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ORIGINAL PAPER

Renal sympathetic denervation induces changes in heart rate variability and is associated with a lower sympathetic tone

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Abstract

Background Renal nerve stimulation (RNS) is used to localize sympathetic nerve tissue for selective renal nerve sympathetic denervation (RDN). Examination of heart rate variability (HRV) provides a way to assess the state of the autonomic nervous system. The current study aimed to examine the acute changes in HRV caused by RNS before and after RDN.

Methods and results 30 patients with hypertension referred for RDN were included. RNS was performed under general anesthesia before and after RDN. Heart rate (HR) and blood pressure (BP) were continuously monitored. HRV characteristics were assessed 1 min before and after RNS and RDN. RNS before RDN elicited a maximum increase in systolic BP of 45 (±22) mmHg which was attenuated to 13 (±12) mmHg ($p<0.001$) after RDN. RNS before RDN decreased the sinus cycle length from 1210 (±201) ms to 1170 (±203) ms ($p=0.03$), after RDN this effect was blunted ($p=0.59$). The LF/HF ratio in response to RNS changed from $\Delta+0.448$ (±0.550) before RDN to $\Delta-0.656$ (±0.252) after RDN ($p=0.02$). Selecting patients off beta-blockade ($n=11$), the RNS-induced changes in HRV components before versus after RDN were more pronounced (LF/HF ratio $\Delta+0.900\pm1.171$ versus $\Delta-0.828\pm0.519$, $p=0.01$), whereas changes in HRV parameters in patients on beta-blockade ($n=19$) were no longer significant. In patients with diabetes mellitus ($n=7$), RNS induced no changes in HRV parameters (LF/HF ratio $\Delta-0.039\pm0.103$ versus $\Delta-0.460\pm0.491$, $p=0.92$).

Conclusion RNS induces changes in HRV suggesting increased sympathetic activity. Conversely, after RDN, the RNS-induced changes in HRV suggesting a lower sympathetic autonomic balance. These changes were most pronounced in beta-blocker naïve patients and not present in patients with diabetes mellitus. These findings could support RNS-guided RDN to optimize results.

Keywords Renal sympathetic denervation · Heart rate variability · Hypertension · Sympathetic nervous system

Introduction

Dysregulation of the autonomic nervous system, particularly imbalance between sympathetic and vagal tone, has been implicated in the development of hypertension. In this context, renal sympathetic denervation (RDN) has emerged as a potential treatment for resistant hypertension [1–3]. By denervating the renal arteries, general sympathetic tone is reduced by decreased norepinephrine spillover and muscle-sympathetic nerve activity [1, 4]. The efficacy of RDN remains a topic of debate after the Symplicity HTN-3 trial, in which RDN did not meet its primary efficacy endpoint [2]. Issues such as the lack of a procedural endpoint for denervation were pointed out as a potential reason for this [5]. Recently, we reported the use of renal nerve stimulation

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(RNS) to localize sympathetic nerve tissue for selective RDN and demonstrated that RNS-induced BP changes were strongly correlated with clinical outcome 3–6 months after RDN [6, 7]. Analysis of heart rate variability (HRV) has been widely used as a non-invasive assessment tool for autonomic nervous system function [8, 9]. Hypertension is associated with a higher autonomic sympathetic tone [10–13], and decreased HRV is a predictor of all-cause cardiac mortality [14–19]. The acute effects of RNS and RDN on HRV remain to be elucidated. Therefore, in our present study, we aimed to describe the acute changes in HRV caused by RNS both before and after RDN.

Methods

All patients undergoing RNS-guided RDN in the Isala Hospital in the Netherlands, between May 2013 and October 2016 were analyzed. The indication for RDN was drug-resistant hypertension. Patients were eligible if they were aged between 18 and 80 years, had a baseline office systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg and a mean SBP ≥ 130 mmHg or DBP ≥ 80 mmHg on 24-h ambulatory blood pressure measurements (ABPM), despite stable antihypertensive treatment with at least three antihypertensive drugs (preferably including a diuretic) for at least 1 month or intolerant for antihypertensive drugs. Patients were screened for eligibility for RDN by a multi-disciplinary team, including cardiologists, internists with hypertension subspeciality, and a radiologist. Glomerular filtration rate had to be > 45 mL/min/1.73 m^2 according to the MDRD formula. Patients with secondary causes of hypertension, a history of renal artery stenosis or abnormal renal artery anatomy (assessed by CT-angiography), diabetes mellitus type 1, chronic oxygen use, or contraindication to anticoagulation therapy or heparin were excluded. Atrial fibrillation (AF) or frequent premature ventricular or atrial beats during the procedure was an exclusion criterion as well, because HRV cannot be reliably assessed during arrhythmias. Insufficient quality of the arterial BP curves was an exclusion criterion for the analysis. Patients enrolled in another investigational drug or device study were also excluded. All patients were willing and able to comply with the protocol and had provided written informed consent. The study was approved by the local medical ethical committee (ABR number 47172) and was conducted according to the Declaration of Helsinki.

Procedure

The procedure was performed by experienced cardiac electrophysiologists. All patients were under general anesthesia, induced by propofol and the procedure was supervised by a cardiac anesthesiologist. Throughout the RDN procedure, no changes were made in the use of vasoactive medication and no use of inotropic medication was necessary. Two sheaths were placed in the right femoral artery, one for continuous BP measurement and another for catheter access. A total of 5000 IU of heparin were administered during the procedure. In addition, in patients not previously on acetylsalicylic acid, we administered 500 mg of acetylsalicylic acid intravenously. The RNS protocol has been described in detail previously [6]. Aorto-renal angiography was performed using a pigtail catheter. Two types of catheters were used. Initially, a conventional quadripolar catheter (EP-XT, C.R. Bard, Inc., Murray Hill, NJ, USA) was used in combination with the single-electrode ablation catheter (Symplicity Flex Renal Denervation Catheter, Medtronic, Minneapolis, MN, USA). Subsequently, patients were ablated with the multi-electrode basket ablation catheter (EnligHTN, St Jude Medical, Saint Paul, MN, USA), enabling both ablation and high-frequency stimulation by delivering electrical pulses through the electrodes of this multi-electrode basket catheter, with bipolar stimulation from electrodes 1–2 and 3–4. For a more detailed description of the RNS procedure, we refer to our previous report, elaborating in detail on pacing and output settings [6]. The use of two different catheter types can potentially introduce bias, so we compared the RNS-induced BP and HR increases for both groups. After RNS-guided mapping was performed in both arteries (total of at least eight stimulation sites), a standard RDN procedure was performed. In each renal artery, depending on the renal artery anatomy, 4–28 ablation points were delivered by subsequent sets of RF energy applications. All side branches were denervated if diameters allowed catheter passage. During radiofrequency (RF) energy application, tip temperature and impedance were monitored. Heart rate (HR) and blood pressure (BP) were continuously monitored (LabSystem Pro, Bard, USA) during RNS and the RDN procedure by a femoral artery line.

HRV analysis

HRV frequency domains were assessed 1 min before and after RNS both before and after RDN using the Kubios HRV 2.2 Software. The software used the fast Fourier transform to calculate the frequency domains. The total power was calculated by the sum of the very low-frequency (VLF), low-frequency (LF), and high-frequency (HF) components. The LF component was defined as frequency ranging from 0.04 to 0.15 Hz and the HF component ranging from 0.15 to 0.4 Hz. The VLF component will not be described as short-term recordings (≤ 5 min) that do not reliably reflect this component of HRV caused by changes in sympathetic tone [9]. The mean RR interval (ms) and its total variance of power (ms^2) were calculated. The LF and HF powers were

expressed in both absolute units (ms^2) and normalized units (n.u.) (%). Normalized or relative LF and HF power is the absolute power divided by the partial power as defined as the power between 0.04 and 0.5 Hz. In addition, the LF:HF power content ratio was calculated. Since beta-blocker use affects the HRV, baseline and HRV data are presented for the entire group and separately for the patients with and without the use of beta-blockers [20, 21]. HRV was also separately assessed in patients with and without diabetes mellitus, since we know that diabetes mellitus type 2 is associated with an overall decrease in the HRV caused by altered autonomic balance due to neuropathy [22].

Statistical analysis

Statistical analysis was performed using IBM SPSS statistics version 20 (IBM inc., Armon, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD) or standard error of the mean (SEM) or median with range when appropriate. Categorical variables were reported by frequencies and percentages. Variables were tested for normality of distribution. For the comparison of normally distributed variables, a paired *t* test was used to compare the means before and after RDN, for the non-normally distributed variables the non-parametric variant (Wilcoxon signed ranked test) was used. A *p* value of ≤ 0.05 was considered statistically significant.

Results

42 patients underwent RDN with the use of RNS in the period from May 2013 to October 2016. 30 patients were included in the analysis for this study; the other 12 patients were excluded because of non-analyzability of the acute HR data ($n=9$) or presence of AF ($n=3$). Mean age was 63 (± 7) years and half of the population was male. Mean ABPM at baseline was 145 (± 12)/82 (± 13) mmHg and patients were using an average of four antihypertensive drugs. Further demographic and clinical characteristics, BP measurements, renal artery anatomy, and antihypertensive drugs at baseline are presented in Table 1. Eight patients had a history of AF but no anti-arrhythmic drugs were used; patients were only using beta-blockers. The baseline characteristics of the patients on ($n=19$) and off ($n=11$) beta-blockade are separately presented in Table 1. Patients using beta-blockers had more often a medical history of hypercholesterolemia (79 versus 36%, $p=0.02$) and were using the same number of antihypertensives. Both the office and ambulatory BP measurements at baseline did not significantly differ between the groups on and off beta-blockers.

In the first ten patients, the single-electrode ablation catheter (Symplicity Flex Renal Denervation Catheter, Medtronic, Minneapolis, MN, USA) was used; in the following 20 patients, the multi-electrode basket ablation catheter (EnligHTN, St Jude Medical, Saint Paul, MN, USA) was used. A median of ten (4–28) RF applications per renal artery was performed.

Blood pressure and heart rate response to RNS

The mean BP response to RNS at the site of maximum response was + 45 (± 22)/25 (± 12) mmHg before RDN, compared with + 12 (± 13)/7 (± 7) mmHg ($p<0.001$) after RDN, as presented in Fig. 1. In the first ten patients, the single-electrode ablation catheter (Symplicity Flex Renal Denervation Catheter, Medtronic, Minneapolis, MN, USA) was used, and these patients had a RNS-induced BP increase of 50.2 ± 14 mmHg before RDN and 12.1 ± 14.7 mmHg after RDN. In the following 20 patients, the multi-electrode basket ablation catheter (EnligHTN, St Jude Medical, Saint Paul, MN, USA) was used, and these patients had a RNS-induced 44.0 ± 26 before RDN and 12.6 ± 11.6 mmHg after RDN. These effects were not statistically different, with before and after RDN with a *p* value of, respectively, 0.48 and 0.93.

The sinus cycle length decreased significantly from 1210 (± 201) ms to 1170 (± 203) ms in response to RNS before RDN ($p=0.03$). After RDN, RNS induced no significant change in the sinus cycle length (991 ± 590 versus 986 ± 588 ms, $p=0.58$).

HRV responses to RNS in the entire study population

Frequency domain measurements of HRV are presented in Table 2, respectively, before and after RNS before RDN and after RDN. The total powers are listed in Table 2 and their corresponding LF and HF components have been calculated and are displayed in Figs. 2 and 3.

Before RDN, RNS did not affect the LF component (from 0.421 ± 0.043 to 0.437 ± 0.037 Hz, $p=0.59$) and the HF component (from 0.580 ± 0.043 to 0.563 ± 0.038 Hz, $p=0.59$). The LF/HF ratio was not significantly affected due to RNS before RDN (from 1.142 ± 0.213 to 1.590 ± 0.547, $p=0.704$).

After RDN, RNS induced a significant increase in HF component (from 0.522 ± 0.048 to 0.602 ± 0.041, $p=0.02$), and a significant decrease in LF component (from 0.478 ± 0.048 to 0.398 ± 0.041, $p=0.02$). The RNS-induced LF/HF ratio was significantly reduced (1.607 ± 0.364 to 0.945 ± 0.174, $p=0.01$).

To compare the RNS-induced HRV changes before and after RDN, we used the delta before versus delta after. The RNS-induced change in LF component was Δ + 0.017 (± 0.044) Hz prior to RDN compared to Δ − 0.080 (± 0.031) Hz after RDN ($p=0.03$). RNS-induced change in HF component was Δ − 0.017 (± 0.044) Hz before RDN compared

Table 1 Baseline characteristics

Characteristics	All patients ($n=30$)	On beta-blockade ($n=19$)	Off beta-blockade ($n=11$)
Age (years)	63 ± 7	62 ± 10	64 ± 6
Sex (male)	15 (50%)	12 (63%)	8 (73%)
Body-mass index (kg/m^2)	29.1 ± 4.3	29.5 ± 5	28.4 ± 3
Current smokers	1 (3%)	1 (5%)	0 (0%)
Medical history			
Hypercholesterolemia*	19 (63%)	15 (79%)	4 (36%)
Type 2 diabetes mellitus	7 (23%)	6 (32%)	1 (9%)
Coronary heart disease	5 (17%)	5 (26%)	0 (0%)
Atrial fibrillation	8 (26.7%)	5 (26%)	3 (27%)
Number of antihypertensive medications	4 ± 1	4 ± 1	4 ± 2
Type of antihypertensive medication			
Diuretic	19 (63%)	11 (58%)	8 (73%)
Aldosterone receptor blocker	4 (13%)	2 (11%)	2 (18%)
Beta-blocker*	19 (64%)	19 (100%)	0 (0%)
Calcium channel blocker*	20 (67%)	10 (53%)	10 (90%)
ACE-inhibitor	10 (33%)	6 (32%)	4 (36%)
Angiotensin receptor blocker	18 (60%)	11 (58%)	7 (64%)
Aliskiren	1 (3%)	1 (5%)	0 (0%)
Centrally acting α2-sympatholytics	1 (3%)	1 (5%)	0 (0%)
A1-receptor blockers	10 (33%)	5 (26%)	5 (45%)
eGFR (mL/min/1,73 m^2)	91 [44–113]	93 [44–214]	90 [63–112]
Ambulatory BP (mmHg)			
24 h systolic	145 ± 13	144 ± 13	148 ± 13
24 h diastolic	82 ± 12	79 ± 12	87 ± 10
Daytime systolic	146 ± 13	145 ± 14	148 ± 11
Daytime diastolic	83 ± 11	81 ± 11	87 ± 11
Night-time systolic	132 ± 14	132 ± 15	131 ± 12
Night-time diastolic	72 ± 13	69 ± 12	78 ± 11
Office BP (mmHg)			
Systolic	168 ± 23	165 ± 22	172 ± 26
Diastolic	95 ± 15	91 ± 16	102 ± 11
Heart rate (bpm)	66 ± 11	64 ± 12	68 ± 7

eGFR estimated glomerular filtration rate calculated using the Cockcroft–Gault formula. Data are presented as number of patients (percentage) or mean ± SD, or range where appropriate

ACE angiotensin-converting enzyme, *BP* blood pressure

*Significantly different $p<0.05$ in the group on and off beta-blockade

to Δ + 0.080 (± 0.031) Hz after RDN ($p=0.03$) (see Fig. 2). Furthermore, the mean LF/HF ratio response to RNS also significantly changed from Δ + 0.448 (± 0.550) before RDN, compared to Δ − 0.656 (± 0.252) after RDN ($p=0.02$) (Fig. 3).

HRV responses to RNS in patients with or without beta-blockers

Nineteen patients were using beta-blockers during the RNS/RDN procedure and eleven patients were beta-blocker naïve. In the patients without beta-blocker use ($n=11$), the RNS-induced change in LF component was significantly different before versus after RDN (Δ + 0.055 ± 0.056 versus Δ − 0.090 ± 0.053 Hz, $p=0.02$), as well as the HF component (Δ − 0.055 ± 0.056 versus Δ + 0.090 ± 0.053 Hz, $p=0.02$) and the LF/HF ratio (Δ + 0.900 ± 1.171 versus Δ − 0.828 ± 0.519, $p=0.01$). In the patients using a beta-blocker ($n=19$), the RNS-induced change in LF component did not differ before versus after RDN (Δ − 0.056 ± 0.063 versus Δ − 0.074 ± 0.038 Hz, $p=0.38$), as well as the HF component (Δ + 0.056 ± 0.063 versus Δ + 0.074 ± 0.038 Hz,

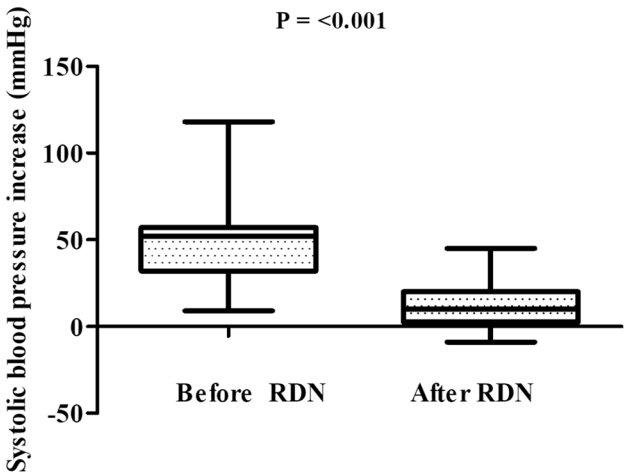

Fig. 1 RNS-induced SBP increase at site of maximum response before RDN (Δ + 45 (± 22) mmHg) and after RDN (Δ + 12 (± 13) mmHg), $p < 0.001$

$p = 0.38$) and the LF/HF ratio (Δ + 0.186 ± 0.565 versus Δ − 0.538 ± 0.245, $p = 0.38$). See Fig. 4.

HRV responses to RNS in patients with and without diabetes mellitus

Seven in the total 30 patients had diabetes mellitus. In the patients without diabetes mellitus ($n = 23$), the RNS-induced change in LF component was significantly different before versus after RDN (Δ + 0.034 ± 0.049 versus Δ − 0.100 ± 0.031 Hz, $p = 0.01$), as well as the HF component (Δ − 0.034 ± 0.049 versus Δ + 0.100 ± 0.031 Hz, $p = 0.01$) and the LF/HF ratio (Δ + 0.678 ± 0.708 versus Δ − 0.712 ± 0.297, $p = 0.01$). In the patients with diabetes mellitus ($n = 7$), the RNS-induced change in LF component did not differ before versus after RDN (Δ − 0.039 ± 0.104 versus Δ − 0.009 ± 0.085 Hz, $p = 0.47$), as well as the HF component (Δ + 0.039 ± 0.104 versus Δ + 0.009 ± 0.085 Hz, $p = 0.47$) and the LF/HF ratio (Δ − 0.039 ± 0.103 versus Δ − 0.460 ± 0.491, $p = 0.92$).

Discussion

The current study investigated the effect of RNS on HRV, both before and after RDN. RNS induced changes in HRV suggesting an increased sympathetic tone before RDN.

Table 2 HRV frequency domain measurements before and after RNS both before and after RDN

Variables	Before RDN		After RDN	
	Before RNS	After RNS	Before RNS	After RNS
RR interval (ms)	1210 ± 201	1170 ± 203*	991 ± 590	986 ± 588
Ln Total power (ms^2)	8.9 ± 2.3	8.6 ± 2.3	8.7 ± 2.4	7.8 ± 2.2
Ln LF power (ms^2)	6.9 ± 1.4	7.3 ± 1.5	8.0 ± 1.8	6.0 ± 1.4
Ln HF power (ms^2)	8.5 ± 1.8	8.1 ± 1.7	8.3 ± 1.8	7.5 ± 1.7
LF power (n.u.)	0.42 ± 0.04	0.44 ± 0.04	0.48 ± 0.05	0.43 ± 0.04*
HF power (n.u.)	0.57 ± 0.04	0.56 ± 0.04	0.52 ± 0.05	0.57 ± 0.04*
LF/HF-ratio (%)	1.14 ± 0.21	1.59 ± 0.55	1.67 ± 0.39	1.04 ± 0.19*

Data are represented as a mean and standard deviation for heart rate, and as ln of the mean and standard errors of the mean for other variables

LF low frequency, *HF* high frequency, *n.u.* normalized unites

*Significantly different ($p < 0.05$) before versus after RNS

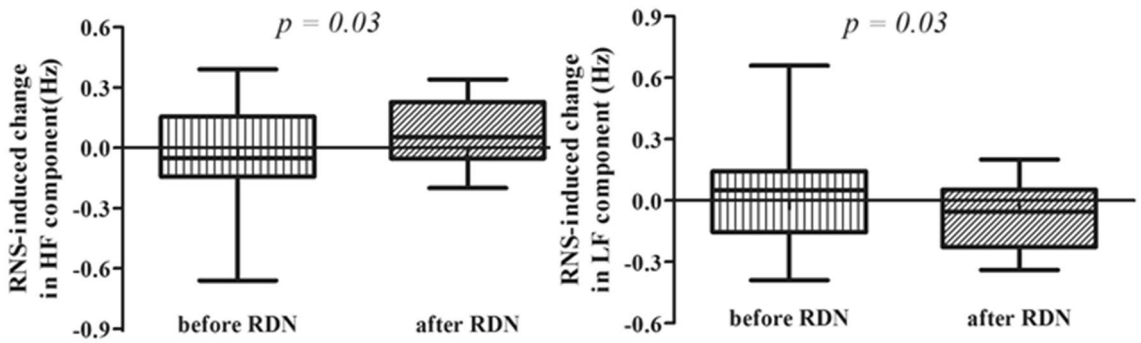

Fig. 2 RNS-induced change in LF and HF component before and after RDN

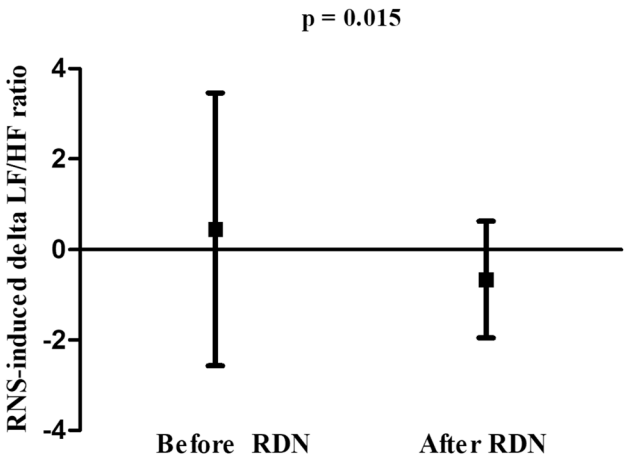

Fig. 3 RNS-induced change in the LF/HF ratio before and after RDN, presented as mean and SD. The mean LF/HF ratio response to RNS was +0.45 (±3.0) before RDN, compared to −0.66 (±1.3) after RDN ($p=0.021$)

Conversely, after RDN, the RNS-induced changes in HRV suggesting a lower sympathetic autonomic balance. These changes were most pronounced in beta-blocker naïve patients. These findings could support RNS-guided RDN to optimize results.

The aim of the present study was to look for additional evidence supporting the role of RNS and RDN in diminishing sympathetic overdrive. To our knowledge, we are the first reporting about RNS-induced changes in HRV. Previous studies have only investigated the effects of RDN on HRV, such as the study of Verloop et al. who described the effects of RDN in a drug-naïve population with metabolic syndrome, and have used HRV as secondary end point as measurement of sympathetic activity. They showed in 26 patients at 12 months after treatment that there was no significant difference in HRV measurements. However, we believe this study is completely different compared to the study of Verloop et al., since we are using RNS as procedural end point of the RDN procedure [23].

First of all, in accordance with our previous studies [6, 7, 24], we showed a marked effect of RNS on BP and this BP effect was blunted after RDN (Fig. 1). Second, in addition to these large RNS-induced BP effects, we showed a moderate, although significant effect on sinus cycle length and this effect was also blunted after RDN. Third, before RDN no significant changes due to RNS in HRV components were observed. However, after RDN the LF/HF ratio decreased significantly due to a decrease in the LF component and an increase in the HF component reflecting a change in the sympathovagal balance toward a higher parasympathetic tone after RDN. Also the change in HRV components (LF, HF, and LF/HF ratio) before RDN was significantly different versus after RDN; showing before RDN a more sympathetic drive and after RDN a more parasympathetic drive (Figs. 2, 3). Finally, patients using beta-blockers during the procedure showed no significant changes in any of the parameters measuring the difference in HRV before versus after RDN, while in the group of patients off beta-blockade the described significant RNS-induced changes in HRV components before versus after RDN were still present consistent with the entire population albeit more pronounced (Fig. 4). Also patients with diabetes mellitus showed no significant RNS-induced changes in HRV components before versus after RDN.

Changes in sinus rate are controlled by the autonomic nervous system and there is a linear relationship between HR and the vagal or sympathetic tone within the physiological range of beat to beat sinus rate variations [25]. HRV analysis has been used as a non-invasive tool to study these changes in sympathetic and vagal tone, as a reflection of alterations of both limbs in the autonomic nervous system [9]. Among the components of HRV, the LF component of HRV is widely recognized to reflect a mixture of both the sympathetic and parasympathetic tone, whereas HF component is linked to vagal mediation of HRV and the LF/HF ratio is recognized as an index of sympathovagal balance [26]. Changes in HRV depend on the level and sort of sympathetic and vagal stimuli. The onset of alterations in HR elicited by vagal nerve activity is relatively fast, whereas time delay is much longer between onset of increased sympathetic neural activity and subsequent changes in HR [27, 28]. These differences are secondary to differences in conduction time of the nerve fibers, synaptic cleft properties, receptor kinetics, and post receptor intracellular signaling pathways. Of note, the magnitude of sympathetic stimulation plays an important role in HRV. Mild enhancement of sympathetic tone is associated with an increase of HRV indices. However, if the sympathetic stimulation is intense or prolonged, an overall decrease in HRV without correlation with the reduction in sympathetic activity would be seen [29].

In our study, the described BP changing effects of RNS are much more pronounced compared to the alterations in HR. The sympatho-excitatory renal afferent reflex most likely causes the rise in BP induced by electrical stimulation, because the rise in BP was observed 15–30 s after starting electrical stimulation which is comparable with effects induced by an enhanced sympathetic nervous activity through stellate ganglion stimulation in canine studies as reported previously. Given the above described pathophysiology, we believe that the acute RNS-induced HR oscillations are most likely derived from a combination of afferent renal sympathetic nerve signaling enhancing the central sympathetic tone and baroreflex, vagally mediated response to changes in BP. As the onset of HR response due to increased sympathetic activity is associated with a long time constant and we only present the

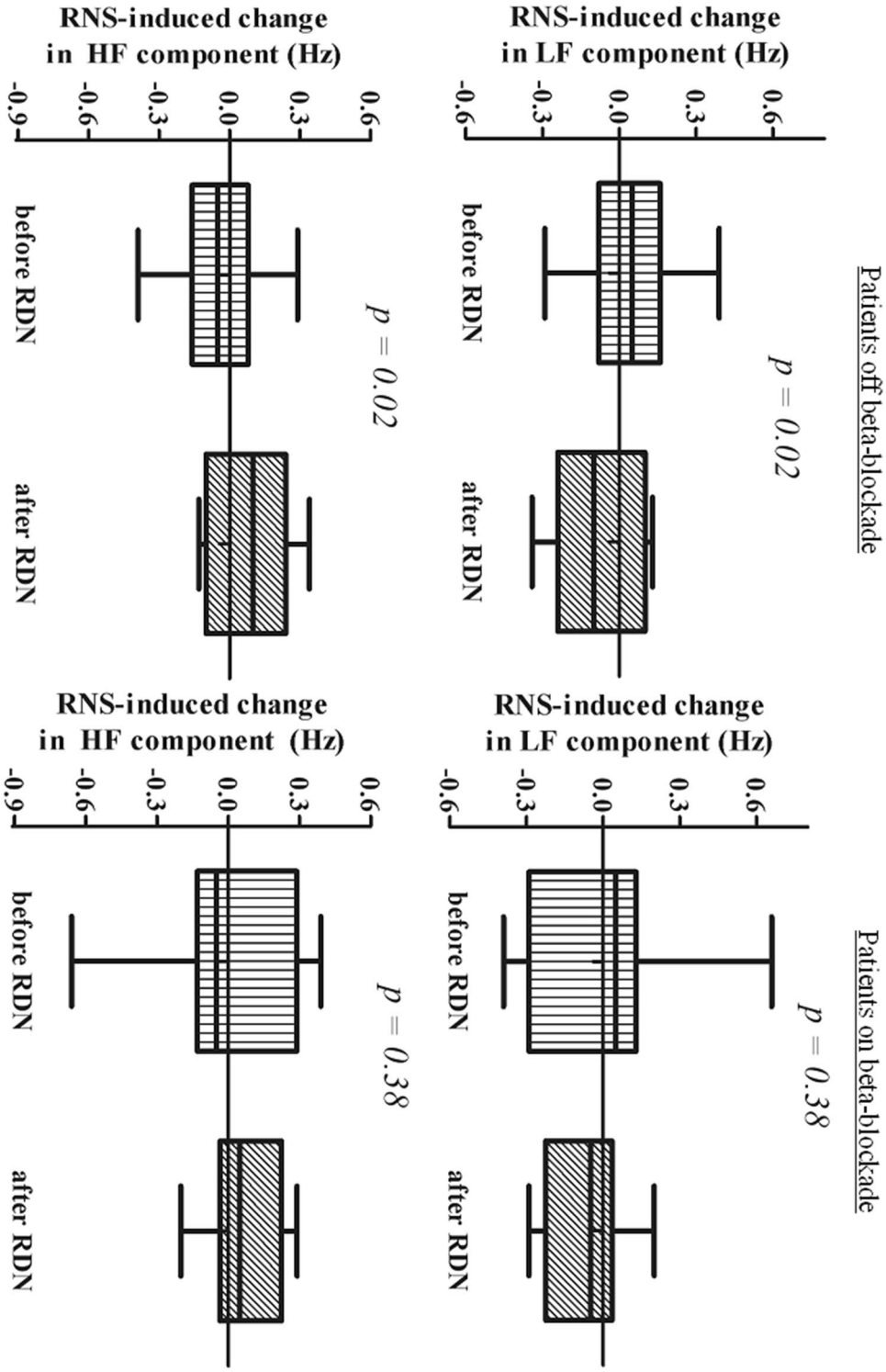

Fig. 4 RNS-induced change in the LF and HF components before versus after RDN in patients with the use and without the use of beta-blockers

acute RNS-induced changes. Of note, a limitation of our study is that HRV has only been assessed 1 min before and after both before and after RDN. Nonetheless, the analysis of the different HRV components supports the idea of RNS influencing the autonomic nervous system both before and after RDN. The RNS-induced change in LF/HF ratio before RDN was significantly different versus the change in LF/HF ratio after RDN. Before RDN, we observed an increase in the LF/HF ratio versus a decrease after RDN; reflecting before RDN a more sympathetic tone of the sympathovagal balance and after RDN predominance of the vagal tone. We observed no changes

in the relative components of the HRV before RDN, we believe these changes were most likely prevented by beta-adrenergic blocker administration [20, 21]. Of note, this has influenced our results since 63% of the study population was using a beta-blocker during the RDN procedure. However, in our study, we did not exclude patients on beta-blockade since discontinuation is not always safe in the population with resistant hypertension referred for RDN. Influence of beta-blocker use on our results was confirmed by studying the group of patients using a beta-blocker, in this group none of the parameters (RNS-induced change in LF, HF, and LF/HF ratio before versus after RDN) measuring the difference in HRV before versus after RDN appeared to differ significantly. On the contrary, in the patients off beta-blockade, the change in LF, HF, and LF/HF ratio before and after RDN remained statistically significant. Comparing these results to the entire group suggests even an almost 1.5 times stronger effect of RNS in patients without beta-blockade. The modulating effect of beta-blockade is an extra argument why RNS influences the autonomic nerve system. So, HRV responses elicited by RNS were more pronounced in patients without beta-blockade, while the effects of RNS were blunted if the patient was on beta-blockade. Another explanation for the different results in patient on versus off beta-blockers could be that patients on beta-blockade and general anesthesia are already well protected and RDN may not be quite useful as in those not on beta-blockers.

Furthermore, patients on beta-blockade seem had a tendency to higher frequency of diabetes mellitus and coronary heart disease. This could also have slightly influenced the results since we know that patients with diabetes mellitus and coronary artery disease have decreased HRV [16, 22, 30]. This suggestion is confirmed by our analysis of the patients with diabetes mellitus who showed no significant changes in any of the HRV parameters. Of note, 7 of the in total 30 patients had diabetes mellitus, so we cannot draw firm conclusions based on this limited number of patients with diabetes mellitus. However, it is an interesting finding with possible implications for the patient selection for RDN. Future research will collect data from a larger group of RDN patients with diabetes to provide a more definite answer to this important question.

Interestingly, after RDN, RNS not only elicited a significant decrease in sympathetic tone, but we observed also an increase in parasympathetic tone. From beta-blockers and centrally acting sympatho-inhibitory drugs, it is known that they are able to improve the baroreflex control of HR, possibly through vagal facilitation [31, 32]. In our opinion, this supports the rationale of RDN with a reduced sympathetic and increased parasympathetic outflow after denervating sympathetic nerves of the renal arteries. Given our results we hypothesize an indirect effect of RDN on HR via the afferent route whereas the BP effects of RDN are probably due to both an afferent effect via the central nervous system and efferent route directly to the kidneys.

Limitations of the study are the small study population and the lack of the use of any measurement of drug adherence, since we know that drug non-adherence is a major problem in patients with treatment-resistant hypertension [33]. Furthermore, the use of two different types of catheters could have influenced our results. However, we have demonstrated that the RNS-induced BP responses before and after RDN were not significantly different in the different catheter groups. So, we believe that the observed effects on HRV have not been influenced by the different catheter use. Another possible limitation of the study is the use of general anesthesia during the procedure, which could have inhibited the sympathetic nervous system and diminished the RNS-induced blood pressure and HRV changes. Of note, we maintained stable depth of anesthesia during the entire RDN procedure guided by the continuous bispectral index monitoring during the procedure. Therefore, it is not likely that the anesthesia had a pronounced effect on the RNS-induced change in blood pressure changes before and after RDN.

In conclusion, this study shows significant RNS-induced changes in the power spectrum of HRV after RDN compared to before RDN. The changes suggest alterations in the sympathovagal balance with increased vagal and reduced sympathetic outflow influencing the heart after RDN in patients with drug-resistant hypertension; which is the aim of the RDN treatment.

Since this study only represents acute RNS-induced changes in HRV both before and after RDN, further research regarding long-term HRV changes after RNS-guided RDN in patients with treatment-resistant hypertension is needed as this may predict long-term cardiovascular outcome.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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