)] and PVC [median 1.2 (0.1–13.9)] was low and values of HRV were within normal limits and not different between responders and non-responders. After 6 months, patients with a baseline HR > 72 min had a significant reduction in HR by 2.3 ± 7.1 bpm. Parameters of HRV did not significantly change during follow-up. In patients with ≥ 6 PAC per hour at baseline, a significant median reduction of − 12.4 (− 37.4 to − 2.3) PAC after 6 months was documented ($p = 0.002$), which occurred independently from BP effects. The number of PVC was not significantly altered after RDN.

Conclusion In patients with resistant hypertension and elevated HR or high burden of PACs, RDN was associated with a reduction of HR and number of PAC. Parameters of HRV were not changed after RDN nor were predictive of response to RDN.

Keywords Premature atrial captions · Sympathetic activity · Atrial fibrillation · Blood pressure

Introduction

The multifactorial pathophysiology of hypertension involves the sympathetic and parasympathetic nervous system [1]. Alterations of heart rate variability (HRV) can indicate imbalance of the autonomic nervous system in patients with hypertension [2]. In particular, the power in the high-frequency range (HF) is regarded as an indicator of vagal tone, while the ratio between powers in the low- and high-frequency ranges (LF/HF ratio) has been suggested as indicator of sympathovagal balance [3]. Catheter-based renal sympathetic denervation (RDN) can reduce activity of the sympathetic nervous system (SNS) and decrease blood pressure (BP) in hypertensive patients [4–7]. Furthermore,

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different electrophysiological effects, such as reduction in heart rate (HR) [8, 9] and alteration in ventricular refractoriness, occurrence of ventricular premature beats, reduced inducibility and complexity of atrial and ventricular arrhythmias have been documented following RDN in both experimental settings and humans [10–12]. In a study by Tsioufis et al., a reduction of the burden of supraventricular and ventricular premature captions extra beats as well as normalization of parameters of HRV was described in a small number of patients following RDN [11]. The present study aimed at investigating the effects of RDN on HR and HRV in a larger population of patients with resistant hypertension and to investigate different Holter parameters as possible predictors of BP response after RDN.

Methods

Study subjects

Eligible patients were ≥ 18 years and fulfilled the criteria of resistant hypertension defined as office systolic blood pressure of ≥ 160 mmHg (≥150 mmHg for type 2 diabetics), despite treatment with ≥ 3 antihypertensive drugs (including a diuretic), with no changes in medication for a minimum of 2 weeks prior to enrolment. Patients were included if they were not pregnant and had a glomerular filtration rate ≥ 45 mL/min/1.73 m^2. Patients with renal artery anatomy ineligible for treatment (main renal arteries < 4 mm in diameter or < 20 mm in length, abnormality or stenosis in either renal artery, a history of prior renal artery intervention including balloon angioplasty or stenting, multiple main renal arteries in either kidney), type 1 diabetes, myocardial infarction, unstable angina pectoris, cerebrovascular accident within the last 6 months, or hemodynamically significant valvular disease were excluded from the study.

Study procedures

Office SBP, diastolic BP (DBP), and ambulatory BP monitoring (ABPM) readings were obtained at baseline and after 6 months. Office BP readings were taken in a seated position with an automatic oscillometric Omron HEM-705 monitor (Omron Healthcare, Vernon Hills, IL) after 5 min of rest. ABPM was performed using an oscillometric Spacelabs 90207 monitor (Spacelabs Healthcare, Issaqua, WA) with readings taken every 15 min at daytime and every 30 min at nighttime. 24-h Holter monitoring was performed at baseline and after 6 months after procedure. All Holter monitoring were performed in an out-of-hospital setting. Further examinations included complete history and physical examination, assessment of office and 24-h ambulatory blood pressure, recording of a resting electrocardiogram, review of medication, and blood chemistry. Bilateral RDN was analyzed using the single-electrode radiofrequency (RF) Symplicity Flex© catheter (Medtronic, Mountain View, California) as previously described [13]. All procedures were performed by interventionists with an operative experience of at least 50 RDN procedures. Holter recordings were analyzed by two independent investigators (IK, TS) using the software Pathfinder© (Spacelabs Healthcare, Washington). From Holter recording, heart rate profile (mean, daytime, nighttime), the number of premature atrial (PAC) and ventricular captions (PVC), as well as time and frequency domain-based HRV were analyzed according to the recommendations by the task force [14]. All analyses were performed by two investigators, who were blinded to patient characteristics.

Statistical analysis

Data are presented as mean ± standard deviation (SD), median (interquartile range) or number (%) unless otherwise specified. Comparisons within groups were performed using the Pearson Chi-square test for categorical variables and the Wilcoxon rank sum test, the Kruskal–Wallis *H* test, or a paired *t* test for continuous variables where appropriate. Repeated-measures analysis of variance model was used for between-group changes, and Pearson's test was used for correlations of continuous variables unless otherwise specified. Multivariable linear regression analyses were performed to assess the association of clinical, anatomical, and procedural parameters and change in SBP at 6 months. A two-tailed *p* value of < 0.05 was regarded as statistically significant. All statistical analyses were performed with SPSS statistical software (version 21.0, SPSS Inc., Chicago, IL).

Results

Baseline characteristics of the 105 patients are depicted in Table 1. Mean age was 63.5 ± 10 years and 67% were male. Despite an intake of 5.3 ± 1.6 antihypertensive agents, mean BP at baseline was 171.1 ± 24.6/91.5 ± 15 mmHg. Office and 24-h BP after 6 months were both significantly reduced: office SBP by 21.8 ± 25.2 mmHg, office DBP by 8 ± 18.7 mmHg, and PP by 11.7 ± 19.9 mmHg (*p* for all < 0.001). 24-h SBP and DBP were reduced by 7.8 ± 18.6 ($p < 0.001$) and 3.7 ± 11.1 ($p = 0.001$) mmHg, respectively. Non-response was defined as a reduction of 24-hour SBP of < 5 mmHg. This criterion was fulfilled by 44 (42%) patients.

Non-responders differed from other patients by a significant lower baseline office and 24-hour BP (Table 1).

Holter parameters at baseline are summarized in Table 2. At baseline, mean 24-h heart rate was 65.7 ± 9.9 bpm. In

Table 1 Baseline characteristics and blood pressure changes

	All		Responders		Non-responders		
	Value	*n*	Value	*n*	Value	*n*	*p*
Demographics							
Age (years)	63.5 ± 10	105	64.5 ± 10.2	61	62 ± 9.5	44	0.213
Male gender	70 (67%)	105	40 (66%)	61	30 (68%)	44	0.836
Type II diabetes	49 (47%)	105	30 (49%)	61	19 (43%)	44	0.559
CAD	28 (27%)	105	17 (28%)	61	11 (25%)	44	0.825
Blood pressure measurements							
Office SBP (mm Hg)	171.1 ± 24.6	105	174.7 ± 25.5	61	166.2 ± 22.5	44	< 0.001
Office DBP (mm Hg)	91.5 ± 15	105	93.9 ± 12.8	61	88.3 ± 17.2	44	0.001
Pulse pressure (mm Hg)	79.6 ± 20.7	105	80.9 ± 22	61	77.9 ± 18.8	44	0.474
ABPM SBP (mm Hg)	148.3 ± 20.4	105	155.6 ± 20.7	61	138.1 ± 14.9	44	< 0.001
ABPM DBP (mm Hg)	84.3 ± 13.4	105	88.1 ± 12.6	61	79.1 ± 13	44	0.001
Antihypertensive treatment							
Antihypertensive agents	5.3 ± 1.6	105	5.2 ± 1.7	61	5.3 ± 1.6	44	0.745
ACE-I/ARB/Aliskiren	95 (91%)	105	55 (90%)	61	40 (91%	44	1.0
Beta-blockers	87 (83%)	105	48 (79%)	61	39 (88%)	44	0.203
Diuretics	81 (77%)	105	47 (77%)	61	34 (77%)	44	1.0
Aldosterone antagonists	20 (19%)	105	12 (20%)	61	8 (18%)	44	1.0
CCB	87 (83%)	105	51 (84%)	61	36 (82%)	44	0.8
Central sympatholytics	58 (55%)	105	37 (61%)	61	21 (48%)	44	0.234
Alpha-blockers	21 (20%)	105	11 (18%)	61	10 (23%)	44	0.624

Values are means ± SD or numbers (%)

CAD coronary artery disease, *GFR* glomerular filtration rate, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *No.* number, *ACE-I* angiotensin-converting enzyme inhibitors, *ARB* angiotensin receptor blockers, *CCB* calcium channel blockers

Table 2 Baseline Holter parameters in blood pressure responder and non-responder

	All		Responder		Non-responder		*p**
	Value	*n*	Value	*n*	Value	*n*	
Heart rate measurements							
Total (min^{-1})	65.7 ± 9.9	105	66 ± 10.2	61	65.4 ± 9.6	44	0.772
Daytime (min^{-1})	67.3 ± 10.5	64	67.3 ± 10.8	38	67.1 ± 10.4	26	0.933
Night (min^{-1})	59.2 ± 9	64	59.1 ± 9	38	59.3 ± 9.1	26	0.922
Premature contractions							
PAC/h	1.2 (0.3–6.2)	77	1.4 (0.4–10)	44	0.7 (0.2–4.4)	33	0.240
PVC/h	1.2 (0.1–13.9)	77	0.7 (0.1–13.8)	44	2.3 (0.2–13.7)	33	0.52
Heart rate variability							
SDNN (ms)	127.2 ± 39	93	125.5 ± 40.1	56	129.7 ± 37.8	37	0.61
SDANN (ms)	104.9 ± 36.1	65	107.2 ± 38.2	39	104 ± 33.3	26	0.425
RSMSSD	35.5 (22.5–61.8)	93	35 (21–55)	56	37 (23–79)	37	0.405
ULF (ms^2)	8389 (5898–15,402)	68	8446 (5919–15,871)	39	8297 (5211–14,875)	30	0.333
VLF (ms^2)	1500 (1000–2431)	68	1396 (979–2273)	41	1546 (984–3191)	27	0.246
LF (ms^2)	438 (256–866)	68	378 (209–843)	41	558 (294–918)	27	0.281
HF (ms^2)	216 (126–395)	68	209 (117–389)	41	220 (140–720)	27	0.603
LF/HF (ms^2)	1.79 (1.19–2.9)	68	1.57 (1.21–2.67)	41	2.09 (1.18–3.38)	27	0.495

Values are means ± SD, median (interquartile range), or numbers (%)

PAC premature atrial contractions, *PVC* premature ventricular contractions

*p value for comparison between responder and non-responder

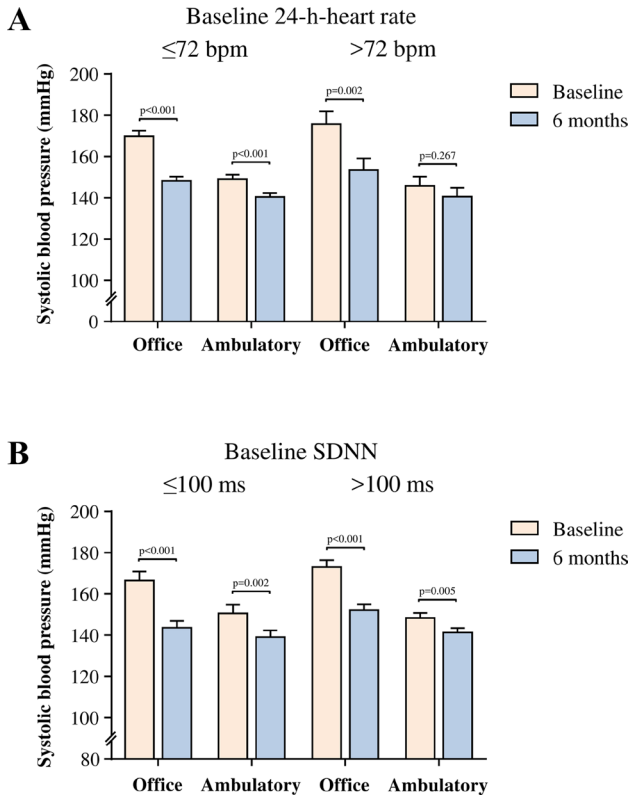

Fig. 1 Office and ambulatory systolic blood pressure grouped according to baseline 24-h heart rate (**a**) and baseline SDNN (**b**). bpm = beats per minute

median, the prevalence of PAC and PVC was low and values of HRV were within normal limits. No significant differences existed between 24-h BP responders and non-responders. Patients were grouped according to 24-h HR (≥74 bpm = 4th quartile) and to SDNN (≤100 ms = 1st quartile) as possible indicators of elevated sympathetic activity (Fig. 1). Changes in office and ambulatory SBP were comparable in all groups independently of baseline 24-h HR and SDNN. No Holter parameters including HRV measurements were associated with change in office and 24-h BP.

Additionally, the changes in Holter parameters after 6 months were analyzed in the whole cohort (Table 3). Average heart rate did not change significantly during follow-up. However, patients in the fourth quartile of baseline 24-h HR (>72 bpm) showed a significant reduction by 2.31 ± 7.1 bpm after 6 months (Fig. 2). The prevalence of premature contractions significantly decreased after 6 months. Given the overall low prevalence of premature contractions, subgroup analyses of patients in the fourth quartile at baseline were conducted. In patients with ≥ 6 PAC ($n = 20$) per hour at baseline (Fig. 3), a significant reduction of PAC burden after 6 months was documented [median change − 12.4 (− 37.4 to − 2.3)]. Changes of PAC were not associated with blood pressure changes in this subgroup ($r = -0.234$; $p = 0.335$) neither were the number of PVC per hour significantly changed in this subgroup.

Table 3 Changes in heart rate and HRV

	Baseline		6 months		p*
	Value	n	Value	n	
Heart rate measurements					
Total (min^{-1})	65.7 ± 9.9	105	65.3 ± 10	105	0.772
Daytime (min^{-1})	67.3 ± 10.5	71	68.3 ± 10.6	71	0.480
Night (min^{-1})	59.2 ± 9	71	60.1 ± 9.2	71	0.701
Premature contractions					
PAC/h	1.2 (0.3–6.2)	77	1.2 (0.2–4.2)	77	0.201
PVC/h	1.2 (0.1–13.9)	77	0.9 (0.1–10.5)	77	0.619
Heart rate variability					
SDNN (ms)	127.2 ± 39	93	125.4 ± 42	93	0.227
SDANN (ms)	105.9 ± 36.1	71	104.9 ± 36.1	71	0.513
RSMSSD	35.5 (22.5–61.8)	93	32 (22–55)	93	0.268
ULF (ms^2)	8389 (5898–15,402)	68	8560 (5158–13,191)	68	
VLF (ms^2)	1500 (1000–2431)	68	1231 (712–2210)	68	0.038
LF (ms^2)	438 (256–866)	68	352 (191–723)	68	0.082
HF (ms^2)	216 (126–395)	68	215 (84–430)	68	0.602
LF/HF (ms^2)	1.79 (1.19–2.9)	68	1.6 (1.1–2.8)	68	0.561

Values are means ± SD, median (interquartile range), or numbers (%)

PAC premature atrial contractions, *PVC* premature ventricular contractions

*p value for comparison between baseline and 6 months

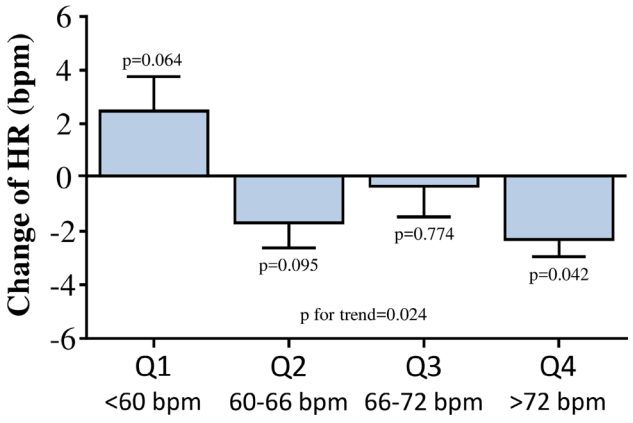

Fig. 2 Changes of heart rate (HR) according to baseline 24-h HR. Q1–4 = first to fourth quartile. bpm = beats per minute

Discussion

We investigated the effects of a sympatho-modulatory treatment by RDN on HR and HRV in patients with resistant hypertension. Beside significant reduction in office and ambulatory BP, a modest reduction in HR in patients with a heart rate > 72 bpm at baseline was observed. The number of PAC reduced as well in those with an elevated PAC burden at baseline. Time and frequency domain-based HRV parameters were not significantly altered and were not associated with BP change. Besides baseline SBP and use of an aldosterone antagonist, no other parameter—in particular no Holter-derived parameter— predicted future BP changes.

Recent sham-controlled trials (SPYRAL OFF, SPYRAL ON, RADIANCE SOLO) demonstrated a significant reduction of BP by catheter-based RDN in hypertensive patients with and without antihypertensive drugs [15–17], though with quite some variability in response. Indeed, even in these recently published sham-controlled studies, about 30% all patients showed minor or no reduction in blood pressure. In the present study, changes in BP (24-hour ABP − 7.8/− 3.7 mmHg after 6 months) and rate of non-response (27%) are in line with the aforementioned trials. Several reasons such as inappropriate patient selection and ineffective RDN procedure have been discussed as possible reasons for non-response to the procedure [18, 19]. The identification of patient characteristics associated with improved outcome following RDN is of utmost importance. Herein, neither standard HRV measures nor other Holter-derived parameters could predict future BP changes in our study.

An increased HR above 80 bpm is regarded as a factor identifying an elevated cardiovascular risk in recent guidelines [20]. While pharmacological HR reduction with beta-blockers or ivabradine has been shown to improve outcome in heart failure, randomized controlled trials showing similar effects by reducing HR in patients with hypertension are lacking [21]. Sympathetic activity increases HR and facilitates atrioventricular conduction, whereas parasympathetic activity counterbalances these effects [22]. RDN has been shown to reduce resting HR in patients with resistant hypertension most likely by modulation of sympathetic activity [8, 23]. Interestingly, the degree of HR change is related to the height of baseline HR. Heart rate in patients with lower baseline values remained unchanged, whereas in patients with higher HR a pronounced reduction was documented. These findings were in line with the present study, as patients with a mean 24-h-HR > 72 bpm showed a significant reduction of HR after RDN, while in the other patients HR remained unchanged. The prognostic value of permanent reduction of HR in certain hypertensive patients with initial elevated HR remains unclear and deserves future investigations.

Related to the high prevalence, HTN is the most relevant risk factor for the development of atrial fibrillation (AF) [24]. Pharmaceutical therapies for treatment of HTN, in particular renin–angiotensin system (RAS) blockers, have been shown to reduce the incidence of AF [25]. Frequent PAC are

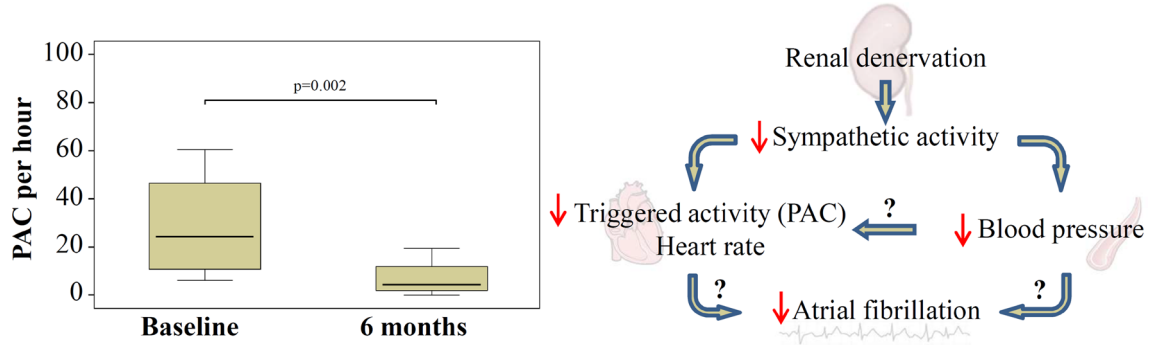

Fig. 3 Number of premature atrial contractions (PAC) per hour in patients with ≥ 6 PAC per hour at baseline (= fourth quartile). Potential mechanisms leading to the observed cardiac effects and potential impact on atrial fibrillation

acute triggers of AF [26, 27]. Moreover, an excessive atrial ectopy defined as > 30 PAC/hour or runs of > 20 PAC have been associated with an increased stroke risk [28]. In the present study, RDN was associated with a reduction of PAC in those patients with a high PAC burden at baseline (≥ 6 PAC per hour). Interestingly, in this relatively small subgroup of 20 patients, no correlation with BP changes after RDN was found. Smaller studies have shown beneficial effects on recurrence of AF after RDN, in particular in adjunction to pulmonary vein isolation in patients with resistant hypertension [29–34]. In these trials, patients had uncontrolled HTN at baseline and a relevant reduction of BP was observed in the PVI plus RDN group, while BP remained unchanged in the PVI-only groups. Potential mechanisms may include BP-related effects such as reduced atrial stretch, or neurohumoral effects such as reduced sympathetic activity and alterations in RAS activity (see Fig. 3). Larger multi-cente randomized trials with standardized PVI and RDN procedures as the SYMPLICITY-AF study (ClinicalTrials.gov Identifier: NCT02064764) are currently enrolling patients.

Measurements of HRV, in particular frequency domain measurements, are used as non-invasive tools for assessment of autonomic activity [2, 3]. While LF may be related to sympathetic activity, the HF component represents vagal tone [35]. The ratio of LF/HF is regarded as an index of overall autonomic balance. In the present study, HRV was measured in an outpatient setting before and after RDN without any provocation or external stimuli. Furthermore, the proportion of patients taking medications influencing HR and thereby HRV such as beta-blockers (83%) or central sympatholytics (55%) was reasonably high. This may explain why HRV parameters were within normal ranges in the investigated hypertensive patients at baseline and did not alter significantly after RDN. These findings are in line with previously published trials, e.g., the ReSET or the DREAMS study [36, 37]. Another way of looking at renal sympathetic nerve system-induced myocardial changes is renal nerve stimulation (RNS). A recent study documented a decreased LF/HF ratio induced by RNS after RDN indicating lower sympathetic tone [38]. Interestingly, these RNS-induced changes during the procedure were less pronounced in patients taking beta-blockers. In our study, the proportion of patients not taking either beta-blockers or central sympatholytics was too low to investigate the effects of RDN on HRV in these patients separately. These issues need to be clarified in ongoing studies in drug-naïve patients [15, 16]. Herein, neither significant changes of HRV after RDN were observed nor any predictive HRV parameter for BP response after RDN was identified, in line with previously published evidence [36, 37]. Based on our and other recent findings, the value of HRV as an indicator of autonomous nervous system activity and predictor of response to RDN treatment in hypertensive patients may be limited. Further investigations, in particular in the context of external stimuli such as RNS and other patient conditions such as heart failure, are needed.

Limitations

The study might have some limitations. First, it is a non-randomized study without a control group. Therefore, placebo or Hawthorne effect cannot be completely ruled out. Changes of blood pressure may be party influenced by a regression to the mean effect, which means that an extreme value on the first measurement tends to a lower value when measured again. But this effect was yet not confirmed for repetitive measurements such as Holter ECG or ABPM, on which the present analysis focused on. Furthermore, RDN was performed with the unipolar Symplicity Flex RDN system (Medtronic). Significant advances in knowledge on renal anatomy as well as developments in multipolar ablation systems have been made [39, 40]. In the present study, RDN was performed by experienced operators who have performed > 50 RDN procedures. The effectiveness of RDN in the present study can be estimated by the significant BP drop, which is in line with current studies [15–17]. Finally, HRV assessment was done in an ambulatory setting, which might not reflect HRV assessed during standardized conditions.

Conclusions

RDN leads to a reduction of BP and HR mediated by a decreased sympathetic activity in patients with resistant hypertension. Additionally, the number of PACs was reduced. Holter measurements were not predictive of BP response to RDN. These findings support the idea of antiarrhythmic effects of RDN. Further studies are needed to investigate RDN for treatment of atrial arrhythmias and to clarify the predictive value of RNS-induced changes of HRV for long-term BP response.

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References

1. Böhm M, Linz D, Ukena C, Esler M, Mahfoud F (2014) Renal denervation for the treatment of cardiovascular high risk-hypertension or beyond? Circ Res 115:400–409

2. Schroeder EB, Liao D, Chambless LE, Prineas RJ, Evans GW, Heiss G (2003) Hypertension, blood pressure, and heart rate variability: the atherosclerosis risk in communities (ARIC) study. Hypertension 42:1106–1111
3. Eckberg DL (1997) Sympathovagal balance: a critical appraisal. Circulation 96:3224–3232
4. Krum H, Schlaich M, Whitbourn R, Sobotka PA, Sadowski J, Bartus K et al (2009) Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study. Lancet 373:1275–1281
5. Schlaich MP, Sobotka PA, Krum H, Lambert E, Esler MD (2009) Renal sympathetic-nerve ablation for uncontrolled hypertension. New Engl J Med 361:932–934
6. Hering D, Lambert EA, Marusic P, Walton AS, Krum H, Lambert GW et al (2013) Substantial reduction in single sympathetic nerve firing after renal denervation in patients with resistant hypertension. Hypertension 61:457–464
7. Grassi G, Seravalle G, Brambilla G, Trabattoni D, Cuspidi C, Corso R et al (2015) Blood pressure responses to renal denervation precede and are independent of the sympathetic and baroreflex effects. Hypertension 65:1209–1216
8. Ukena C, Mahfoud F, Spies A, Kindermann I, Linz D, Cremers B et al (2013) Effects of renal sympathetic denervation on heart rate and atrioventricular conduction in patients with resistant hypertension. Int J Cardiol 167:2846–2851
9. Böhm M, Mahfoud F, Townsend RR, Kandzari DE, Pocock S, Ukena C et al (2019) Ambulatory heart rate reduction after catheter-based renal denervation in hypertensive patients not receiving anti-hypertensive medications: data from SPYRAL HTN-OFF MED, a randomized, sham-controlled, proof-of-concept trial. Eur Heart J 40:743–751
10. Linz D, Mahfoud F, Schotten U, Ukena C, Hohl M, Neuberger HR et al (2013) Renal sympathetic denervation provides ventricular rate control but does not prevent atrial electrical remodeling during atrial fibrillation. Hypertension 61:225–231
11. Tsioufis C, Papademetriou V, Tsiachris D, Dimitriadis K, Kasiakogias A, Kordalis A et al (2014) Drug-resistant hypertensive patients responding to multielectrode renal denervation exhibit improved heart rate dynamics and reduced arrhythmia burden. J Hum Hypertens 28:587–593
12. Ukena C, Bauer A, Mahfoud F, Schreieck J, Neuberger HR, Eick C et al (2012) Renal sympathetic denervation for treatment of electrical storm: first-in-man experience. Clin Res Cardiol 101:63–67
13. Mahfoud F, Schlaich M, Kindermann I, Ukena C, Cremers B, Brandt MC et al (2011) Effect of renal sympathetic denervation on glucose metabolism in patients with resistant hypertension: a pilot study. Circulation 123:1940–1946
14. Heart rate variability (1996) Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 17:354–381
15. Townsend RR, Mahfoud F, Kandzari DE, Kario K, Pocock S, Weber MA et al (2017) Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): a randomised, sham-controlled, proof-of-concept trial. Lancet 390:2160–2170
16. Azizi M, Schmieder RE, Mahfoud F, Weber MA, Daemen J, Davies J et al (2018) Endovascular ultrasound renal denervation to treat hypertension (RADIANCE-HTN SOLO): a multicentre, international, single-blind, randomised, sham-controlled trial. Lancet 391:2335–2345
17. Kandzari DE, Böhm M, Mahfoud F, Townsend RR, Weber MA, Pocock S et al (2018) Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. Lancet 391:2346–2355
18. Mahfoud F, Böhm M, Azizi M, Pathak A, Durand Zaleski I, Ewen S et al (2015) Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design. Eur Heart J 36:2219–2227
19. Lüscher TF, Mahfoud F (2014) Renal nerve ablation after SYMPLICITY HTN-3: confused at the higher level? Eur Heart. J 35:1706–1711
20. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M et al (2018) ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 39:3021–3104
21. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al (2016) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 37:2129–2200
22. Levy MN, Zieske H (1969) Autonomic control of cardiac pacemaker activity and atrioventricular transmission. J Appl Physiol 27:465–470
23. Böhm M, Ukena C, Ewen S, Linz D, Zivanovic I, Hoppe U et al (2016) Renal denervation reduces office and ambulatory heart rate in patients with uncontrolled hypertension: 12-month outcomes from the global SYMPLICITY registry. J Hypertens 34:2480–2486
24. Kannel WB, Wolf PA, Benjamin EJ, Levy D (1998) Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol 82:2N–9N
25. Schneider MP, Hua TA, Bohm M, Wachtell K, Kjeldsen SE, Schmieder RE (2010) Prevention of atrial fibrillation by Renin-Angiotensin system inhibition a meta-analysis. J Am Coll Cardiol 55:2299–2307
26. Iwasaki YK, Nishida K, Kato T, Nattel S (2011) Atrial fibrillation pathophysiology: implications for management. Circulation 124:2264–2274
27. Binici Z, Intzilakis T, Nielsen OW, Kober L, Sajadieh A (2010) Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation 121:1904–1911
28. Larsen BS, Kumarathurai P, Falkenberg J, Nielsen OW, Sajadieh A (2015) Excessive Atrial Ectopy and Short Atrial Runs Increase the Risk of Stroke Beyond Incident Atrial Fibrillation. J Am Coll Cardiol 66:232–241
29. Pokushalov E, Romanov A, Corbucci G, Artyomenko S, Baranova V, Turov A et al (2012) A randomized comparison of pulmonary vein isolation with versus without concomitant renal artery denervation in patients with refractory symptomatic atrial fibrillation and resistant hypertension. J Am Coll Cardiol 60:1163–1170
30. Pokushalov E, Romanov A, Katritsis DG, Artyomenko S, Bayramova S, Losik D et al (2014) Renal denervation for improving outcomes of catheter ablation in patients with atrial fibrillation and hypertension: early experience. Heart Rhythm 11:1131–1138
31. Romanov A, Pokushalov E, Ponomarev D, Strelnikov A, Shabanov V, Losik D, et al (2017) Pulmonary vein isolation with concomitant renal artery denervation is associated with reduction in both arterial blood pressure and atrial fibrillation burden: data from implantable cardiac monitor. Cardiovasc Therap 35.
32. Kiuchi MG, Chen S, Hoye NA, Purerfellner H (2018) Pulmonary vein isolation combined with spironolactone or renal sympathetic denervation in patients with chronic kidney disease, uncontrolled hypertension, paroxysmal atrial fibrillation, and a pacemaker. J Interv Card Electrophysiol 51:51–59
33. Feyz L, Theuns DA, Bhagwandien R, Strachinaru M, Kardys I, Van Mieghem NM et al (2019) Atrial fibrillation reduction by

renal sympathetic denervation: 12 months' results of the AFFORD study. Clin Res Cardiol 108:634–642
34. de Jong MR, Hoogerwaard AF, Adiyaman A, Smit JJJ, Ramdat Misier AR, Heeg JE et al (2018) Treatment of atrial fibrillation in patients with enhanced sympathetic tone by pulmonary vein isolation or pulmonary vein isolation and renal artery denervation: clinical background and study design : The ASAF trial: ablation of sympathetic atrial fibrillation. Clin Res Cardiol 107:539–547
35. Sassi R, Cerutti S, Lombardi F, Malik M, Huikuri HV, Peng CK et al (2015) Advances in heart rate variability signal analysis: joint position statement by the e-Cardiology ESC Working Group and the European Heart Rhythm Association co-endorsed by the Asia Pacific Heart Rhythm Society. Europace 17:1341–1353
36. Peters CD, Mathiassen ON, Vase H, Bech Norgaard J, Christensen KL, Schroeder AP et al (2017) The effect of renal denervation on arterial stiffness, central blood pressure and heart rate variability in treatment resistant essential hypertension: a substudy of a randomized sham-controlled double-blinded trial (the ReSET trial). Blood Press 26:366–380
37. Verloop WL, Spiering W, Vink EE, Beeftink MM, Blankestijn PJ, Doevendans PA et al (2015) Denervation of the renal arteries in metabolic syndrome: the DREAMS-study. Hypertension 65:751–757
38. Hoogerwaard AF, de Jong MR, Adiyaman A, Smit JJJ, Delnoy P, Heeg JE et al (2019) Renal sympathetic denervation induces changes in heart rate variability and is associated with a lower sympathetic tone. Clin Res Cardiol 108:22–30
39. Tzafriri AR, Mahfoud F, Keating JH, Markham PM, Spognardi A, Wong G et al (2014) Innervation patterns may limit response to endovascular renal denervation. J Am Coll Cardiol 64:1079–1087
40. Mahfoud F, Tunev S, Ewen S, Cremers B, Ruwart J, Schulz-Jander D et al (2015) Impact of lesion placement on efficacy and safety of catheter-based radiofrequency renal denervation. J Am Coll Cardiol 66:1766–1775