

Renal Denervation: Results of a Single-Center Cohort Study

Renale Denervation: Ergebnisse einer Single-Center Kohortenstudie

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Abstract



Purpose: To investigate the effect of renal denervation on office-based and 24-h ambulatory blood pressure measurements (ABPM) in a highly selective patient population with drug-resistant hypertension.

Materials and Methods: Patients with drug resistant hypertension eligible for renal denervation were included in the study population. Office blood pressure and ABPM were assessed prior to and after renal denervation. To detect procedure related renal or renal artery damage, magnetic resonance imaging (MRI) and angiography (MRA) were performed pre-interventional, one day post-interventional, and one month after renal denervation.

Results: Mean follow-up time between renal denervation and blood pressure re-assessment was 9.5 ± 3.9 months. Between August 2011 and March 2013, 17 patients prospectively underwent renal denervation. Pre-interventional mean office blood pressure and ABPM were $177.3 \pm 20.3/103.8 \pm 20.4$ mmHg and $155.2 \pm 20.5/93.7 \pm 14.5$ mmHg, respectively. Post-interventional, office blood pressure was significantly reduced to $144.7 \pm 14.9/89.5 \pm 12.1$ ($p < 0.05$). ABPM values remained unchanged ($147.9 \pm 20.3/90.3 \pm 15.6$, $p > 0.05$). The number of prescribed antihypertensive drugs was unchanged after renal denervation (4.7 ± 2.0 vs. 4.2 ± 1.2 , $p = 0.18$). No renovascular complications were detected in follow-up MRI.

Conclusion: After renal denervation, no significant decrease in ABPM was observed. These results may indicate a limited impact of renal denervation for drug resistant hypertension.

Key Points:

- ▶ Renal denervation showed no significant effects on 24-h ambulatory blood pressure measurements.
- ▶ A significant decrease in office blood pressure measurements may be explained by a potential detection bias.
- ▶ Renal artery alterations were not observed on follow-up MRI scans.

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Zusammenfassung



Ziel: Erfassung der Blutdruckveränderung nach renaler Denervation in einem hochselektiven Patientenkollektiv mit therapierefraktärer Hypertonie mittels Praxis- und 24-Stunden-Blutdruckmessung.

Material und Methoden: Zwischen August 2011 und März 2013 wurde bei 17 Patienten mit therapierefraktärer Hypertonie eine renale Denervation durchgeführt. Prä- und postinterventionell wurde der Blutdruck mittels Praxisblutdruckmessung und 24-Stundenmessung bestimmt. Zur Detektion von interventionsassoziierten Veränderungen wurden MRT-Untersuchungen der Nieren und Nierenarterien präinterventionell, am Tag nach renaler Denervation und nach einem Monat durchgeführt.

Ergebnisse: Die postinterventionellen Blutdruckmessungen (Praxisblutdruck und 24-Stundenblutdruck) wurden durchschnittlich $9,5 \pm 3,9$ Monaten nach renaler Denervation durchgeführt. Der mittlere Praxisblutdruck sank signifikant von $177,3 \pm 20,3/103,8 \pm 20,4$ mmHg (systolisch/diastolisch) vor renaler Denervation auf $144,7 \pm 14,9/89,5 \pm 12,1$ ($p < 0,05$) nach renaler Denerva-

tion. Der mittlere Blutdruck in der 24-Stundenmessung nahm nicht signifikant von $155,2 \pm 20,5/93,7 \pm 14,5$ mmHg auf $147,9 \pm 20,3/90,3 \pm 15,6$ ($p > 0,05$) ab. Die durchschnittliche Anzahl eingenommener Antihypertensiva nahm nicht signifikant ab ($4,7 \pm 2,0$ vs. $4,2 \pm 1,2$, $p = 0,18$). Komplikationen oder Spätfolgen wurden nicht beobachtet.

Schlussfolgerung: Durch die renale Denervation kommt es nicht zu einer signifikanten Reduktion der prognostisch wichtigen 24 Stundenblutdruckwerte. Diese Ergebnisse deuten auf einen eingeschränkten Nutzen der renalen Denervation bei therapierefraktärer Hypertonie hin.

Introduction

Arterial hypertension is one of the greatest and most serious challenges facing the healthcare system worldwide [1]. It is estimated that approximately one billion people are affected by the disease [2], with 30 million living in Germany alone [3]. Left untreated, arterial hypertension increases the risk for serious cardiovascular events such as stroke, heart attack or heart failure [4]. While optimal drug therapy is available, hypertension is drug-resistant in approximately 5 to 10% of patients [5]. Hypertension is classified as drug-resistant if triple antihypertensive therapy at maximal or maximally tolerated dosage (including at least one diuretic) is unable to elicit consistent blood pressure values of < 140 mmHg systolic and < 90 mmHg diastolic [6]. Among other factors, a hyperactive sympathetic nervous system plays an important role in the development of hypertension [7]. While earlier therapy attempts using surgical sympathectomy in the middle of the 20th century already led to a significant reduction in blood pressure, the side effects were considerable [8]. The blood pressure reduction that was achieved with this surgical procedure was sustained over the entire observation period, which lasted up to 13 years [9]. Since 2009 a new, catheter-based, percutaneous transluminal approach has allowed minimally invasive, selective ablation of the sympathetic nerve fibers of the renal arteries [10]. This procedure is available as an additional therapy option, particularly to patients whose blood pressure could not be sufficiently lowered despite intensive drug therapy. In several studies a decrease in blood pressure following renal denervation in patients with drug-resistant hypertension could be observed [11, 12]. The observations are based primarily on one-time blood pressure measurements performed at doctor's office or a hypertension clinic ("office-based"). This article examines the effect of renal denervation on the average 24-hour ambulatory blood pressure monitoring and office-based blood pressure measurement in a highly selective patient cohort with drug-resistant hypertension. To detect later damage, pre- and post-interventional MRI examinations of the renal arteries were performed.

Material and methods

Patient cohort

The study was approved by the relevant ethics committee. The inclusion criterion was having systolic blood pressure exceeding 160 mmHg as measured at a medical office with

the patient having been on antihypertensive therapy consisting of at least 3 drugs (one being a diuretic). In addition, none of the patients exhibited any sufficient decrease in blood pressure even under treatment with spironolactone. Secondary types of hypertension (e.g. renal or endocrine hypertension) were excluded prior to performing renal denervation. Pre- and post-interventional blood pressure measurements were taken as part of outpatient care. Each patient underwent 24-hour ambulatory blood pressure monitoring prior to and following renal denervation. Persons performing the blood pressure measurements were not blinded with regard to the intervention. Post-interventional office-based blood pressure measurements and 24-hour ambulatory blood pressure monitoring were to be performed after 9 months.

Renal denervation

Renal denervation was performed according to the usual technique. After a femoral access (6F-sheath) was created, a flush angiography of the aorta was performed using DSA (digital subtraction angiography) (contrast agent: Solu-trast® 300, Bracco, Italy). The split renal denervation was then performed guided by repetitive DSA checks using an ablation catheter (Symplicity™, Medtronic, USA), which was introduced into the ostium of the renal artery with the aid of a guide catheter corresponding to the routing of the particular renal artery. Ablation points were arranged in a helical pattern and spaced approximately 5 mm all the way to the ostium of the renal artery. During the entire intervention, each patient was monitored and administered a sedative analgesic by an anesthesiologist. Following renal denervation, patients were administered heparin intravenously for 24 hours with a target PTT of 60 seconds and were on a thrombocyte aggregation inhibitor (aspirin 100 mg/day) for 4 weeks.

MRI examinations

Each patient underwent a MRI examination (Intera 1.5 T, Philips Healthcare, Best, Netherlands) of the kidneys and renal arteries one day prior to and one day following renal denervation. According to the study protocol, another renal artery MRI was performed one month following renal denervation. To detect post-interventional changes in the kidneys and renal arteries, the following sequences were acquired (see Table 1 for sequence parameters): balanced Steady State with Free Precision (bSSFP) coronal and axial, bSSFP with water-selective slice excitation axial, navigator-triggered T2-weighted turbo spin echo sequence with black-blood-inversion coil, multi-phase magnetic resonance imaging (T1-weighted 3D-gradient echo sequence). A weight-adjusted dose of 0.1 mmol per kilogram of body weight (mmol/kg BW) of gadubotrol (Gadovist®, Bayer Healthcare, Germany) was administered as contrast agent.

Statistics

Data analysis was performed using SPSS Statistics 22.0 (IBM, Armonk, NY). A p-value of less than 0.05 was considered indicative of a significant difference. Continuous variables were tested for normal distribution. Patient characteristics are represented according to absolute frequency for categorical variables and according to mean value (\pm standard error) for parametrically distributed variables. A sys-

Table 1 Sequence parameters of the MRI examination protocol. The following sequence parameters were acquired: balanced Steady State with Free Precision (bSSFP) coronal and axial, bSSFP with water-selective slice excitation axial, navigator-triggered T2-weighted turbo spin echo sequence with black-blood-inversion coil, multi-phase magnetic resonance imaging (T1-weighted 3D-gradient echo sequence).

	bSSFP coronal	bSSFP axial	bSSFP axial	black-blood T2 TSE	T1 – 3D-GRE
field of view [mm]	400 × 340	400 × 340	300 × 105	370 × 290	450 × 400
TR [ms]	2.5	2.4	6.6	2000	2.9
TE [ms]	1.26	1.2	3.3	28	0.94
flip angle [°]	65	65	75	90	25
voxel size [mm]					
acquired	1.92 × 1.56 × 6	1.92 × 1.56 × 8	1.25 × 1.25 × 3	1.5 × 1.65 × 3	1.17 × 1.68 × 2.98
reconstructed	1.39 × 1.39 × 6	1.39 × 1.39 × 8	0.63 × 0.63 × 1.5	0.9 × 0.9 × 3	0.88 × 0.88 × 1.49
parallel imaging (SENSE)	no	no	no	yes (SENSE factor 1.5)	yes (SENSE factor 4)
fat suppression	–	–	water-selective excitation	SPIR	–
sequence duration [mm:ss]	00:19	00:36	00:19	04:48	00:47

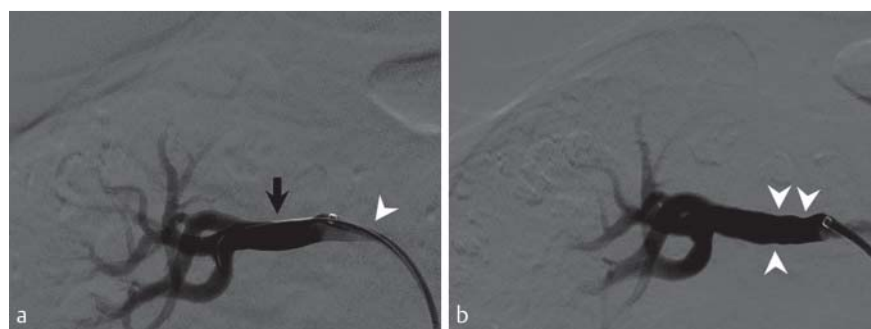


Fig. 1 a Digital subtraction angiography (DSA) of the right renal artery prior to renal denervation. A 6F guide catheter (white arrow) was introduced using a Terumo guide wire (black arrow). b After renal denervation. Wall edema (white arrow) of the renal artery resulting from thermal ablation is clearly visible.

tematic differentiation of two empirical group medians was performed for variables with normal distribution using the t-test for paired random samples and for variables without normal distribution using the Wilcoxon test.

Results

A total of 17 patients (75% (13/17) men, 24% (4/17) women) were prospectively included and underwent renal denervation between August 2011 and March 2013. The mean age at the time of renal denervation was 54.9 ± 10.6 years (Table 2).

For 16 of the 17 patients (94%) ablation was performed on both renal arteries. In the case of one patient (1/17 (6%)) renal denervation was performed on the left side only, since the right kidney had been removed 20 years prior due to pyelonephritis and nephrolithiasis.

An average of 5.8 ± 2.1 ablation points were placed in the right artery, while the figure for the left artery was 4.8 ± 1.4 ($p = 0.09$). The mean drop in impedance was $16.2 \pm 3.4 \Omega$ for the right side and $14.8 \pm 3.0 \Omega$ for the left side ($p = 0.24$). On average 86.5 ± 51.9 ml of contrast agent was consumed.

No clinical or technical complications occurred during renal denervation. DSA performed immediately following renal artery ablation detected edema of the renal artery walls in 9 of 17 (53%). This edema was still present in the final DSA performed at the end of the intervention in 8 of 17 (44%) patients (Fig. 1). Post-interventional MRI showed persistent edema of the renal artery wall one day following intervention in 2 of 17 patients (12%). Follow-up MRIs performed one month following intervention yielded unremarkable findings with regard to both organ damage

Table 2 Baseline parameters for the patient cohort. Data are presented as median \pm standard deviation. Nominally scaled variable are indicated in terms of absolute frequency.

parameter	value
age [years]	54.9 ± 10.6
males	13/17 (76%)
females	4/17 (24%)
body mass index [kg/m ²]	28.6 ± 4.9
creatinine [mg/dl]	1.28 ± 1.10
eGFR [ml/min/1.73m ²]	73.8 ± 41.4

eGFR = estimated glomerular filtration rate

in general and the renal arteries in particular for all patients (17/17, 100%).

Blood pressure measurements (office-based and 24-hour ambulatory blood pressure measurement) were repeated on average 9.5 ± 3.9 months (median 9.7 months) following renal denervation as part of outpatient follow-up care. The 24-hour ambulatory blood pressure monitoring showed no significant drop in systolic and diastolic blood pressure following renal denervation compared to the measurements prior to renal denervation (systolic from 155.2 ± 20.5 mmHg to 147.9 ± 20.3 mmHg and diastolic from 93.7 ± 14.5 mmHg to 90.3 ± 15.6 mmHg; $p = 0.58$ and $p = 0.88$, see Fig. 2).

In contrast, office-based blood pressure measurements taken during follow-up care examinations were significantly reduced compared to the measurements taken prior to renal denervation (systolic from 177.3 ± 20.3 mmHg to 144.7

parameter		prior to renal denervation	following renal denervation	p-value
24-hour ambulatory blood pressure	systolic	155.2 ± 20.5	147.9 ± 20.3	0.58
	diastolic	93.7 ± 14.5	90.3 ± 15.6	0.88
office-based blood pressure [mmHg]	systolic	177.3 ± 20.3	144.7 ± 14.9	<0.01
	diastolic	103.8 ± 20.4	89.5 ± 12.1	0.01
heart rate [beats/min]		71.3 ± 13.1	76.9 ± 13.7	0.41
antihypertensive drugs [n]		4.71 ± 2.00	4.18 ± 1.2	0.18

Table 3 Average blood pressure values and number of antihypertensive drugs taken before and after renal denervation. Data are presented as median ± standard deviation.

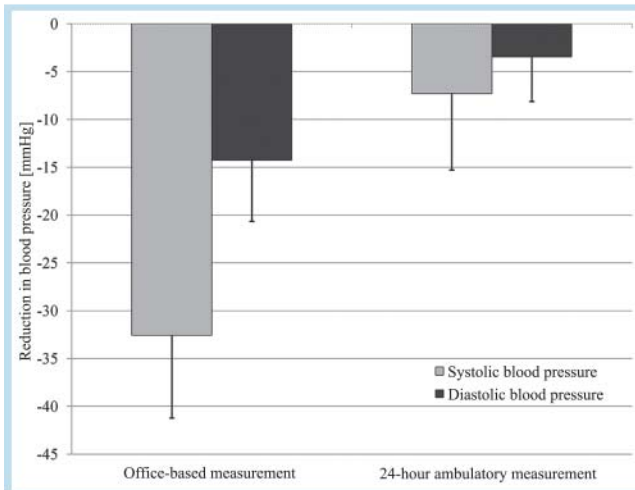


Fig. 2 Median blood pressure reduction according to office-based blood pressure measurement and according to 24-hour ambulatory blood pressure measurement following renal denervation. According to office-based measurement, systolic blood pressure decreased by -32.6 mmHg (95%-confidence interval: -24.0 to -41.2 mmHg) and diastolic blood pressure decreased by -14.3 mmHg (-7.9 to -20.7 mmHg) ($p < 0.01$ and $p = 0.01$, respectively). According to ambulatory monitoring, systolic blood pressure decreased by -7.3 mmHg (0.7 to -15.3 mmHg) and diastolic blood pressure decreased by -3.5 mmHg (1.2 to -8.2 mmHg) ($p < 0.58$ and $p = 0.88$, respectively). The bar graphs represent mean blood pressure reduction (error bars = 95 %-confidence interval).

± 14.9 mmHg and diastolic from 103.8 ± 20.4 mmHg to 89.5 ± 12.1 mmHg; $p < 0.01$ and $p = 0.01$).

The average number of antihypertensive drugs taken by the patients decreased insignificantly following renal denervation from 4.7 ± 2.0 to 4.2 ± 1.2 ($p = 0.18$, [Table 3](#)).

Discussion

24-hour ambulatory blood pressure values are more robust and less influencable than office measurements and constitute, when elevated, an independent risk factor for hypertension-related damage [13]. This can be attributed, for one, to the frequency of the measured values during routine daily stress, which permits better evaluation of the blood pressure profile under therapy [14]. Using 24-hour ambulatory blood pressure monitoring avoids and reveals the true nature of the pronounced fluctuations between single measurements, such as those commonly seen in the case of “white coat” hypertension [15]. Approximately 5 to 10% of patients with elevated blood pressure have what is known as drug-resistant hypertension. For drug-resistant

hypertension as well, only 24-hour monitoring has prognostic validity concerning cardiovascular morbidity and mortality, while office-based blood pressure measurements performed on these patients have no prognostic value [16]. Renal denervation has been a therapy option for patients with drug-resistant hypertension since 2009 [10], with success rates of 84 to 92 % being reported [10, 17]. In a majority of studies, however, treatment was monitored using only office-based blood pressure measurements and not the prognostically more relevant 24-hour ambulatory blood pressure monitoring.

The present study used a highly selective patient cohort (prior to intervention, all patients exhibited no reduction in blood pressure even under spironolactone therapy) to examine to what extent the results of renal denervation are a function of how blood pressure was measured. For this purpose, each patient underwent 24-hour ambulatory blood pressure monitoring as part of their outpatient follow-up care on average 9.5 ± 3.9 months following therapy. In addition, each patient underwent pre-interventional and post-interventional MRI of the kidneys and renal arteries to detect possible organ and vascular damage.

Following renal denervation, systolic blood pressure measured at the medical office decreased significantly in our cohort by an average of -18.4% (systolic: -32.6 mmHg and diastolic: -14.3 mmHg) (9.5 ± 3.9 months following renal denervation). This result is highly consistent with those of other, previously published studies. The non-randomized proof-of-principle Symplicity Hypertension (HTN)-1 observed a decrease in blood pressure of $-24/-11$ mmHg in office-based measurements after a period of 9 months [10]. The randomized, yet non-blinded Symplicity HTN-2 even reported a reduction in office-based blood pressure of $-32/-12$ mmHg in the denervation group 6 months following renal denervation [17].

Interestingly, 24-hour ambulatory blood pressure monitoring during the same period showed only a 4.7% drop in our cohort’s systolic blood pressure during the same period (systolic -7.3 mmHg and diastolic -3.5 mmHg), which does not constitute a statistically significant reduction in blood pressure.

A meta-analysis conducted by Howard et al. [18] examined this discrepancy between blood pressure reduction according to office-based measurement and 24-hour monitoring in both pharmacological studies and renal denervation studies. In pharmacological studies, the reduction in blood pressure according to office measurements and according to 24-hour ambulatory monitoring became more similar as blinding and randomization increased (so-called regression-to-the-mean effect). In fully blinded and randomized studies the reduction in office-based blood pressure is thus

identical to the reduction in 24-hour ambulatory blood pressure. If these results are transferred to the non-randomized/non-controlled denervation studies [10, 17], one could thus expect a blood pressure reduction of approximately 13 mmHg in a randomized and controlled denervation study [18].

This is highly consistent with the results of a subgroup analysis of the Symplicity HTN-2 involving 20 patients who also underwent subsequent 24-hour ambulatory blood pressure monitoring. In this example, blood pressure reduction according to 24-hour ambulatory monitoring was clearly lower than that according to office-based measurement (reduction in blood pressure after 6 months: $-11/-7$ mmHg) [17]. The recently published results of the first randomized and blinded renal denervation study (Symplicity HTN-3) warrant the reevaluation of renal denervation as a therapy option [19]. This study did not achieve its primary and secondary effectivity endpoints (reduction of systolic blood pressure by more than 5 mmHg than that of the control group according to office measurement and 24-hour monitoring, respectively.) However, the reduction in systolic blood pressure in the renal denervation group was only 2.4 mmHg greater than that of the control group after 6 months (according to office-based measurements). The difference was even smaller for 24-hour monitoring (2.0 mmHg).

The doubts surrounding the superiority of renal denervation over optimal drug therapy are also supported by a current study in which a new round of adjusted drug therapy was compared with blood pressure reduction following renal denervation in patients with drug-resistant hypertension [20]. In this cited study, the systolic office blood pressure decreased in the therapy-adjusted group after 6 months by 160 ± 14 mmHg to 132 ± 10 mmHg ($P < 0.01$), while only by 156 ± 13 mmHg to 148 ± 7 mmHg ($P = 0.42$) in the renal denervation group. The study was prematurely discontinued due to ethical concerns [20].

These current results and our own data show that using renal denervation must still be regarded as an experimental procedure and that no clinical benefits have been clearly demonstrated to date.

A possible explanation for the better blood pressure reduction results in the aforementioned studies [10, 12, 17] may be, in addition to the regression-to-the-mean-effect, the so-called detection bias or the absence of a control group. Because the study presented in this article was likewise not blinded, the discrepancy between blood pressure reduction according to office-based measurement and 24-hour ambulatory monitoring is primarily caused by a detection bias, i. e., by an incorrectly positive evaluation of office blood pressure on the part of the examiner, and by the regression-to-the-mean-effect. Future studies must therefore define 24-hour blood pressure monitoring as primary study endpoint. Renal denervation is a safe and easy-to-perform procedure. It was performed on our entire patient cohort without any complications occurring in the course of the procedure. The post-interventional MRI follow-up examinations performed on the day after renal denervation revealed intramural, ablation-induced edema of the renal artery wall in only two patients. Follow-up care examinations yielded unremarkable findings in this regard for all patients (17/17, 100%). Overall, our results are consistent with the likewise

very low rate of complications reported in previously published studies [10, 11, 17, 19]. However, it should be noted that de novo renal artery stenosis following renal denervation has been reported [21, 22].

The small patient cohort is a limitation of the present study. On the other hand, the study was composed of a highly selective group of "truly" drug-resistant hypertension patients for whom even spironolactone therapy did not bring about sufficient reduction in blood pressure. Another limitation is the absence of a control group. This allowed only interindividual comparison of the post-interventional measurements. Because changes to antihypertensive medication were not systematically recorded, it is not possible to make any statements on the impacts therapy modification (e. g. in the case of switching a group of active substances). The present study demonstrated no significant reduction in 24-hour ambulatory blood pressure values following renal denervation. Renal denervation should therefore not be offered as a routine procedure at this point, and its use should currently be limited to clinical studies.

Clinical Relevance of the Study

- ▶ 24-hour ambulatory blood pressure monitoring performed as a follow-up to renal denervation revealed no significant reduction in blood pressure.
- ▶ No complications were observed during the procedure and no later damage to the kidneys or renal arteries was detected in the long-term follow-up MRI examinations.
- ▶ Currently, renal denervation should not be performed outside clinical studies.

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