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Individual-patient visit-by-visit office and ambulatory blood pressure measurements over 24 months in patients undergoing renal denervation for hypertension ☆

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ABSTRACT

Background: Renal denervation (RDN) is a promising treatment option in addition to medical antihypertensive treatment in patients suffering from resistant hypertension. Despite the growing interest in RDN, only few long-term results are published so far.

Methods: We systematically investigated the effects of RDN on ABPM in a consecutive series of patients with resistant hypertension out to 24 months. Office BP measurements and ABPM assessment were offered at 3, 6, 12 and 24 months. The patients with an average systolic BP reduction of more than 10 mm Hg in office BP 6 months after RDN were classified as responders. Additional to this classical responder concept, we categorized response to RDN by an individual-patient visit-by-visit evaluation of office BP and 24-hour-BP, separately.

Results: We included 32 patients. In 21 patients (65.6%) we found a mean systolic BP reduction >10 mm Hg in office BP six months after RDN. These patients were classified as responders. In responders, mean office BP dropped from 175.3 ± 15.9/96 ± 14.2 mm Hg to 164.8 ± 24.4/93.2 ± 10.4 mm Hg ($p = 0.040/p = 0.323$) and mean 24-h BP in ABPM decreased from 146.8 ± 17.0/89.1 ± 11 mm Hg to 136.8 ± 15.0/83.2 ± 10.7 mm Hg after 24 months ($p = 0.034/p = 0.014$).

Additionally, we performed a visit-by-visit evaluation of all patients and results were divided in larger-than-median and smaller-than-median response. By this evaluation, we found a high variation of office BP reductions and the 24-hour BP results demonstrated a significant BP reduction in patients with larger-than-median response, which sustained over the 24 months of follow-up.

Conclusions: In contrast to the observed variation of office BP measurements, ABPM demonstrated a reproducible and sustained significant BP reduction in patients with larger-than-median response to RDN.

1. Introduction

Increased cardiovascular morbidity and mortality turn resistant hypertension into an important public health concern [1–4]. Over-activity of the sympathetic nervous system is a major contributor to maintenance and progression of hypertensive disease [4–6]. In this context, new treatment options, like trans-femoral sympathetic renal nerve denervation (RDN) seem to be a great promise for better blood pressure (BP) control [6–8].

Several publications on long term efficacy of RDN have shown significant BP reductions in different study cohorts with a follow-up from 12 to 36 months [9–11]. However, the treatment response in these studies has mostly been evaluated by the use of office BP measurements and only a small number of patients achieved the 12-months, the 24 months and the 36 months of follow-up (47 of 82, 18 of 138, and 88 of 153 patients), respectively [9–11].

Compared with office BP measurements, ambulatory blood pressure measurement (ABPM) is known to be superior in predicting cardiovascular events in patients with hypertension [12–15]. In addition, ABPM provides serial BP measurements and information on different subsets of BP, like day- and night-time BP, resulting in a high reproducibility and circadian distribution of BP levels, respectively [16,17]. Therefore,

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treatment evaluations in clinical trials and also in clinical practice, become much more efficient by the use of ABPM [16–19]. Despite the growing interest in RDN, only few long-term data about BP changes in ABPM after RDN are published so far [20].

The recently published Symplicity HTN-3 trial, failed to achieve its primary efficacy end point: no significant BP reductions were found in the treated patients compared with the control group in this randomized controlled trial [21]. Thus, the Symplicity HTN-3 trial fanned the flames of the already fervid discussion on the sense or non-sense of this new and invasive treatment option for arterial hypertension.

Therefore, we systematically investigated the long-term effects of RDN on BP levels in ABPM in addition to office BP measurements for 24 months in a consecutive series of patients with resistant hypertension by an individual-patient visit-by-visit evaluation.

2. Methods

In this prospective observational trial, patients with resistant hypertension were treated with RDN. Resistant hypertension was defined by a mean systolic office BP > 160 mm Hg (>150 mm Hg in patients with diabetes) after three measurements in our outpatient office. All patients had to be on at least three antihypertensive drugs including one diuretic and secondary causes of hypertension had to be ruled out prior to RDN.

Exclusion criteria were an age below 18, pregnancy and an estimated glomerular filtration rate of less than 45 ml/min per 1.73 m^2 body surface area. The eligibility criteria for renal artery anatomy, as evaluated by MRI angiography before the procedure, were a diameter of more than 4 mm and a length of more than 20 mm.

The study was performed in accordance with the Declaration of Helsinki and written informed consent was obtained from all patients. The local ethic committee approved the study.

For RDN, the Symplicity™ RDN Catheter System (Medtronic Inc., Minneapolis, MN, USA) was used via right femoral approach in all patients. Depending on renal artery anatomy, a maximum of 8 ablations were performed in each renal artery, respectively. Follow-up visits were scheduled after 3, 6, 12 and 24 months. At all visits, ABPM was performed using the "Del Mar Reynolds Medical ABPM System" (Version 2.08.005) in addition to the routine office BP measurements. Devices were preset from 6:00–21:45 defined as day-time (readings every 15 min) and from 22:00–5:30 as night-time (readings every 30 min). The patients were told to follow their usual activities during the monitoring. The arm cuff was placed on the non-dominant upper arm and patients were instructed to steady their arm during each measurement.

The BP response to RDN was defined as the primary endpoint. Therefore, the patients with an average systolic BP reduction of more than 10 mm Hg in office BP 6 months after RDN were classified as responders to RDN. Additional to this classical responder concept, we categorized the response to RDN by an individual-patient visit-by-visit evaluation of office BP and 24-hour-BP, separately. Therefore, the BP differences to the median at each visit were evaluated in all patients. The distribution of these data was drawn as several graphs with two curves for above-median and below-median changes, each starting at a different follow-up time-point.

3. Statistical methods

Statistical analysis was performed using the SPSS 17.0 software (SPSS Inc., Chicago, IL). Data were presented as mean ± standard deviation. For comparisons of BP measurements at each visit, a paired t-test was performed. Calculations with a low number of patients were also proofed by the use of non-parametric tests. A two-sided alpha level of 0.05 was considered as statistically significant. The influence of antihypertensive medication on BP reductions was evaluated by ANOVA analysis and all data were analyzed by per protocol approach.

4. Results

Between June and December 2010, 32 patients underwent RDN at our institution. No peri-procedural complications occurred. The patients' characteristics are illustrated in Table 1.

In all patients, the office BP decreased from 168.8/91.6 mm Hg to 147.4/83.3 mm Hg after 6 months ($p < 0.001/p = 0.005$; for a difference between the baseline and 6-month follow-up), respectively. However, the office BP then increased again to 167.5/96.2 mm Hg 24 months after RDN ($p = 0.77/p = 0.11$; for a difference between the baseline and 24-month follow-up). Figs. 1 and 2 illustrate the course of the office BP and of the 24-hour BP values.

Table 1
Baseline characteristics.

Sex (female)	15	46.9%
Age (years)	18–59	34.4%
	60–69	40.6%
	>70	25.0%
Co-morbidities	CAD	46.9%
	DM	28.1%
	Hyperlipidemia	62.5%
	CVA (history of)	6.3%
	PAD	0%

Patients' baseline characteristics; n = 32; CAD: coronary artery disease; DM: diabetes mellitus; CVA: cerebro-vascular accident, PAD: peripheral artery disease.

Six months after RDN, we found a mean systolic office BP reduction of more than 10 mm Hg in 21 patients (65.6%). These patients were classified as responders.

In contrast, a steady increase in the mean office BP was found in non-responders during the further follow-up period.

In this group, the mean office BP decreased from 175.3/96 mm Hg at baseline to 140.2/81.9 mm Hg after 6 months ($p < 0.001/p < 0.001$; for a difference between the baseline and 6-month follow-up) and then increased again to 164.8/93.2 mm Hg after 24 months but remained significantly lower than at baseline ($p = 0.04/p = 0.32$; for a difference between the baseline and 24-month follow-up).

The responders mean 24-hour-BP was 146.8/89.1 mm Hg at the baseline and decreased to 141.3/84.8 mm Hg after 6 months ($p = 0.095/p = 0.014$; for a difference between the baseline and 6-month follow-up) and to 136.8/83.2 mm Hg after 24 months ($p = 0.034/0.014$; for a difference between the baseline and 24-month follow-up).

Mean daytime-BP in responders was 149.5/91.5 mm Hg at baseline and dropped down to 138.0/84.4 mm Hg ($p = 0.017/p = 0.007$; for a difference between the baseline and 24-month follow-up) while the mean night-time BP decreased from 138.2/80.9 mm Hg to 133.5/77.9 mm Hg ($p = 0.22/p = 0.13$; for a difference between the baseline and 24-month follow-up) after 24 months.

Additional to the classical responder concept, the BP differences to the median at each visit were evaluated in all patients. For each follow-up time-point, the BP differences in systolic office BP and 24-hour BP were analyzed for larger-than-median and smaller-than-median response. These analyses are illustrated in panels with both, the larger-than-median and the smaller-than-median response-curves, respectively, as displayed in Figs. 3 and 4.

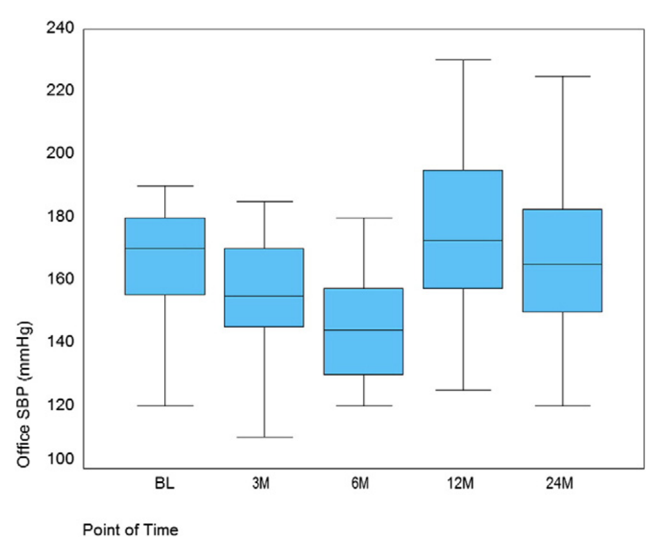

Fig. 1. Boxplot: changes in office BP in absolute values (n = 32). SBP systolic blood pressure.