Long-Term Effects of Renal Denervation on Blood Pressure Burden in Patients with Resistant Arterial Hypertension

Alexander Nahler1*, Thomas Lambert1, Christian Reiter1, Hermann Blessberger1, Jürgen Kammler1, Alexander Kypta1, Miklos Rohla2, Thomas W Weiss2, Kurt Huber1 and Clemens Steinwender1

1Department of Cardiology, Kepler University Hospital Linz, Austria, Europe
2Cardiology and Intensive Care Medicine, Wilhelminen Hospital, Vienna, Austria, Europe

*Corresponding author: Alexander Nahler, Department of Cardiology, Kepler University Hospital Linz, Austria, Tel: 73278066220; Fax: 73278066205; E-mail: alexander.nahler@kepleruniklinikum.at

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Abstract

Background: Catheter based ablation of nerves in the adventitia of renal arteries (renal denervation) by the use of radiofrequency energy can reduce blood pressure levels in patients with resistant arterial hypertension. Blood pressure burden (BPB), defined by the proportion of elevated blood pressure values during day and night time is associated with increased cardiovascular morbidity and mortality. We investigated the long-term effects of renal denervation on blood pressure burden out to 12 months.

Methods: Patients suffering from drug-resistant arterial hypertension (mean systolic office BP>160 mmHg) were treated by renal denervation after exclusion of secondary causes of hypertension. Additionally, ambulatory blood pressure measurement was performed at baseline and after 6 and 12 months, respectively. Patients were classified as responders, if the 24 hours average systolic blood pressure dropped by ≥5 mmHg at the 6 months-follow-up. BPB was defined by the proportion of systolic/diastolic BP values ≥135/85 mmHg during day time and ≥120/70 mmHg during nighttime.

Results: Six months after renal denervation, 41 patients (51.9%) were classified as responders. In these patients, mean systolic/diastolic 24 hours BP reductions were -17.2±15.9/-9.0±11.6 mmHg (p<0.0001/p<0.0001) after 12 months. The mean systolic/diastolic Blood pressure-burden BPB at baseline was 75.6%/57.1% during day time and 100%/62.5% during night time and decreased to 38.9%/26.8% (p<0.001/p<0.001) at day time and 57.1%/20.0% (p<0.001/p<0.001) at nighttime 12 months after renal denervation.

Conclusion: The pronounced improvement of BPB in responders to renal denervation may be an important clinical component of this interventional treatment for arterial hypertension.

Keywords: Blood pressure burden; Renal denervation; Resistant hypertension

Introduction

Sympathetic overdrive has been shown to be a major contributor to the development and progression of arterial hypertension [1-3]. New interventional treatment options, like trans-femoral ablation of sympathetic nerves adjacent to the wall of renal arteries were subsequently introduced to the market [4-9]. After publication of the Symplicity HTN-3 trial, which failed to achieve its primary efficacy end point, a discussion on the efficacy of renal denervation (RDN) emerged [10].

Most clinical trials on the effect of RDN on blood pressure (BP) changes so far were focused on office based BP measurements [4-8]. However, ambulatory blood pressure measurement (ABPM) provides serial BP measurements and information on different subsets of BP, like day- and night time BP, resulting in a high reproducibility and the possibility to evaluate circadian distribution of BP levels, respectively [11,12]. It could be shown that by the use of ABPM, treatment evaluations in clinical trials as well as in clinical practice become more efficient and reliable [11-14].

In addition, blood pressure burden (BPB), based on the proportion of elevated BP values during day- and night time, as obtained by ABPM, is associated with increased cardiovascular morbidity and mortality [14-16]. We investigated the long-term effects of RDN on BPB in a consecutive series of patients undergoing RDN for resistant arterial hypertension.

Material and Methods

Patients with drug-resistant arterial hypertension-defined by a mean systolic office BP>160 mmHg (>150 mmHg in patients with diabetes) after three consecutive measurements in our outpatient office were referred for RDN. All patients were
treated with at least three antihypertensive drugs including a diuretic, unless this class of drug was not tolerated, which was rarely the case. Secondary causes of hypertension were ruled out prior to RDN according to common renal artery anatomy, as evaluated by MRI-angiography or, if contraindicated, CT-angiography before the procedure, were a diameter of >4 mm and a treatable length of >20 mm of both renal arteries.

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 TM RDN Catheter System (Medtronic Inc., Minneapolis, USA) was used via a right femoral approach in all patients. Depending on renal artery anatomy, a maximum of 10 circumferential ablation points were performed in each renal artery. Follow-up visits were scheduled after 6 and 12 months. Before RDN (baseline) and at both follow-up 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 minutes) and from 22:00-5:30 as night time (readings every 30 minutes). Mean day and night time BP levels were calculated by the system based on these settings. 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.

Changes in BPB were defined as the primary endpoint, whereas BP response, as obtained by ABPM, was investigated as the secondary endpoint.

Statistical Analysis

Discrete characteristics are expressed as frequency counts and percentages, and differences between treatment groups were determined by the Chi-square test or the Fisher’s exact test, where appropriate. Continuous, normally distributed variables are expressed as means with standard deviations, whereas non-normally distributed characteristics are expressed as medians. Differences were examined using the student’s t-test or the Mann-Whitney test for comparisons between responders and non-responders, where appropriate. A repeated measures ANOVA with post-hoc testing was used to compare baseline and follow-up 24 hours ABPM blood pressure measurements.

The Friedman test was used for comparisons of baseline and follow-up BPB at 6 and 12 months, as these data were non-normally distributed. In case of a significant Friedman test at a p-value of ≤ 0.05, the Wilcoxon test was used as post-hoc test to determine the significance when comparing baseline data with the individual time points (6 and 12 months follow-up).

According to the common definition in the available literature, patients were classified as responders to RDN, if average systolic BP in ABPM dropped by ≥ 5 mmHg 6 months after RDN and as non-responders in case of a systolic BP reduction < 5 mmHg. [10]

BPB was defined as the proportion of systolic/diastolic BP values ≥ 135/85 mmHg during day time and ≥ 120/70 mmHg during nighttime. The level of significance used for all tests was a two-sided p-value of 0.05. The Software Package for Social Sciences Version 19 (SPSS Inc., Chicago, IL, USA) was used for all statistical calculations.

Results

RDN was performed in 79 patients (female: 46.8%; median age: 66 years). Peri-procedural complications were not observed. During RDN, 5.7 ± 1.1 ablation points were performed in the right renal artery and 5.4 ± 1.1 ablation points in the left renal artery, respectively, with an overall mean number of 10.7 ± 2.2 per patient. There was no significant difference in the number of ablation points between responders (10.7 ± 1.7) and non-responders (10.8 ± 2.8, p=0.88). Patients’ characteristics are illustrated in Table 1 and Table 2. Stratification the patient collective, showed a significantly higher prevalence of treatment with renin-inhibitors in responders at baseline. However, there was no significant difference in drug therapy after 12 months, as shown in Table 3.

Table 1 Baseline characteristics.

| Baseline Characteristics | All (n=79) | Responder (n=41) | Non responder (n=38) | p-value |
|--------------------------|-----------|-----------------|---------------------|---------|
| Demographics             |           |                 |                     |         |
| Age ≤ 59                 | 27 (34.2%)| 12 (29.3%)      | 15 (39.5%)          | 0.4     |
| Age 60-69                | 31 (39.2%)| 19 (46.3%)      | 12 (31.6%)          |         |
| Age ≥ 70                 | 21 (26.6%)| 10 (24.4%)      | 11 (28.9%)          |         |
| Gender (female)          | 37 (46.8%)| 18 (43.9%)      | 19 (50%)            | 0.59    |
| Comorbidities            |           |                 |                     |         |
| CAD                      | 24 (30.4%)| 11 (26.8%)      | 13 (34.2%)          | 0.48    |
|                  | All (n=79) | Responder (n=41) | Non responder (n=38) | p-value |
|------------------|-----------|------------------|----------------------|---------|
| **PAD**          | 3 (3.8%)  | 2 (4.9%)         | 1 (2.6%)             | 1*      |
| **CVA**          | 9 (11.4%) | 5 (12.2%)        | 4 (10.5%)            | 1*      |
| **DM**           | 18 (22.8%)| 8 (19.5%)        | 10 (26.3%)           | 0.47    |
| **Hyperlipidemia**| 45 (57%) | 25 (61%)         | 20 (52.6%)           | 0.45    |

**Renal Function Classification (eGFR, ml/min)**

|         | >90       | 60-90      | 45-60     | 30-45     | 15-30     | <30       | p-value |
|---------|-----------|-----------|-----------|-----------|-----------|-----------|---------|
| >90     | 25 (31.6%)| 14 (34.1%)| 11 (28.9%)|           |           |           | 0.62    |
| 60-90   | 39 (49.4%)| 19 (46.3%)| 20 (52.6%)|           |           |           | 0.58    |
| 45-60   | 13 (16.5%)| 8 (19.5%)  | 5 (13.2%) |           |           |           | 0.55*   |
| 30-45   | 2 (2.5%)  | 0 (0%)     | 2 (5.3%)  |           |           |           | 0.23*   |
| 15-30   | 0 (0%)    | 0 (0%)     | 0 (0%)    |           |           |           |         |
| <30     | 0 (0%)    | 0 (0%)     | 0 (0%)    |           |           |           |         |

**Renal Function Parameter (Creatinin: mg/dl; eGFR: ml/min)**

|                    | Mean creatinin±SD | Mean eGFR±SD  | p-value |
|--------------------|-------------------|---------------|---------|
|                    | 0.95 ± 0.26       | 0.93 ± 0.25   | 0.56    |
|                    | 0.96 ± 0.26       | 78.1 ± 21.6   |         |

Table 2 Ablation points.

| Ablation points | All (n=79) | Responder (n=41) | Non responder (n=38) | p-value |
|-----------------|-----------|------------------|----------------------|---------|
| Mean number+SD  | 10.72 ± 2.24 | 10.68 ± 1.65  | 10.76 ± 2.76          | 0.88*   |
| Minimum         | 5         | 8                | 5                    |         |
| Maximum         | 20        | 16               | 20                   |         |

Number of ablation points in the course of renal denervation; *t-Test.

Table 3 Medication at baseline and after 12 months.

| Medication at baseline | All (n=79) | Responder (n=41) | Non responder (n=38) | p-value |
|------------------------|-----------|------------------|----------------------|---------|
| Number of drugs        | 3.78 ± 1.21 | 3.85 ± 1.13     | 3.71 ± 1.29           | 0.60    |
| ACE-Inhibitor          | 18 (22.8%)  | 9 (22%)          | 9 (23.7%)             | 0.85    |
| AT II receptor-blocker | 24 (30.4%)  | 10 (24.4%)       | 14 (36.8%)            | 0.23    |
| Renin-Inhibitor        | 41 (51.9%)  | 27 (65.9%)       | 14 (36.8%)            | 0.01    |
| Aldosterone-antagonist | 11 (13.9%)  | 5 (12.2%)        | 6 (15.8%)             | 0.75*   |
| Beta-blocker           | 61 (77.2%)  | 32 (78%)         | 29 (76.3%)            | 0.85    |
| Alpha-blocker          | 13 (16.5%)  | 9 (22%)          | 4 (10.5%)             | 0.23*   |
| Ca**-blocker           | 41 (51.9%)  | 22 (53.7%)       | 19 (50%)              | 0.75    |
| Diuretics              | 69 (87.3%)  | 38 (92.7%)       | 31 (81.6%)            | 0.14    |
| Others                 | 12 (15.2%)  | 5 (12.2%)        | 7 (18.4%)             | 0.54*   |

| Medication after 12 months | All (n=79) | Responder (n=41) | Non responder (n=38) | p-value |
|---------------------------|-----------|------------------|----------------------|---------|
| Number of drugs           | 3.71 ± 1.06 | 3.71 ± 1.10     | 3.71 ± 1.04           | 0.99    |
Six months after RDN, we found a mean ABPM reduction of >5 mmHg in 41 patients (51.9%). In these responders, mean systolic/diastolic ABPM reduction was -18.1 ± 9.4/-9.4 ± 5.9 mmHg (p<0.0001/p<0.0001) after 6 months and -17.2 ± 15.9/-9.0 ± 11.6 mmHg (p<0.0001/p<0.0001) after 12 months, respectively.

Mean day time BP in responders was 152.9 ± 15.5/90 ± 12.9 mmHg at baseline and dropped down to 135.4 ± 16.6/82.4 ± 12.2 mmHg after 6 months, while mean night time BP decreased from 142.9 ± 19.1/82.4 ± 14.9 mmHg to 125.3 ± 14.7/72.9 ± 10.5 mmHg (p<0.0001/p<0.0001) after 12 months. All changes in ABPM are shown in Table 4.

### Table 4 Changes in ABPM.

| 24 hours-BP-all patients (n=79) |  |  |  |
|---|---|---|---|
| **Systolic** | **Diastolic** | **p-value** | **p-value** |
| Baseline | 143.4 ± 16.4 | 85.8 ± 12.6 |  |
| 6 months | 137.9 ± 15.8 | 82.4 ± 12.2 | 0.003 |
| 12 months | 135.4 ± 16.5 | 81.2 ± 13.4 | <0.001 |

| 24 hours-BP-responders (n=41) |  |  |  |
|---|---|---|---|
| **Systolic** | **Diastolic** | **p-value** | **p-value** |
| Baseline | 150.9 ± 15.5 | 90 ± 12.9 |  |
| 6 months | 132.8 ± 14.3 | 80.6 ± 11.9 | <0.001 |
| 12 months | 133.7 ± 15.7 | 81 ± 13.5 | <0.001 |

| 24 hours-BP-Non-responders (n=38) |  |  |  |
|---|---|---|---|
| **Systolic** | **Diastolic** | **p-value** | **p-value** |
| Baseline | 135.3 ± 13.3 | 81.3 ± 10.5 | No overall difference |
| 6 months | 143.4 ± 15.7 | 84.3 ± 12.3 | No overall difference |
| 12 months | 137.3 ± 17.3 | 81.3 ± 13.5 | 0.593 |

| Day time BP-all patients (n=79) |  |  |  |
|---|---|---|---|
| **Systolic** | **Diastolic** | **p-value** | **p-value** |
| Baseline | 145.6 ± 16.6 | 87.9 ± 12.5 |  |

The median systolic/diastolic BPB at baseline was 52.6%/33.3% during day time and 75%/37.5% during night time in
ABPM in all patients. Median systolic/diastolic BPB in day time decreased to 39.1%/27.3% (p=0.007/p=0.002; p-values for comparison to baseline) 6 months after RDN and to 38.7%/19.4% (p=0.001/p<0.001; p-values for comparison to baseline) 12 months after RDN.

In responders median day time BPB decreased from 75.6%/57.1% to 29.6%/25% (p<0.001/p<0.001; p-values for comparison to baseline) after 6 months and to 38.9%/26.8% (p<0.001/p<0.001; p-values for comparison to baseline) after 12 months. All changes in BPB are depicted in Table 5.

Table 5 Changes in BP-Burden.

|                     | All Patients (n=79) | p-value | Responders (n=41) | p-value | Non-Responder (n=38) | p-value |
|---------------------|--------------------|---------|-------------------|---------|----------------------|---------|
| **Systolic Day time Burden** |                    |         |                   |         |                      |         |
| Baseline            | 52.60%             |         | 75.60%            |         | 33.30%               |         |
| 6 months            | 39.10%             | p=0.007 | 29.60%            | p<0.001 | 58.50%               | p=0.006 |
| 12 months           | 38.70%             | p=0.001 | 38.90%            | p<0.001 | 38.50%               | p=0.303 |
| **Diastolic Day time Burden** |                    |         |                   |         |                      |         |
| Baseline            | 33.30%             |         | 57.10%            |         | 22.40%               | No overall difference |
| 6 months            | 27.30%             | p=0.002 | 25%               | p<0.001 | 32%                  |         |
| 12 months           | 19.40%             | p=0.001 | 26.80%            | p<0.001 | 18%                  |         |
| **Systolic Night time Burden** |                    |         |                   |         |                      |         |
| Baseline            | 75%                |         | 100%              |         | 37.50%               |         |
| 6 months            | 60%                | p=0.212 | 44.40%            | p<0.001 | 68.80%               | p=0.003 |
| 12 months           | 50%                | p=0.004 | 57.10%            | p<0.001 | 40%                  | p=0.71  |
| **Diastolic Night time Burden** |                    |         |                   |         |                      |         |
| Baseline            | 37.50%             | No overall difference | 62.50% |         | 25%                  | No overall difference |
| 6 months            | 25%                |         | 25%               | p<0.001 | 33.80%               |         |
| 12 months           | 20%                |         | 20%               | p<0.001 | 25%                  |         |

Changes in median systolic and diastolic BP-Burden; Day time: 6:00-21:45 o'clock; Night time: 22:00-5:30 o'clock; subdivided in consideration of treatment response; *p-values for comparison to baseline.

In contrast to responders, we did not observe improvements in ABPM levels and in day- and night time BP levels in non-responders. Consecutively, the median BPB remained unchanged at 12 months of follow-up in these patients.

**Discussion**

By the use of ABPM, we obtained information on the proportion of systolic/diastolic BP values ≥ 135/85 mmHg during day time and ≥ 120/70 mmHg during night time, defined as BPB. The BP profiles of responders to RDN showed significant and sustained improvements in BPB, for day- as well as night time values, which is the main finding of our long-term study.

Arterial hypertension is the most important modifiable risk factor for cardiovascular mortality [15-17]. Especially patients with resistant arterial hypertension have an increased risk of stroke, myocardial infarction, heart failure and chronic kidney disease [18,19].

Although office BP measurements were used for evaluation of the efficacy of RDN in the Symplicity HTN-1 and HTN-2 trials, ABPM is superior to this method [4,5,16]. BP profiles of ABPM have been shown to more reliably predict cardiovascular morbidity and mortality [20-24].

The responder cohort of our patient series showed clinically and statistically significant reductions of mean 24 hours BP, suggesting a sustaining effect of RDN. As already mentioned, we found a pronounced reduction of BPB during day- and night time in the responder group. Whether the observed reductions are due to the Hawthorne effect (greater compliance after RDN as response to being observed), the interaction of therapy modification or the actual effect of sympathetic denervation remains unknown. Data from the mentioned Symplicity HTN-3 trial underlines that conclusions on the true effects of RDN cannot be drawn without a proper sham-controlled arm [10]. It is furthermore important to notice the high percentage of patients (48.1%) with non-response in our study. In contrast to responders, BP levels as well as BPB worsened in these patients after 6 months compared to baseline, but were similar between baseline and the 12 months follow-up.

Causes of non-response to RDN are yet not fully understood [25,26]. Apart from patient selection, procedural parameters may play a pivotal role. However, no reliable tools or parameters are established to verify adequate sympathetic nerve.
destruction during the ablation procedure. Therefore, insufficient tissue contact with inadequate contact force of the catheter-tip may contribute to non-response [26].

Additionally, the definition of response to RDN should be clarified [27,28]. In the Symplicity HTN-1 and HTN-2 trials, patients with a BP reduction of >10 mmHg in office BP measurements were defined as responders [4,5]. It is well established that the reproducibility of BP levels is much higher by using ABPM [11,12]. Focusing only on office BP measurement might lead to an overestimated response of RDN.

Although we know out of Simplicity III that there can be found no significant reduction of BP after RDN, we could show it is possible to reduce the BPB through RDN-stronger than due to oral medication-as seen in our patient cohort. Maybe it is not essential to reduce the absolute BP levels but it can be a positive effect out of reducing the burden of blood pressure on cardiovascular morbidity and mortality. Therefore RDN could nevertheless be a good option for patients with drug resistant arterial hypertension. Of course further trials need to be done for clarification.

Conclusion

The pronounced improvement of BPB in day- and night time profiles in responders is an important component of the effect of RDN. These results should be investigated by randomized sham-controlled trials.

Limitations

A major limitation of our trial is the lack of randomization and an adequate sham-controlled group. Furthermore, there was no evaluation of patient compliance regarding the correct intake of prescribed medication in our follow-up period, which is another critical factor that should be included in further clinical trials.

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