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Impact of renal sympathetic denervation on home blood pressure monitoring in well defined patients with resistant hypertension

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ABSTRACT

Background: Catheter-based percutaneous renal denervation therapy (RDN) is a controversially discussed treatment-strategy for patients with resistant arterial hypertension. Home blood pressure monitoring (HBPM) is superior to office blood pressure (OBP) measurements documenting effects of drug or interventional therapy and for predicting cardiovascular morbidity and mortality. We therefore aimed at comparing effects of RDN on OBP and HBPM.

Methods: 28 patients with resistant hypertension were studied; 21 patients (29–85 years, median 67 years, 5.4 ± 1.3 antihypertensive drugs) were included into the treatment arm and 7 patients (37–70 years, median 68 years, 5.1 ± 2.2 antihypertensive drugs) served as controls. RDN was performed with a Medtronic™ radiofrequency catheter-ablation-system. For OBP and HBPM measurements patients were followed up to 6 months. For controls, a mean of approximately 378 measurements in 167 ± 13.5 days was included into analysis. In RDN patients follow-up was 157.7 ± 61.8 days with a mean of approximately 323 ambulatory measurements. A mean for each week was calculated.

Results: In controls, no significant change of OBP was observed (baseline: systolic 162.2 ± 11.6 mm Hg vs. 6 months: systolic 162.8 ± 22.9 mm Hg; $p > 0.05$). Accordingly, HBPM values didn't change (baseline: systolic 161.2 ± 15.1 mm Hg vs. 6 months: systolic 155.8 ± 24.6 mm Hg, $p > 0.05$). In RDN patients a significant reduction of OBP (baseline: systolic 169 ± 12.5 mm Hg vs. 6 months: systolic 150.6 ± 19.2 mm Hg, $p < 0.01$) and HBPM (baseline: systolic 156.2 ± 12.9 mm Hg vs. 6 months: systolic 139.7 ± 10.2 mm Hg, $p < 0.001$) was observed.

Conclusion: In patients with resistant hypertension RDN significantly reduced HBPM and OBP already one week after treatment.

1. Introduction

Arterial hypertension is a widespread disease and an important cardiovascular risk factor [1–2]. [3–5]. Approximately 10% of hypertensive patients are suffering from resistant arterial hypertension where therapeutic targets are not met [6–7]. Therefore resistant arterial hypertension was defined as a remaining systolic blood pressure (SBP) ≥140 mm Hg despite an antihypertensive treatment with at least three different drugs including one diuretic [8]. The pathophysiology is complex and remains, at least in part, unclear. It is known that the central nervous system is linked and communicates with efferent and afferent renal sympathetic nerve fibers that contribute to the development and perpetuation of hypertension.

Several interventional approaches to control resistant hypertension exist. RDN is one of these approaches reducing central sympathetic activity [9]. RDN uses radiofrequency energy intercepting afferent and efferent renal sympathetic nerves. In treated patients, RDN showed a significant reduction of OBP up to 36 months [10–12] as well as 24 hour ambulatory blood pressure measurements (ABPM) up to 24 months [13]. Furthermore, RDN improved central pressures and arterial stiffness [14–15]. In contrast to previously published promising data [9, 12,16] the Symplicity HTN-3 study [17] – which was the first multicenter, randomized trial – didn't show a significant reduction of systolic blood pressure in the 24 hour ABPM compared to a control group treated with a sham procedure [18].

HBPM is recommended in the management of hypertension since it e.g. excludes the white coat effect and might help improve hypertension control [19]. Furthermore out of office measurements are stronger

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related to hypertension-induced organ damage than OBP [3,20–29]. However, the already published Symplicity HTN-3 focused only on OBP and as a secondary endpoint on 24 h-ABPM [17–18]. Taken together, it is of great importance to demonstrate the effects of RDN on HBPM. For this reason, we addressed the question whether RDN with its known reduction of peripheral blood pressures and improvement of central blood pressures [14,30] might also affect HBPM measurements.

Finally since now it remained unclear, when effects after the RDN procedure might start independently of the OBP or 24 h-ABPM. In the present study, we therefore determined the beginning of a significant blood pressure reduction by using HBPM besides the effects on office blood pressure.

2. Methods

2.1. Study design and patients

All patients had to fulfill the following inclusion criteria [31–32]: I) age over 18 years; II) peripheral office SBP of at least 150 mm Hg at screening; III) stable treatment with three or more antihypertensive drugs in maximum tolerable doses of different classes, including diuretics. Exclusion criteria were the following: I) an estimated glomerular filtration rate (GFR) of less than 45 mL/min per 1.73 m^2; II) substantial valvular heart disease, III) pregnancy or planned pregnancy during the study, IV) history of myocardial infarction, unstable angina, or cerebral vascular event in the previous six months, or V) significant renal artery stenosis and/or previous renal artery intervention. Additionally, secondary hypertension including e.g. obstructive sleep apnea and pseudo-resistance were extensively ruled out. During the screening process, each patient was asked to start with a blood pressure logbook for documentation. The screening visit was two weeks before RDN. 35 patients fulfilled the inclusion criteria. 21 patients were treated with RDN while 7 served as controls. The other 7 patients were not included, because 2 documented HBPM insufficiently, 1 didn't appear to the date of treatment and 4 patients withdrew the written consent. At baseline visit, blood pressure was measured two days before treatment and documented as baseline, which was taken for statistical reference of blood pressure follow-ups. Routine follow-up visits were scheduled as per protocol at one month (+30 days), three months (+90 days) and six months (+180 days) after inclusion. The study was approved by the local ethic committee (AZ 10-211). Before enrollment each patient provided written informed consent.

2.2. Procedure and follow-up

All ablations were performed by two experienced operators. After preparing the access a standard endovascular technique was selected via the right femoral artery. Thereafter the interventionalist probed the renal artery with the ablation catheter, advanced it into the vessel and connected the catheter system to a radiofrequency generator (Medtronic). Applying a maximum of six ablation points per renal artery using a maximum power of 8 W at each single point the procedure was performed by retracting the catheter from the distal to the proximal part of the artery. The second artery was treated accordingly. Unfractionated heparin was applied with an activated clotting time of >250 s. Patients were asked to avoid any change of baseline doses of anti-hypertensive treatment unless judged medically urgent. This was described as any relevant changes in blood pressure associated with signs or even symptoms of severe hypo- or hypertension. As defined by protocol all patients were asked for follow-up visits at one, three and six months after the procedure. These follow-up visits included assessment of adverse events and current medication, measurements of OBP as well as collecting data of the blood pressure pass. Measurements of OBP were done according to protocol-specified guidelines based on Standard Joint National Committee VII, European Society of Cardiology, and European Society of Hypertension recommendations [3] and with an automatic oscillometric Omron HEM-705 monitor (Omron Healthcare, Vernon Hills, IL, USA).

2.3. Endpoints

1. Changes of HBPM from baseline to follow-up. 2. Changes of OBP. According to the relevant studies in the field response was defined as a reduction of office SBP of ≥10 mm Hg [12,32].

2.4. HBPM and blood pressure logbook

All patients used fully automated oscillometric upper arm devices that were approved by the German Hypertension League (DHL e.V.). For a detailed documentation patients were asked to measure and report the blood pressure values on a daily basis, i.e. at least twice per day under the same standard conditions. Patients were trained according to the guidelines for blood pressure measurement of the ESH/German, Hochdruckliga [3,33] and the practice guidelines for home blood pressure monitoring of the ESH [19]. Measurements were performed in the morning within 1 h after waking up, after urinating, before morning antihypertensives, before breakfast and after at least 5 min of rest in a sitting position as well as at bedtime after at least 5 min of rest in a sitting position. A patient specific logbook contained also a detailed guideline-based manual. The logbooks were copied at each follow-up visit and immediately entered in our database manually.

2.5. Statistical analysis

The week prior to the ablation served as reference point. “Baseline” was used as the reference point for the OBP. The HBPM as well as the OBP were compared by a paired t-test during the follow-up. ANOVA on ranks (RANOVA) was applied where applicable comparing both groups. All data are shown as mean ± standard deviation (SD) if not stated otherwise. A p-value of <0.05 was defined as statistically significant. All statistical analyses were performed with SPSS statistical software (SPSS 19 Inc., Chicago, USA). Figures as well as tables were created by SigmaPlot 8.0 (Systat Software Inc., San Jose, USA) and edited by CorelDraw 11.0 (Corel Inc., Mountain View, USA).

3. Results

3.1. Baseline characteristics

After screening 35 patients fulfilled the inclusion criteria and 28 of them were finally included (flow-chart Fig. 1). Baseline characteristics for the RDN (TG) as well as control group (CG) are shown in Table 1. One patient of the TG refused to complete the follow-up at 6 months. This patient's data were excluded from statistical analysis for this time point. Furthermore data of the blood pressure logbook that were missing at any follow-up were excluded from analysis for this time point.

There were no statistical differences for number of measurements, number of days or weeks between TG and CG (analyzed weeks of TG included into statistics: 22.5 ± 8.8 vs. CG 23.8 ± 1.9, p ~ 0.754; analyzed days: TG 157.7 ± 61.8 vs. CG 166.6 ± 13.5, p ~ 0.754; blood pressure measurements: TG 322.9 ± 158.5 vs. CG 377.8 ± 71.8 single measurements, p ~ 0.462).

3.2. RDN improves systolic and diastolic blood pressures in the OBP

3.2.1. OBP measurements — lowering of systolic as well as diastolic blood pressure

In the TG, office SBP was reduced significantly from 169 ± 12.5 mm Hg by approximately 6.3% after one month ($p < 0.05$) and by 11.9% and 10.9% after three and six months, respectively ($p < 0.01$, Table 2, Fig. 2A). Office SBP didn't change in the CG. Peripheral diastolic blood pressure (DBP) showed a trend to improvement at one month