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Renal Denervation in Patients with Resistant Hypertension– Assessment by 3T Renal ^{23}Na-MRI: Preliminary Results

JOHANNES BUDJAN[1], URS BENCK[2], ALEXANDER LAMMERT[2], MELISSA M. ONG[1], MIRYANA MIRCHEVA[2], STEFFEN DIEHL[1], SIMON KONSTANDIN[3,4], LOTHAR R. SCHAD[3], BERNHARD K. KRÄMER[2], STEFAN O. SCHOENBERG[1] and STEFAN HANEDER[1,5]

[1]*Department of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany;*
[2]*Fifth Department of Internal Medicine (Nephrology/Endocrinology/Rheumatology), University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany;*
[3]*Computer Assisted Clinical Medicine, University Medical Center Mannheim, Mannheim, Germany;*
[4]*MR-Imaging and Spectroscopy, Faculty 01 (Physics/Electrical Engineering), University of Bremen, Bremen, Germany;*
[5]*Department of Radiology, University Hospital of Cologne, Cologne, Germany*

Abstract. *Background/Aim: Renal denervation (RDN) has been considered a promising therapy option for patients suffering from therapy-resistant hypertension. Besides, in blood-pressure regularization, the kidneys play a fundamental role in sodium (^{23}Na) homeostasis. This study assesses the effect of RDN on renal ^{23}Na concentration using ^{23}Na magnetic resonance imaging (MRI). Patients and Methods: Two patients with therapy-resistant hypertension underwent RDN. ^{23}Na-MRI, ^{1}H-MRI, including diffusion weighted imaging (DWI), as well as endothelial dysfunction assessment, were performed 1 day prior, as well as 1, 30 and 90 days after RDN. Results: The renal corticomedullary ^{23}Na gradient did not change after RDN for all time points. Additionally, functional imaging and retinal vessel parameters were not influenced by RDN. Results regarding blood pressure changes and arterial stiffness, as well as patients' clinical outcome, were heterogeneous. Conclusion: RDN does not seem to alter renal ^{23}Na concentration gradients, as measured by MRI.*

Arterial hypertension is one of the most important risk factors for cardiovascular morbidity and mortality. Catheter-based renal denervation (RDN) has been considered a therapy option to reduce blood pressure especially in patients suffering from severe treatment-resistant hypertension. As the sympathetic nervous system and the kidneys are an important part of the blood pressure regulation system, both also play a vital role in the pathogenesis of hypertension (1). Specifically, renal sympathetic denervation goes along with a decrease of tubular sodium reabsorption in virtually all tubular segments of the nephron and a decrease of renal juxtaglomerular renin secretion (2). By influencing the sympathetic nervous system-mediated brain-kidney-crosstalk, RDN is expected to lower blood pressure. Initial results of the Symplicity Clinical Trial Program suggested promising effects in regards of short-term, as well as long-term, reduction of systolic and diastolic blood pressure levels of about 30 mmHg and 10 mmHg, respectively (3). Recently, however, the controlled, randomized and prospective Symplicity HTN3 Study did not find a significant difference in reduction of blood pressure at 6 months between sham procedure and RDN, questioning RDN as a therapy option for patients suffering from treatment resistant hypertension (4). However, in subgroup analyses, a significant blood pressure reduction has been found in Caucasians (4) and argued that most of the study sites of the Symplicity HTN3 Study had been relatively inexperienced with regard to the use of the RDN technique.

So far, studies showed no influence of RDN on functional magnetic resonance imaging (MRI), such as MRI perfusion (5). ^{23}Na-MRI is a promising functional MR technique assessing non-invasively the renal concentration of sodium 23 (^{23}Na) (6-10). ^{23}Na concentration increases from the renal cortex in the direction to the medullary pyramids and can be influenced by external factors, such as water uptake (8) or

Correspondence to: Dr. Johannes Budjan, Department of Clinical Radiology and Nuclear Medicine, University Medical Center Mannheim, Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, 68167 Mannheim, Germany. Tel: +49 06213832276, Fax: +49 06213833817, e-mail: johannes.budjan@umm.de

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Table I. *Summary of the RR values and the SphygmoCor data of both patients over the time course before and after RDN.*

		Patient 1			Patient 2		
	Unit	Day -1	Day 30	Day 90	Day -1	Day 30	Day 90
RR - office cuff	Syst/diast in (mmHg)	170/96	148/91	142/89	179/105	147/89	145/91
RR - 24h							
day	Syst/diast in (mmHg)	159/113	151/102	138/98	161/77	150/73	136/75
night	Syst/diast in (mmHg)	160/104	128/84	112/75	123/61	130/64	126/63
RR - Dipping	(%)	–0.6	15.2	18.8	23.6	13.3	7.4
RR - medication	Numbers	6	6	7	9	7	7
SphygmoCor data							
SBP	(mmHg)	148±3.3	124±3.0	133±0.5	190±0.0	139±6.9	144±1.0
DBP	(mmHg)	101±0.5	91±0.5	82±0.0	101±0.0	81±4.5	80±0.5
MBP	(mmHg)	120±0.5	106±0.5	103±0.5	135±0.5	99±5.9	105±0.5
PP		47±3.8	33±3.6	51±0.5	89±0.0	58±2.9	64±1.3
AP	(mmHg)	20±0.0	10±0.5	20±1.0	34±0.5	17±5.7	24±1.4
Aix	(%)	43±0.5	30±1.5	38±1.0	38±0,5	29±8.2	38±1.4
PWV	(m/s)	7.8	6.5	6.3	8.6	11.2	11.3

RR-office cuff, Measured in a sitting position in a resting state and three measurements over 5 minutes (mean RR is given); SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; PP, pulse pressure; AP, augmentation pressure; Aix, augmentation index; PWV, pulse wave velocity; RDN, renal denervation.

water deprivation (11). Differences to healthy tissue have also been found after ablative radiotherapy (12). ^{23}Na-MRI allows a measurement of these physiological and pathophysiological processes *in vivo*. Among other factors, mechanisms related to renal sodium regulation appear to play a role in the pathogenesis of hypertension. However, the literature on sodium regulation in the context of RDN is somewhat heterogeneous in animal studies (13-15). There are no published data investigating the effect of RDN on renal sodium homeostasis and its potential change after therapy in human patients. Therefore, this technical note presents initial results on renal MR sodium imaging before and after RDN flanked by diffusion-weighted imaging (DWI) and extensive clinical work-up of patients, including clinical retinal vessel analysis and assessment of arterial stiffness.

Patients and Methods

Patients and blood pressure measurements. The clinical indication and the RDN procedure itself were not part of the study and performed according to the local, clinical standardized operation procedure. This diagnostic study was approved by the local institutional review board (Medizinische Ethikkommmision 2, Medizinische Fakultät Mannheim) and performed in adherence to the Declaration of Helsinki. Informed consent was obtained from all patients. All diagnostic procedures were performed one day prior to RDN, as well as one, 30 and 90 days after RDN.

Two patients were included until the results of the Symplicity HTN3 trial stopped the recruiting process. Secondary causes for hypertension, such as renal artery stenosis, served as exclusion criteria, whereas severe treatment resistant hypertension as inclusion criteria. Patient 1 was a 44-year-old female with a body mass index (BMI) of 25.4 kg/m^2 and Patient 2 a 70-year-old female with a BMI of 31.2 kg/m^2. Office blood pressure, 24h blood pressure (day/night) and the RR-dipping before and after RDN are summarized in Table I.

RDN was performed without major or minor complications in both patients. The number of denervation points were: Patient 1, 6 right/4 left; Patient 2, 5 each side (Figure 1). Therapy-associated renal artery stenosis or dissection was not encountered in all follow-up examinations.

Retinal vessel analysis and SphygmoCor measurements. Digital video analysis was used for digital fundus imaging for conventional examinations and for retinal vessel analysis ((RVA); Imedos, Jena, Germany). After mydriasis with phenylephrine 10% and tropicamide 1%, pictures centered for the macula, the inferior arcade and optic disc were recorded from both eyes. The software calculated arterio-venous ratios (AVR) using arteries and veins within two diameters of the optic disc (Imedos). AVR was assessed in a blinded fashion (16, 17). Reduced diameter of retinal arteries is seen as consequence of arterial hypertension and was also determined.

Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MPB) and indices for the arterial stiffness as pulse pressure (PP), augmentation pressure (AP), augmentation index (Aix) and pulse wave velocity (PWV) were assessed as previously described in detail (18-21). Before and after (30 and 90 days) RDN, a commercially available applanation tonometer (SphygmoCor, AtCor Medical Ltd, Sydney, Australia) in combination with standard analysis software (version 8.0, SphygmoCor Cardiovascular Management Suite; AtCor Medical, Itasca, IL, USA) was used to determine the indices for arterial stiffness (20, 21).

Magnetic resonance imaging. Both patients received identical abdominal 1H-MR protocols at a 3T whole-body scanner (Magnetom Skyra; Siemens Healthcare, Erlangen, Germany) including T2-weighted, standard morphological sequences, as well as DWI. For

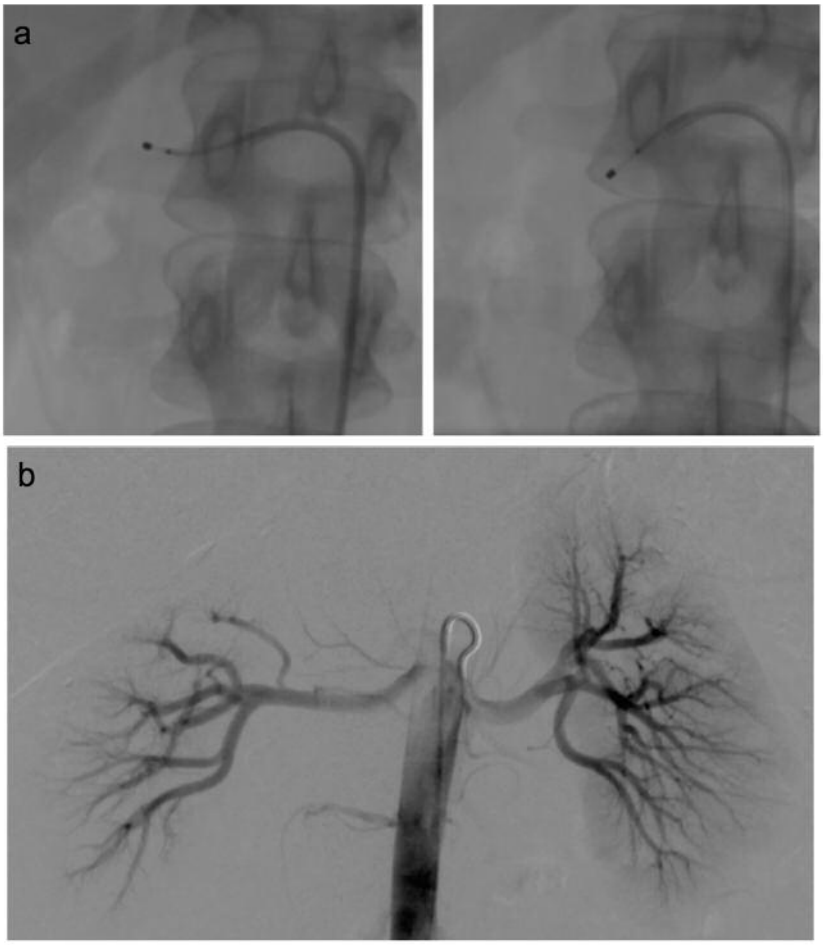

Figure 1. *Intra-procedural images of renal denervation (RDN) in Patient 1 showing the ablation catheter placed in the right renal artery at different ablation points (a). Control post-interventional angiogram revealed no procedure-related complication (b).*

DWI, three b-values (50, 800, 2,000 s/mm^2) were measured and used to calculate apparent diffusion coefficient (ADC) maps.

^{23}Na-imaging was performed at a clinical 3T whole-body scanner (Magnetom Tim Trio; Siemens Healthcare) equipped for ^{23}Na-imaging using a double-tuned (^{1}H/^{23}Na) transmit receive array (Rapid Biomedical, Rimpar, Germany) and a 3D density-adapted projection reconstruction sequence (22). ^{23}Na-imaging technique and post-processing were performed as described previously (8). To account for a potential intraday variability of renal sodium concentration, the examinations were performed at the same time on day -1, 1, 30 and 90, respectively, and the patients were asked to abstain from water 4 h prior to the MR examination.

Image analysis. The diffusion-weighted images were assessed by manual segmentation of both kidneys in the apparent diffusion coefficient (ADC) maps of the respective time points. The ADC of the kidneys parenchyma was averaged for both kidneys.

As described previously, reconstructed ^{23}Na-images were evaluated in a 3-dimensional manner choosing planes with the longest, most central view, of each definable corticomedullary complex (consisting of renal cortex and the adjacent medullary

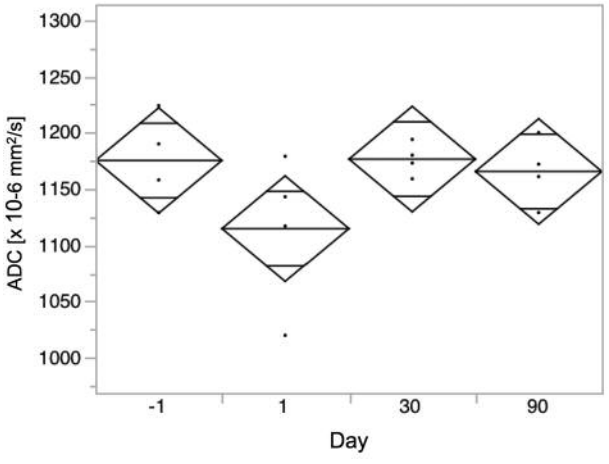

Figure 2. *Diamond plot showing the mean apparent diffusion coefficient (ADC) values over the time course before (Day -1) and after (Day 1, 30, 90) renal denervation (RDN) for both patients. Points represent mean ADC values for individual kidneys.*

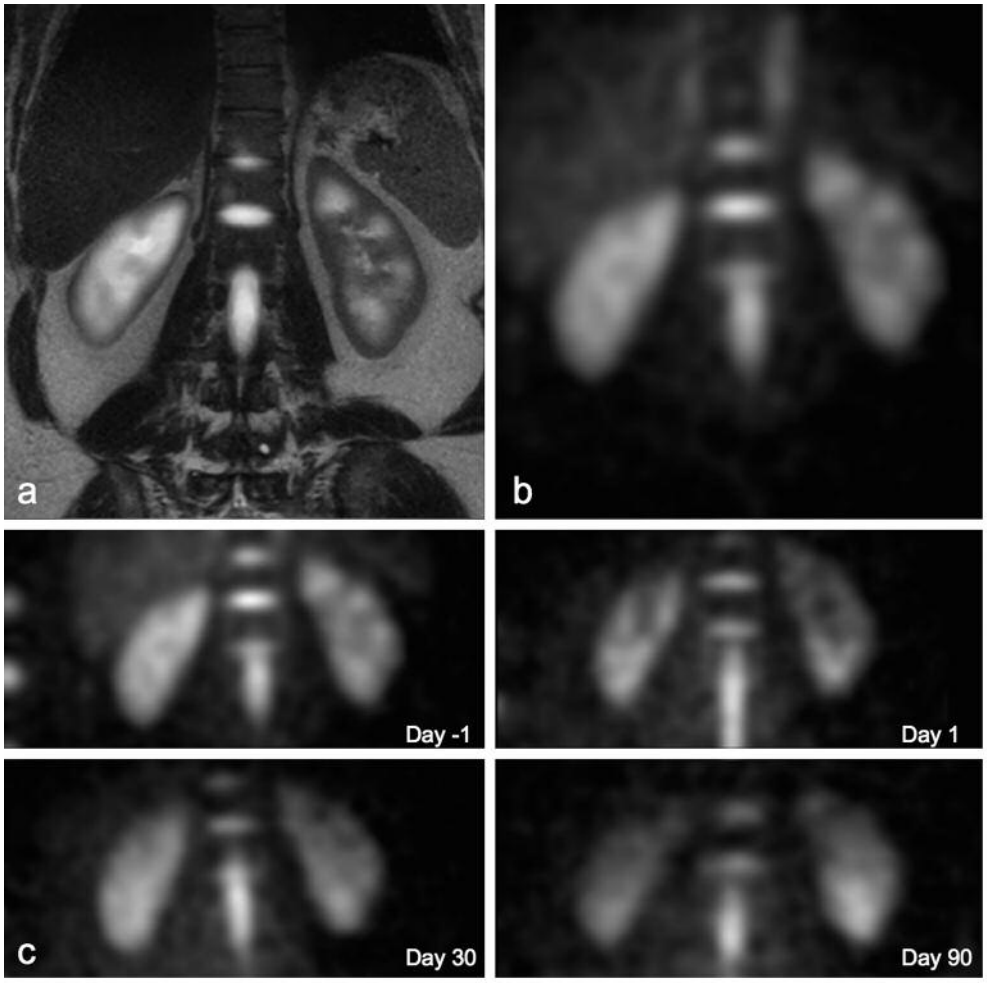

Figure 3. *Image examples of Patient 1 showing (a) a coronal T2w Half Fourier Acquisition Single Shot Turbo Spin Echo (HASTE) overlaid with a ^{23}Na-image to show the morphological relations, (b) a coronal ^{23}Na-image and (c) the ^{23}Na-images over the time course before and after renal denervation (RDN).*

pyramid) (10). Linear regions of interest (ROIs) starting from the cortex and extending in the direction of the pelvicalyceal system were placed with a length of 20 pixels each. Three ROIs per upper, middle and lower portion of both kidneys were evaluated, resulting in a total of 18 measurements per patient and time point. The absolute pixel by pixel values of the ROIs were averaged separately for right and left kidney (6). ^{23}Na-signal-to-noise (SNR) was calculated as the signal intensity divided by the average of the standard deviation of three ROIs selected in a signal-free area (23). For the comparison of the corticomedullary gradients, the SNR values were normalized to the maximum value (set to 1) of the respective ROI (23). The slope of the gradient was calculated as the average difference between two adjacent pixels.

Results

Blood pressure measurements, retinal vessel analysis and SphygmoCor measurements. In both patients reduced office and 24 h RR values were measured after RDN, especially regarding the systolic values (Table I) with a constant RR medication. Before RDN, both patients presented with reduced AVR compared to normative data from the ARIC-Study (24, 25). At day 1 after RDN, retinal AVR slightly decreased in both but returned to baseline levels at day 30, without reaching normal values. In Patient 1 the diameter of retinal arteries presented no change and after a slight reduction the values returned to baseline on day 90 in Patient 2. The SphygmoCor measurement revealed incongruent results with a trend to overall improvement. From a clinical perspective, Patient 1 showed no response to RDN as acceptable blood pressure values were only achieved after an additional antihypertensive drug was added to the medication. In contrast, Patient 2 demonstrated a reduction of both dosage and number of antihypertensive drugs accompanied by a marked improvement in arterial blood pressure.

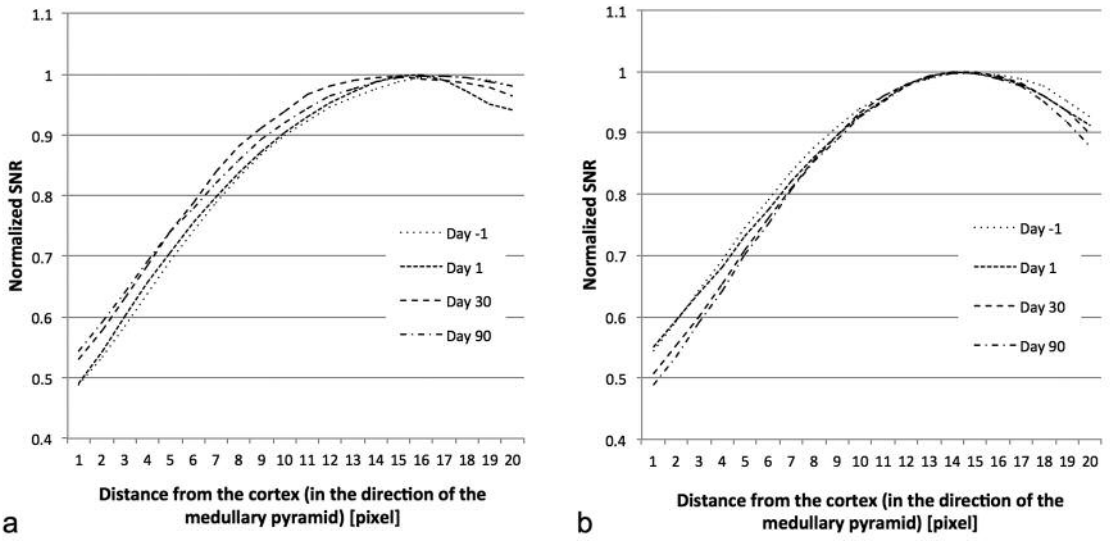

Figure 4. *Chart showing the calculated normalized ^{23}Na-signal-to-noise (SNR) values along the renal corticomedullary axis for both patients (a. Patient 1; b. Patient 2) and for each magnetic resonance (MR) examination (1 day before after renal denervation (RDN); 30 and 90 days after RDN). No relevant changes can be noticed between the corticomedullary gradient.*

MR imaging. Average ADC values did not change after RDN and showed no significant differences between patients and time points (average ADC (all values in 10^{-6} mm^2/s): day -1=1,175, day 1=1,114, day 30=1,176, day 90=1,165; Figure 2).

Mean ^{23}Na-concentration increased alongside the corticomedullary gradient from the cortex to the medulla. The typical slope of the gradient was observed for both patients at all time points and did not change significantly after RDN (Figures 3 and 4). The overall mean slope for the normalized SNR values was 2.8%/pixel for day -1 and 2.9%/pixel for day 1, 30 and 90.

Discussion

Blood pressure control improved moderately in both patients in the follow-up examinations up to 3 months after RDN, whereas retinal vessel analysis, as well as the determined indices of the arterial stiffness, showed incongruent response but remained, in general, stable. Despite the observed decrease of blood pressure and the known diuretic and renin-secretion inhibitory effects of RDN, the ^{23}Na-MRI results showed comparable ^{23}Na corticomedullary gradients prior to and after RDN. In this very limited examination sample, no relation between therapy response and the non-invasively determined ^{23}Na content of the kidneys could be stated.

While initially showing promising results for the therapy of treatment refractory hypertension, the recently published data of the Symplicity HTN3 trial suggested a more critical view on catheter-based renal denervation. Besides the major end-point of blood pressure reduction, a few imaging studies tried to identify local effects of RDN at the kidney. Ott *et al*. recently showed that RDN does not alter renal perfusion, neither directly after RDN nor in a follow-up of 3 months (5). While lowering the central blood pressure, RDN did not affect the auto-regulation of the renal perfusion. Similarly, the intrinsic mechanisms of sodium concentration do not seem to be affected by RDN either. In our study, both patients, who moderately benefited with regard to the RR values, presented no significant changes in ^{23}Na, the corticomedullary gradient or the ADC values after RDN. The major limitation of this technical note is the limited number of patients. With the announcement of the upcoming results of the Symplicity HTN3 trial in January 2014, recruitment for RDN derived from clinical indication was hampered profoundly; consequently, we stopped further inclusion in this study.

Conclusion

In summary, RDN seems to show no effect on renal sodium concentration as measured by MRI and, consequently, ^{23}Na-imaging does not seem to be a reliable marker for potential therapy response.

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