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Improvement of albuminuria after renal denervation ☆

Christian Ott [a], Felix Mahfoud [b], Axel Schmid [c], Tilmann Ditting [a], Roland Veelken [a], Sebastian Ewen [b], Christian Ukena [b], Michael Uder [c], Michael Böhm [b], Roland E. Schmieder [a,*]

[a] Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Germany
[b] Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg/Saar, Germany
[c] Department of Radiology, University of Erlangen-Nuremberg, Germany

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ABSTRACT

Objectives: The primary objective of this study was the effect of renal denervation (RDN) on elevated urinary albumin-to-creatinine ratio (UACR) in treatment-resistant hypertensive patients. In addition, patients were stratified according their UACR at baseline into micro- (30–300 mg/g, n = 37) and macroalbuminuria (≥300 mg/g, <2200 mg/g, n = 22).
Background: Increased albuminuria indicates cardiovascular and renal damage in hypertension. RDN emerged as an innovative interventional approach to reduce blood pressure (BP) and may thus reduce albumin urinary excretion.
Methods: Fifty-nine treatment-resistant hypertensive patients with elevated UACR at baseline underwent catheter-based RDN using the Symplicity Flex™ catheter (Medtronic Inc., Santa Rosa, CA).
Results: In the whole and pre-specified subgroups both office and 24-h ambulatory BP were significantly reduced 6 months after RDN. In parallel, a significant reduction in UACR occurred in all patients (160 (65–496) versus 89 (29–319) mg/g creatinine, $p < 0.001$) and in both subgroups (microalbuminuria: 83 (49–153) versus 58 (17–113) mg/g creatinine, $p = 0.001$; macroalbuminuria: (536 (434–1483) versus 478 (109–1080) mg/g creatinine, $p < 0.001$). In accordance, the prevalence of micro- and macroalbuminuria decreased significantly. Regression analysis revealed a modest positive relationship between the decrease of UACR and the fall of systolic BP ($\beta = 0.340$, $p = 0.039$) independent of renal function. Renal function remained unchanged after RDN.
Conclusions: In summary, following RDN, the magnitude of albuminuria as well as the prevalence of micro- and macroalbuminuria decreased in treatment-resistant hypertensive patients. Since albuminuria is an independent renal and cardiovascular risk factor, our findings suggest a reduction of renal and cardiovascular risk in these patients.

1. Introduction

Albuminuria is a powerful independent predictor of cardiovascular (CV) and renal disease as well as death not only in patients with different conditions including hypertension, renal disease, diabetes, and vascular disease, but also in the general population [1–6]. Moreover, albuminuria is linearly and without threshold associated with CV mortality, even after adjustment for CV risk factors and estimated glomerular filtration rate (eGFR) [2,6]. A multiplicative association without evidence for interaction was shown for albuminuria and eGFR with all-cause mortality [2].

Sympathetic nerve activity contributes to both arterial hypertension and cardiovascular and renal disease [7–11]. Efferent sympathetic activity leads to renin synthesis and release, proximal tubular sodium reabsorption and decreased renal perfusion and function. Furthermore, afferent sensory signaling to the central nervous system also appeared to be also a crucial role since dorsal rhizotomy that stops afferent signaling prevented the development of hypertension accompanied by increased renal afferent sympathetic nerve activity [12]. An experimental rat model showed that phenol injection in the lower pole of one kidney resulted in a development of hypertension accompanied by increased renal sympathetic nerve activity, but no impairment of renal function. These changes could be prevented by dorsal rhizotomy [13]. In the general population, after exclusion of chronic kidney disease (CKD), a strong association between increased urinary albumin excretion (≥30 mg/d) and elevated norepinephrine and epinephrine levels was shown, independent of BP values [14]. Exogenous norepinephrine acutely promotes glomerular protein leakage, which is enhanced in

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* Corresponding author at: Department of Nephrology and Hypertension, University of Erlangen-Nuremberg, Ulmenweg 18, 91054 Erlangen, Germany. Tel./fax: +49 9131 853 6245 (-6215).
E-mail address: roland.schmieder@uk-erlangen.de (R.E. Schmieder).

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microalbuminuric insulin-dependent diabetes mellitus (IDDM) compared to normoalbuminuric IDDM [15].

Renal denervation (RDN) has emerged as an interventional approach to achieve a substantial and sustained blood pressure (BP) reduction in severe treatment resistant hypertension (TRH) [11,16–19], but also in moderate TRH [20]. Moreover, it was repeatedly shown that RDN did not adversely affect renal function, as assessed by eGFR [11,21], and renal perfusion, as assessed by magnetic resonance imaging with arterial spin labeling [22], duplex ultrasound [21] or renal scintigraphy [23]. In contrast, data on albuminuria, representing renal damage, are limited and no clear benefit in patients with albuminuria at baseline has been documented after RDN [21,23,24]. To this end we analyzed the efficacy of RDN on albuminuria as a primary study objective in patients with treatment-resistant hypertension and elevated albuminuria at baseline.

2. Methods

2.1. Study cohort

In this study 59 patients with TRH, defined as office BP ≥ 140/90 mm Hg, despite being treated with at least 3 antihypertensive drugs including a diuretic (JNC 7 [25] and European Society of Hypertension/European Society of Cardiology (ESH/ESC) guidelines [26]), on a stable drug regimen, who underwent RDN were included. Patients who underwent RDN were consecutively enrolled if urinary albumin to creatinine ratio (UACR) was elevated in the first morning urine sample (>30 mg/g creatinine). Patients were subsequently stratified according to their UACR into microalbuminuria (30–300 mg/g, n = 37) and macroalbuminuria (≥300 mg/g, <2200 mg/g, n = 22). Patients with nephrotic syndrome or active renal disease defined as being unstable within the last 3 months were excluded from this protocol. In line with the recent position papers of the ESH [27,28], main exclusion criteria were renal artery anatomy that is ineligible for treatment (main renal arteries <4 mm in diameter or <20 mm in length, hemodynamically or anatomically significant renal artery abnormality or stenosis in either renal artery, history of prior renal artery intervention including balloon angioplasty or stenting) and any secondary cause of hypertension except treated obstructive sleep apnea syndrome and CKD.

The local ethics committees from the two participating centers approved the study protocol and the study was performed according to Declaration of Helsinki and "Good Clinical Practice" (GCP) guidelines. Written informed consent was obtained from all patients before study entry. The study was registered at www.clinicaltrials.gov (ID: NCT01687725).

2.2. Catheter-based renal denervation

For RDN, the femoral artery was accessed with standard endovascular technique. A radiofrequency catheter (Symplicity Flex™ catheter, Medtronic Inc., Santa Rosa, California) was advanced in each renal artery. As described previously in detail [16], at least four radiofrequency ablations (energy delivery for 120 s each), controlled and regulated by a radiofrequency generator, were applied longitudinally and rotationally within the lengths of each renal artery. Patients received 5000 IU heparin and diffuse visceral pain during the procedure was managed with anxiolytics and analgesics.

2.3. Office and 24-h ambulatory blood pressure

Office BP was measured after 5 min of rest in a sitting position with an oscillometric device (study center Erlangen: Dinamap Pro100V2 [Criticon, Norderstedt, Germany]; study center Homburg/Saar: Omron HEM-705 monitor [Omron Healthcare, Vernon Hills, IL] with a printer for documentation). Initially BP was measured in both arms, subsequent BP measurements were done in the arm with the higher BP readings and the average of 3 measurements was taken. Ambulatory 24-h BP measurements were taken with validated, according to the ESH International Protocol (ESH-IP) [29] (e.g., Spacelab No. 90207, Redmont, California), automatic portable devices.

2.4. Measurement of urinary albumin and creatinine

All samples were measured centrally by the lab of the universities of Erlangen-Nuremberg and Homburg/Saar, respectively, according to established methods. In brief, urine albumin concentration was measured by a turbidimetric method. The inter-assay coefficient of variation was 3.44%. Creatinine concentration in urine was measured photometrically by the Jaffe method. The inter-assay coefficient of variation was 2.03%. UACR was calculated by dividing urinary albumin concentration by urinary creatinine concentration [30].

2.5. Renal function

Routine methods were used for the determination of creatinine (modified Jaffé-method). The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [31].

2.6. Statistical analyses

All analyses were performed using the IBM SPSS Statistics for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA). Normal distribution of data was confirmed by Kolmogorov–Smirnov tests before further analyses. Normally distributed data were compared by un-paired and paired student *t*-tests and are expressed as mean ± standard deviation (SD). Data of UACR were not normally distributed; therefore, median and interquartile ranges are reported. UACR values were log-transformed before statistical analysis. Data were compared by Wilcoxon and McNemar tests where appropriate. Univariate correlation was performed using Pearsons's correlation coefficient. Multivariate regression analysis was used to determine predictors of UACR change. A two-sided p-value of <0.05 was considered statistically significant.

3. Results

Clinical characteristics of the whole cohort and patients stratified according to their baseline UACR into micro- and macroalbuminuria are depicted in Table 1. Patients were middle-aged, mostly male, and overweight, with no differences in office and 24-h ambulatory BP monitoring (ABPM) between patients with micro- and macroalbuminuria.

3.1. Blood pressure

Six months after RDN, office SBP was reduced in all groups (whole cohort: 169 ± 23 versus 151 ± 26, p < 0.001; microalbuminuria: 170 ± 24 versus 149 ± 25, p < 0.001; macroalbuminuria: 168 ± 20 versus 154 ± 29, p = 0.019) and DBP (whole cohort: 91 ± 17 versus 81 ± 14, p < 0.001; microalbuminuria: 92 ± 18 versus 81 ± 14, p < 0.001; macroalbuminuria: 90 ± 16 versus 81 ± 13, p = 0.007).

In patients with available 24-h ABPM before and after RDN (n = 43), mean 24-h ABPM was reduced in the whole cohort 6 months after RDN (systolic: 156 ± 18 versus 145 ± 21 mm Hg, p < 0.001; diastolic: 87 ± 15 versus 80 ± 12 mm Hg, p < 0.001), microalbuminuria (n = 25) (systolic: 155 ± 18 versus 144 ± 22 mm Hg, p = 0.005; diastolic: 88 ± 16 versus 80 ± 13 mm Hg, p = 0.003) and macroalbuminuria (n = 18) (systolic: 157 ± 17 versus 147 ± 20 mm Hg, p = 0.004; diastolic: 85 ± 15 versus 80 ± 12 mm Hg, p = 0.049).

3.2. Heart rate

There was a reduction in heart rate in all groups (whole cohort: 72 ± 13 versus 66 ± 12 beats per minute (bpm), p = 0.001; microalbuminuria: 72 ± 14 versus 66 ± 15 bpm, p = 0.012; macroalbuminuria: 72 ± 12 versus 67 ± 9 bpm, p = 0.041) after 6 months of RDN.

3.3. Urinary albumin to creatinine ratio

A significant reduction in UACR occurred in the whole cohort 6 months after RDN (160 (65–496) versus 89 (29–319) mg/g creatinine, p < 0.001) (Fig. 1) and in both subgroups (microalbuminuria: 83 (49–153) versus 58 (17–113) mg/g creatinine, p = 0.001 and macroalbuminuria: 536 (434–1483) versus 478 (109–1080) mg/g creatinine, p < 0.001). Likewise, we observed significant reductions of UACR in patients with diabetes (313 (90–553) versus 113 (45–551) mg/g creatinine p = 0.001) as well as without diabetes (86 (60–204) versus 78 (24–164) mg/g creatinine p = 0.003).

Six months after RDN, in all patients, the prevalence of macro- and microalbuminuria decreased such that 25% of the patients were now within the normal range of UACR (<30 mg/g creatinine) (p < 0.001) (Fig. 2). In accordance, in the microalbuminuric subgroup, the prevalence of microalbuminuria was decreased, with 38% of patients newly within the normal range of UACR, and similarly, in the macroalbuminuric subgroup the prevalence of macroalbuminuria decreased, meaning that 36% of patients now only had microalbuminuria and 5% were newly within the normal range of UACR (all p < 0.001, respectively) (Fig. 2).