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The effect of percutaneous renal denervation on muscle sympathetic nerve activity in hypertensive patients

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ABSTRACT

Objective: The rationale of percutaneous renal denervation (RDN) is based on extensive studies suggesting that renal nerves contribute to hypertension and that they comprise a sensible treatment target. Muscle sympathetic nerve activity (MSNA) is considered to be one of the few reliable methods to quantify central sympathetic activity. The aim of this current study is to determine the effect of RDN on MSNA in a standardized fashion.
Methods: MSNA was determined in 13 patients before and 6 months after RDN. Anti-hypertensive medication was stopped before MSNA. If cessation of medication was considered unsafe, a patient was instructed to use the exact same medication on both occasions.
Results: Ten sets of MSNA recordings were of good quality for analysis. Mean age was 57 ± 3 years and mean eGFR was 85 ± 18 mL/min/1.73 m^2. MSNA was determined twice during a medication free interval in 5 patients; 1 patient used the exact same medication twice, and 4 patients used different drugs. Mean BP changed from 206 ± 7 over 116 ± 4 mm Hg, to 186 ± 6 over 106 ± 3 mm Hg, 6 months after RDN ($p = 0.06$ for systolic BP, $p = 0.04$ for diastolic BP). Mean resting heart rate did not change ($p = 0.44$). MSNA did not change after RDN: 37 ± 4 bursts/min and 43 ± 4 bursts/min ($p = 0.11$) at baseline and after RDN, respectively. In the 6 patients with standardized medication use during the MSNA sessions, results were comparable.
Conclusions: Treatment with RDN did not result in a change in MSNA. Changes in BP did not correlate with changes in MSNA.

1. Introduction

Globally, 34% of the adult population has hypertension and this prevalence is still rising [1]. Despite a broad availability of effective pharmaceutical agents, only about 30% of the treated patients reach treatment goals [2]. Increased activation of the sympathetic nervous system is identified as an important factor in the development and progression of hypertension [3]. In this context, a catheter-based approach has been developed to disrupt the renal sympathetic nerves, using radiofrequency energy. The first clinical studies, in a relatively small number of patients, showed that this technique appears safe and effective [4–6]. Office systolic blood pressure (SBP)/diastolic blood pressure (DBP) reduced by 32/12 mm Hg six months after RDN [5].

The central hypothesis of this procedure is that by interruption of the renal efferent and afferent nerves by percutaneous renal denervation (RDN), central sympathetic outflow decreases towards the kidneys and various other organs, resulting in a BP lowering effect. Muscle sympathetic nerve activity (MSNA) is considered to be one of the few reliable methods to quantify central sympathetic activity. MSNA is the centrally originated postganglionic sympathetic nerve activity directed towards the resistance vasculature. There is convincing evidence that MSNA is modulated by renal afferent nerve activity [7]. So, it seems attractive to use MSNA as a surrogate for afferent nerve activity and to hypothesize that RDN lowers MSNA. We have vast experience with this technique [8–17]. The within-subject reproducibility of the basal supine MSNA signal is very good, so this technique has extensively been used to quantify chronic effects of interventions [8–17].

A few studies investigating the effect of RDN on MSNA are recently published, and report mixed effects of RDN on MSNA [18–21]. A

Abbreviations: ABPM, Ambulatory blood pressure measurement; BP, Blood pressure; DBP, Diastolic blood pressure; ECG, Electrocardiogram; eGFR, Estimated glomerular filtration rate; MSNA, Muscle sympathetic nerve activity; PAC, Plasma aldosterone concentration; PRA, Plasma renin activity; RDN, Renal denervation; SBP, Systolic blood pressure; UMC, University Medical Center.

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possible limitation of these studies is that patients used diverse antihypertensive drugs with various effects on MSNA during the recordings. The aim of current study was to determine the effect of RDN on MSNA while taking particularly care of standardization of medication use at the time of the two measurements.

2. Methods

2.1. Study population

Thirteen patients with resistant hypertension (defined as a SBP ≥ 160 mm Hg, despite use of ≥3 antihypertensive drugs), or fulfilling the same BP criteria but without optimal pharmacological treatment due to intolerance for antihypertensive drugs, planned to be treated with RDN were included in this study. Before treatment with RDN, patients were screened using a standardized protocol; firstly to confirm the diagnosis of hypertension, secondly to exclude secondary forms of hypertension and finally to obtain renal artery imaging to assess renal artery anatomy before treatment with RDN [22].

At baseline 24-h ambulatory BP monitoring was taken noninvasively using the Microlife WatchBp 03 device (Microlife Inc., Widnau, Switzerland), to exclude patients with white coat hypertension.

Before RDN (within one week) and 6 months after RDN a set of measurements was performed: BP-measurements, heart rate and MSNA. Anti-hypertensive medication was stopped, when considered safe, before these measurements as described in Table 1. This had been done by our group in previous studies [16,9]. The decision to stop antihypertensive drugs was based on clinical judgment with emphasis on (cardiovascular) medical history. During the medication free interval, patients were regularly contacted by a physician. Also, patients are informed to contact when they develop symptoms. If cessation of medication was considered unsafe, a patient was instructed to use the exact same medication twice for both sessions.

The study protocol was carried out with the approval of the Ethics Committee of the University Medical Center Utrecht, and all patients gave written informed consent.

2.2. Measurements

All subjects underwent an identical set of measurements in the morning, in supine position in a quiet room with an ambient temperature of 22 to 24 °C. Patients were asked to empty their bladder to minimize possible sympathetic activity caused by bladder extension. MSNA was recorded with a unipolar tungsten microelectrode placed in a muscle nerve fascicle of the right peroneal nerve using the technique of Wallin et al. [23], as described by us previously [8–11,13,15–17]. After instrumentation, subjects rested for 20 min. The correct position of the electrode was evaluated by means of a Valsalva maneuver, while electrocardiogram (ECG), heart rate and MSNA were continuously recorded. During restart of breathing after the Valsalva maneuver, a short pause in neural activity can be seen, this was considered to be the background noise. This procedure was done at the beginning and at the end of the study session. BP was measured in supine position during the MSNA session after the needle has been positioned in a stable position, at the arm with an automatic non-invasive calibrated BP-device. So BP was measured while patients were pain free and in a relaxed and standardized position. Means of at least three measurements are presented.

The neural signal was filtered (bandwidth, 500–2000 Hz), rectified and integrated (time constant, 0.1 s). Nerve activity was monitored online (software: Poly 5, Inspectors Research Systems, Amsterdam, The Netherlands) and stored on disk together with ECG, both at a sample frequency of 200 Hz, for offline analysis. Sympathetic bursts were identified by their characteristic morphology and relationship to R waves on the ECG. We have previously reported that intra-observer and inter-observer reproducibility are 4.5 ± 0.5% and 6.2 ± 0.7%, respectively [10]. Heartbeat intervals were measured from the ECG. The stored integrated MSNA signal was analyzed by a software specially developed by our group [24–27].

Glomerular filtration rate (eGFR) was estimated (at the day of MSNA measurement) on the basis of the CKD-epi formula [28]. Some data were used from the clinical work-up for patients with hypertension: urine was collected during 24 h to determine the albumin–creatinine ratio. Blood samples were drawn to measure plasma aldosterone concentration (PAC; pmol/L) and plasma renin activity (PRA; fmol/L/s) after 90 min of standing.

Table 1
Scheme of gradual discontinuation of medication.

4 weeks before measurements	Stop: diuretics (including aldactone) and aliskiren Gradually reduced: beta blockers and central working antihypertensive drugs are reduced in two weeks:	
	Day 1: 100%	Day 8: 0%
	Day 2: 50%	Day 9: 25%
	Day 3: 50%	Day 10: 0%
	Day 4: 50%	Day 11: 25%
	Day 5: 50%	Day 12: 0%
	Day 6: 0%	Day 13: 25%
	Day 7: 50%	Day 14: 0%
2 weeks before measurements	Stop: ACE-inhibitors, AT1-antagonists, calcium-antagonists, alpha-blockers, direct vasodilatators.	

2.3. Percutaneous renal denervation

RDN was performed using the Symplicity Catheter System, a 6Fr compatible, single-use RF probe. Before introduction of the RF-probe, renal angiograms were performed via a transfemoral approach to confirm anatomic eligibility. Subsequently, the system was introduced in the renal artery and the catheter electrode was positioned in contact with the vessel wall at the desired location and the catheter was connected to an automated RF generator. Multiple applications of RF energy in a spiral pattern along the renal artery with 5 mm interspace were performed. After the procedure, the puncture site was closed with a closure device and the groin was compressed for 4 to 6 h. Patients took 100 mg of acetylsalicylic-acid 5 days before and 4 weeks after the procedure.

2.4. Data analysis

Continuous baseline characteristics are given as mean ± SD. Categorical baseline data are given as number and percentage. Data which are compared (baseline vs follow-up) are shown as mean ± SEM. MSNA is expressed as the number of bursts of sympathetic activity per minute and as the number of bursts per 100 heart beats to correct for differences in heart rate. The change in SBP (an average of 3 measurements per session), heart rate and MSNA were calculated. A negative value represents a decrease in SBP 6 months after RDN. The Wilcoxon signed rank test was used for paired sample analysis. Spearman correlation was used to test correlations. A two sided p value of <0.05 was considered to be statistically significant. All analyses were performed with the SPSS statistical package version 20 (IBM SPSS Data Collection, Chicago, IL).

3. Results

Thirteen patients were included in this study, one patient died during follow-up from a non-procedure related cause, 12 patients completed follow-up. Ten sets of MSNA recordings were of sufficient quality for analysis: two recordings of the same patient (pre and post recoding) were excluded because of a signal to noise ratio, making it impossible to appropriately recognize bursts. Baseline characteristics of these 10 patients are depicted in Table 2. Secondary causes of hypertension were excluded before treatment with RDN. Four patients had micro-albuminuria and one macro-albuminuria. No adverse events related to the medication stop occurred.

MSNA was determined twice during identical conditions in six patients: a medication free interval in 5 patients and 1 patient used the exact same medication twice. Although aimed to do in identical conditions, in 4 patients medication use showed dissimilarities during the 2 study sessions. Table 3 shows the individual data on medication during the MSNA sessions. Unfortunately, it was not possible to stop antihypertensive drugs twice in all patients; patient 5 did have a transient ischemic attack during follow-up, therefore it was considered unsafe to stop all antihypertensive drugs again. Patient 4 did not want to stop all drugs a second time and patient 8 did not stop antihypertensive treatment at baseline due to previous hypertensive crises with neurologic complaints. Because of a great BP-reduction, antihypertensive medication was reduced during follow-up. Therefore temporary use of the same treatment comparable to baseline was therefore not feasible in this patient.

Eligible anatomy was confirmed before delivery of RF-energy to the treatment site. On average 11.6 (±1.3) denervation points was applied per patient. One patient was admitted 2 weeks after RDN because of hypotension, requiring fluid administration and cessation of antihypertensive drugs. No complications with long term consequences or adverse events related to the procedure occurred during 6 months of follow-up. Kidney function did not change after RDN ($p = 0.33$).

Mean BP, recorded during the MSNA session, changed from 206 (±7)/116 (±4) mm Hg at baseline, to 186 (±6)/106 (±3) mm Hg 6 months after RDN ($p = 0.06$ for SBP and 0.041 for diastolic BP (DBP)). Mean resting heart rate during the MSNA session, did not change: 69 (±3) bpm before and 67 (±2) bpm after RDN ($p = 0.44$). In the total group, MSNA expressed as bursts per minute, did not change after RDN: 37 (±4) bursts/min at baseline compared to 43 (±4) bursts/min ($p = 0.11$) after RDN. MSNA corrected for changes