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Impact of Baroreflex Activation Therapy on Renal Function – A Pilot Study

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Key Words
Baroreflex activation therapy · Resistant hypertension · Hypertensive nephropathy · Albuminuria · Proteinuria

Abstract
Background/Aims: Resistant hypertension and chronic kidney disease (CKD) are interlinked via sympathetic overdrive. Baroreflex activation therapy (BAT) has been shown to chronically reduce blood pressure (BP) in patients with resistant hypertension. The effect of BAT on renal function in CKD patients with resistant hypertension has not been reported. The aim of this study was to investigate the effect of sympathetic inhibition on renal function in CKD patients. ***Methods:*** 23 CKD patients with resistant hypertension were prospectively treated with BAT. Analyses were performed before and 6 months after the start of BAT. The renal function was analyzed by creatinine, cystatin C, glomerular filtration rate (GFR), renin, aldosterone, fractioned and 24-hour sodium excretion and analyses of urine marker proteins. The purpose of the control group was to investigate the influence of treating patients in a center for hypertension and regression to the mean on investigated variables. ***Results:*** The office mean BP decreased from 116.9 ± 20.9 mm Hg to 104.2 ± 22.2 mm Hg ($p < 0.01$), while the number of prescribed antihypertensive classes decreased from 6.6 ± 1.6 to 6.1 ± 1.7 ($p = 0.02$). Proteinuria and albuminuria decreased from a median of 283.9 and 47.7 to 136.5 ($p = 0.01$) and 45.0 mg/g creatinine ($p = 0.01$) with pronounced effects in higher CKD stage III + IV compared to I + II ($p < 0.01$). CKD-EPI cystatin C equation improved from 53.6 ± 22.7 to 60.4 ± 26.1 ml/min ($p = 0.02$). While creatinine and GFR were impaired after a period of 6 months, no changes of proteinuria, albuminuria, or BP were obtained in control patients. ***Conclusion:*** The data of this prospective trial demonstrate potential nephroprotective effects of BAT in therapy-resistant hypertension in CKD patients by a reduction of BP, proteinuria and moreover, a stabilization of estimated GFR.

Introduction

Resistant hypertension is defined as failure to achieve the goal blood pressure (BP) when adhering to maximally tolerated doses of 3 appropriate antihypertensive drugs including a diuretic [1]. The kidney disease: improving global outcomes (K-DIGO) guidelines for the management of BP in chronic kidney disease (CKD) recommend that both diabetic and nondiabetic patients without albu-

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minuria suffering from non-dialysis-dependent CKD should have BP controlled ≤140/90 mm Hg, whereas BP target for patients with significant albuminuria (microalbuminuria or macroalbuminuria) with or without diabetes should be ≤130/80 mm Hg [2]. Furthermore, according to the current definition, hypertensive patients who reach the BP target by means of four or more drugs are considered resistant [3, 4]. On the one hand, existence of CKD is frequently associated with resistant hypertension [5]. On the other hand, observational studies suggest a strong association between hypertension or proteinuria and the risk for renal function decline or end-stage renal disease (ESRD) [6] as well as cardiovascular events.

There is documented evidence that an adrenergic activation occurs in essential hypertension, particularly in advanced stages of renal failure, and the degree of the sympathetic activation is directly related to the severity of the hypertension state [7]. The adrenergic activation, albuminuria, and a decreased glomerular filtration rate (GFR) display an adverse impact on cardiovascular morbidity and mortality in CKD patients [7, 8]. Besides extrarenal effects, sympathetic overactivity influences renal sodium excretion and reabsorption, renal perfusion, glomerular filtration rate, and renin release [9, 10]. Moreover, increased activity of the sympathetic nervous system is associated with estimated glomerular filtration rate (eGFR) and proteinuria suggesting that the activation of this system is a progression factor in CKD patients [11].

Recently, novel interventional treatment options to selectively suppress the sympathetic nervous system activity have become available for clinical use and might be more potent than pharmacological approaches in normalizing sympathetic overactivity, thereby affording increased nephroprotection [12, 13]. Prior safety data about patients with resistant hypertension treated with baroreflex activation therapy (BAT) showed a mild decrease in GFR, a significant elevation in serum creatinine, and a stable albuminuria, which was to be considered a normal hemodynamic response to the drop in BP [14, 15]. The effects of BAT are mediated by the attenuation of sympathetic as well as by the augmentation of parasympathetic activity [16], which has been demonstrated to exert clinically significant treatment benefits in cases of resistant hypertension [1]. The European Renal Best Practice Work Group suggests that this new technique should be offered only in the setting of a trial in CKD patients. However, until now there is a lack of data in these high-risk patients. Therefore, the aim of the current study is to ascertain if the inhibition of the sympathetic nervous system by BAT might exert organoprotective effects with regard to renal function in CKD patients suffering from resistant hypertension.

Here we present our data from a prospective observational trial of BAT treatment in CKD patients with resistant hypertension on proteinuria, fractioned and 24-hour sodium excretion and equations for estimating GFR as surrogates of renal damage.

Methods

Patients, BAT, and Study Protocol

CKD patients defined by the KDIGO criteria 2012 ([2] fulfilling the diagnosis of resistant hypertension [17] and BP above national and international target (≤130/80 mm Hg) (DHL, http://www.hochdruckliga.de/tl_files/content/dhl/downloads/DHL-Leitlinien-2011.pdf) and ESH/ESC Guidelines [18] and [2, 19, 20]) were prospectively included into this study. Before enrolment either the secondary reason for hypertension were excluded or the patients got optimal treatment.

In particular, patients who had the combination of the following criteria were consecutively enrolled: (a) office systolic blood pressure ≥130 mm Hg, confirmed by multiple measurements, despite treatment with non-pharmacological measures and use of at least three antihypertensive drugs (including a diuretic) on maximally tolerated doses or confirmed intolerance to medications; (b) glomerular filtration rate estimated by the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation, eGFR <90 ml/min and/or having at least microalbuminuria); and (c) age ≥18 years. Exclusion criteria were pregnancy, acute myocardial infarction, unstable angina, stroke, or transitory ischemic attack within the previous 6 months; stenosis of the carotid artery >70%. All patients involved in this study were treated for hypertension for at least one year. Baseline medication was unchanged for at least 3 months before the implantation of the device.

For BAT, the Barostim neo™ (CVRx, Minneapolis, USA) was used as described previously [21, 22]. The BAT device consists of a lead, which is sutured directly on carotis sinus, and a pulse generator implanted in an infraclavicular position by performing a minimal-invasive procedure, including intraoperative testing for optimal placement of the lead for BP response [21, 22]. The optimal response during the lead position was assumed if 30 seconds of electrical stimulation (125 μs, 6 mV, 80 Hz) of the carotid sinus reduces SBP by at least 10 mm Hg and heart rate by 5 beats/min. BAT was initiated 4 weeks after the implant and the stimulation was individually increased by the adaption of programmed parameters during the monthly follow-up. Study visits were performed before the BAT implantation and 6 months after BAT activation, while BAT was ongoing in all investigated patients. Modification of antihypertensive medication by the treating physician was allowed during the observation period to adjust according to the individual office and/or BP self-measurements. All patients provided informed consent before the initiation of the protocol-mandated procedures. The study has been carried out according to the Declaration of Helsinki and was approved by the local Ethical Committee of Goettingen (19/9/11).

The following variables were monitored during the follow-up period: systolic and diastolic office BP, number of antihypertensive medications, eGFR, proteinuria, albuminuria, aldosterone, renin as well as urinary sodium.

Retrospective analysis of patients treated in our department from 2012 to 2014 meeting inclusion criteria but refusing BAT, was performed to provide a control group. In particular, patients who had the combination of the following criteria were included: (a) meeting inclusion criteria while (b) not meeting any exclusion criteria as defined for this study and (c) patients clinical (baseline characteristics, BP data) and laboratory data (serum creatinine, proteinuria, albuminuria) were documented in a 6 months follow-up period.

Blood Pressure Analysis

BP measurements were obtained in a sitting position with the patient's arm supported at the level of the heart. The optimal cuff size was determined by a prior measurement of the upper arm circumference. Office BP assessments were done at the same time and by the same investigator on each occasion. The mean of the last 3 readings was used as the office cuff pressure.

It is known that for nonrandomized antihypertensive trials, reduction in ambulatory BP is smaller than the office BP drops because of either overestimation of baseline office BP and/or underestimation of final office BP [23]. To investigate changes in ambulatory BP, ambulatory blood pressure measurement (ABPM) was performed. ABPM and heart rate monitoring was performed with a validated device (Spacelabs 992010 recorder; Spacelabs Healthcare, Nürnberg, Germany). The devices were programmed to obtain measurements every 15 min from 6 a.m. to 10 p.m., and every 30 min from 10 p.m. to 6 a.m. Patients were asked to continue their regular activities. Only recordings with at least 80% valid measurements were accepted.

Patients with a systolic BP (SBP) reduction of ≥10 mm Hg in office-base measurements and/or ≥5 mm Hg in ABPM average were subsequently defined as responders to BAT [24].

Routine Analyses

Plasma sodium, creatinine, proteinuria, and albuminuria as well as urine sodium were analyzed by standard methods. Second morning midstream urine was used. Conditions for baseline and follow-up proteinuria determination were similar (same time of the day, physical activity, diet). Urine samples were collected, centrifuged at 1,000 g for 10 min at 4°C to remove cell debris and casts. The CKD-EPI creatinine equation, CKD-EPI cystatin C equation, and CKD-EPI creatinine–cystatin C equation were calculated by the formulas described previously [25]. Serum aldosterone and renin concentration were analyzed by commercial tests from IBL International (Hamburg, Germany) and Diasorin Deutschland GmbH (Dietzenbach, Germany) according to the protocols provided by the manufacturer. Fractioned sodium excretion was calculated by the formula (Urine sodium × plasma creatinine) / (Plasma sodium × urine creatinine). 24-hour urinary sodium excretion was estimated from a fasting morning sample using the Kawasaki-formula, which has been shown to provide a reliable estimation of 24-hour sodium excretion in patients with hypertension taking antihypertensive drugs [26, 27]. Twenty four hour sodium excretion was additionally adjusted for the CKD-EPI cystatin C and CKD-EPI creatinine C equation.

Statistics

The data were evaluated using the statistical Software Statistica 10 and Microsoft Excel 2010. Baseline data were compared between BAT and the control group using either an independent samples *t*-test for means or a Chi-squared test for proportions. To analyze the potential differences between baseline and 6-months in the investigated variables, either a paired 2-sided *t*-test or a Wilcoxon matched pairs test was used, depending on the shape of the data. Therefore, a Shapiro-Wilk-test was used to test if data were normally distributed. To investigate the potential confounding factors, analysis of variance (ANOVA) was performed.

The Chi-squared test was used for comparing categorical variables. Data were reported as mean ± standard deviation (SD) or as median (interquartile range (IQR)) for baseline and 6-months values as appropriated. The Pearson's correlation coefficient was used to describe the relationship between two metric variables; in some cases, extreme values were excluded. The threshold for statistical significance was chosen to be $p < 0.05$.

Results

Patients

Twenty-three CKD patients with therapy-resistant hypertension were analyzed. Baseline data are shown in table 1. This cohort included patients with chronic renal failure stage ≥3 or higher (n = 15) including one patient with ESRD stage 5D and one renal transplant recipient stage 4T. Six patients had a history of renal denervation, which was performed at least 9 months prior implantation of BAT. Two-factorial ANOVA revealed that prior renal denervation was not a confounding factor for the change of office SBP ($p = 0.76$), change of albuminuria ($p = 0.92$), and change of proteinuria ($p = 0.60$). Women had a significant lower CKD stage ($p < 0.01$), but a bias of this variable on BAT effects (reduction of proteinuria $p = 0.71$; reduction of ambulatory SBP $p = 0.72$) could be ruled out. Except the distribution of gender, which did not affect the changes of the investigated variables proteinuria ($p = 0.82$), albuminuria ($p = 0.26$), eGFR ($p = 0.17$), and mean arterial BP ($p = 0.11$), patients' demographic and clinical characteristics did not differ between the BAT and control group (table 1).

Blood Pressure and Antihypertensive Treatment

Table 2 shows office blood pressure, ABPM data, and antihypertensive treatment at baseline and after 6 months. Patients were hypertensive with a mean office blood pressure of 161 ± 31.9 mm Hg over 87.4 ± 15.2 mm Hg and a mean ABPM pressure of 142.3 ± 16.4 mm Hg over 79.6 ± 11.7 mm Hg diastolic, despite a mean number of 6.6 prescribed antihypertensive drugs.

Table 1. Patients' characteristics at baseline

n	BAT (n = 23)	Control (n = 21)	p
Gender			
Male	11 (48)	18 (86)	0.02
Female	12 (52)	3 (14)	
Age, years	60.9±9.8	60.4±10.9	0.88
BMI, kg/m^2	32.8±6.1	n.a.	
Prior renal denervation	6 (26)	4 (19)	0.58
Number of antihypertensives	6.6±1.6	5.8±1.3	0.07
eGFR, ml/min	63.6±27.8	62.8±25.0	0.17
Proteinuria, mg/g creatinine	283.9 (83.5–555.1)	134.4 (73.7–187.7)	0.82
Albuminuria, mg/g creatinine	47.7 (16.9–261.6)	16.9 (9.5–49.6)	0.26
Mean BP, mm Hg	116.9±20.9	112.8±12.0	0.11
Type of nephropathy (abs. (%))			
Hypertensive nephropathy	15 (65)	12 (57)	0.58
Diabetic/hypertensive nephropathy	6 (26)	8 (38)	0.60
IgA-Nephritis	2 (9)	1 (5)	0.61
Renal transplantation	1 (4)	0 (0)	0.33
CKD-stage (CKD-EPI equation)			0.58
I	2 (9)	4 (19)	
II	6 (26)	6 (29)	
III	9 (39)	9 (43)	
IV	5 (21)	2 (10)	
VD	1 (4)	0 (0)	
Relevant concomitant diseases			
Congestive heart failure	2 (9)	0 (0)	0.17
Coronary heart disease	7 (30)	7 (33)	0.84
Diabetes mellitus	6 (26)	8 (38)	0.39
Hyperlipoproteinemia	18 (78)	12 (57)	0.13
History of smoking	17 (74)	12 (57)	0.24

Values are mean ± SD or n (%). n.a. = Not applicable; CKD = chronic kidney disease; CKD-stage IVT = recipients of renal transplant in CKD stage IV; CKD-stage VD = patients with CKD-stage 5 on hemodialysis; CKD-EPI = chronic kidney disease epidemiology collaboration; BMI = body mass index.

After 6 months of BAT, the office systolic and diastolic BP decreased significantly ($p < 0.01$). The mean decrease of systolic ABPM was –5.7 ± 15.4 mm Hg ($p = 0.08$). Regarding the mean change and SD in systolic ABPM observed in this study, power analysis revealed a sample size of 53 patients with a power of 80% and $\alpha = 0.05$ to detect a statistically significant difference between baseline and month 6. The mean number of prescribed antihypertensive drugs decreased to 6.1 ± 1.7 ($p = 0.02$). The number and/or the dose of antihypertensive drugs could be reduced in 16 of 23 patients (70%). According to published recommendations, 4 (17%) patients were classified as nonresponders to BAT [24]. There was no significant change in office mean BP (112.8 ± 12.0 vs. 111.5 ± 12.3 mm Hg; $p = 0.66$) or in the number of prescribed antihypertensives (5.8 ± 1.3 vs. 5.9 ± 1.4; $p = 0.19$) in control patients throughout 6 months.

Proteinuria

Results on proteinuria are shown in table 3 and figure 1. At baseline, micro-/macroalbuminuria was present in 15/23 (65%) of the patients. Proteinuria was decreased after 6 months of BAT by a median –29.2% (–67.6 ± 42.1%) ($p = 0.01$) and albuminuria by a median –19.0% (–60.9 ± 5.1%) ($p = 0.01$), while these parameters remained unchanged in controls (proteinuria (134.4 mg/g creatinine (73.7–187.7) vs. 112.8 mg/g creatinine (60.3–250.0); $p = 0.55$), albuminuria 16.9 mg/g creatinine (9.5–49.6) vs. 17.9 mg/g creatinine (9.3–74.8); $p = 0.59$). The class of micro-/macroalbuminuria also significantly improved after 6 months of BAT ($p = 0.047$) (fig. 1). Additionally, we correlated the decrease of SBP with the percentage decrease of proteinuria and albuminuria and observed a significant positive correlation between the decrease in SBP and albuminuria ($r = 0.452$; $p = 0.045$).

Table 2. Office blood pressure, ABPM and antihypertensive drugs

	BAT			Control		
	baseline (n = 23)	month 6 (n = 23)	p	baseline (n = 21)	month 6 (n = 21)	p
Office BP						
Systolic, mm Hg	161.0±31.9	144.0±32.3	<0.01	155.3±19.1	153.6±17.4	0.70
Diastolic, mm Hg	87.4±15.2	77.7±17.1	<0.01	84.4±12.0	83.4±13.0	0.70
Mean, mm Hg	116.9±20.9	104.2±22.2	<0.01	112.8±12.0	111.5±12.3	0.66
Heart rate, bpm	73.0±12.7	68.4±10.8	0.06			
ABPM*, n = 22						
Systolic, mm Hg	142.3±16.4	136.0±23.7	0.08	n.a.	n.a.	
Diastolic, mm Hg	79.6±11.7	74.8±16.4	0.09	n.a.	n.a.	
Mean, mm Hg	102.6±12.3	97.2±18.6	0.08	n.a.	n.a.	
Maximum, mm Hg	179.1±20.7	179.2±33.3	0.98	n.a.	n.a.	
Pulse pressure, mm Hg	59.9±18.6	58.5±18.8	0.30	n.a.	n.a.	
Night systolic, mm Hg	136.7±17.0	128.7±23.7	0.04	n.a.	n.a.	
Dipping, %	6.9±6.7	8.1±9.1	0.50	n.a.	n.a.	
Number of antihypertensives	6.6±1.6	6.1±1.7	0.02	5.8±1.3	5.9±1.4	0.16
Patients receiving (drug classes)						
ACE-inhibitor	10 (44)	10 (44)		10 (48)	10 (48)	
AT1-blocker	13 (57)	13 (57)		13 (62)	13 (62)	
Aldosterone receptor antagonist	4 (17)	3 (13)		6 (26)	6 (26)	
Renin-inhibitor	7 (30)	6 (26)		3 (14)	3 (14)	
Beta-blocker	18 (78)	17 (74)		16 (76)	16 (76)	
Calcium-channel blockers	17 (74)	17 (74)		17 (81)	17 (81)	
Loop diuretics	13 (57)	14 (61)		11 (52)	13 (62)	
Thiazide	20 (87)	18 (78)		13 (62)	13 (62)	
Alpha-1 receptor blocker	19 (83)	14 (61)		14 (67)	14 (67)	
Alpha-2-adrenergic agonist	20 (87)	16 (70)		16 (76)	16 (76)	
Antihypertensive withdrawal and/or dose reduction		16/23 (70)			0/21 (0)	

Values are mean ± SD or n (%). * n = 22 for 24 h ambulatory blood pressure measurement (ABPM) data. BP = Blood pressure.

Changes of ambulatory SBP as well as the change of proteinuria showed a negative correlation with baseline proteinuria by r = –0.398 (p = 0.08) and r = –0.6998 (p < 0.01), respectively (correlations are shown in online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000368723).

Excretory Renal Function

Serum creatinine (p = 0.66), eGFR-MDRD (p = 0.82), and CKD-EPI creatinine equation (p = 0.98) did not differ in the follow-up compared to baseline. After 6 months of BAT, the mean change in cystatin C and CKD-EPI creatinine cystatin C equation were –0.14 ± 0.40 (p = 0.10), +3.3 ± 9.3 (p = 0.11), respectively, whereas CKD-EPI cystatin C equation significantly increased (+6.7 ± 12.7; p = 0.02). Data are summarized in table 3. In controls, serum creatinine (1.35 ± 0.51 mg/dl vs. 1.55 ± 0.75 mg/dl; p = 0.04) and eGFR (62.8 ± 25.0 ml/min vs. 54.5 ± 23.4 ml/min; p < 0.01) were significantly impaired 6-months after the first consultation.

Renin-Aldosterone Axis and Sodium Excretion

Renin (p = 0.32), aldosterone (p = 0.90), and the aldosterone-/renin-quotient (p = 0.39) remained unchanged after 6 months of BAT treatment. Though the prescription rate of diuretics did not change after 6 months of BAT, fractioned sodium excretion and 24-hour sodium excretion calculated by the Kawasaki formula tended to increase without a statistically significant change. Twenty four hour sodium excretion adjusted to CKD creatinine equation as well to CKD cystatin C equation showed a trend to increase from 2.13 (1.32–3.97) to 2.68 (1.44–4.54) mmol/day/ml/min (p = 0.10) and from 2.66 ± 1.65 to 3.00 ± 2.71 mmol/day/ml/min (p = 0.39), respectively. Data are summarized in table 3.

Table 3. Functional renal parameters at baseline and after 6 months of BAT

	BAT			Control		
	baseline	month 6	p	baseline	month 6	p
Proteinuria, n	23	23		21	21	
Proteinuria, mg/g creatinine	283.9 (83.5–555.1)	136.5 (47.6–274.3)	0.01	134.4 (73.7–187.7)	112.8 (60.3–250.0)	0.55
Albuminuria, mg/g creatinine	47.7 (16.9–261.6)	45.0 (22.9–130.9)	0.01	14.9 (9.5–49.6)	17.9 (9.3–74.8)	0.59
No albuminuria, <30 mg/g creatinine	8 (35%)	12 (52%)		13 (62%)	11 (52%)	
Microalbuminuria, 30–300 mg/g creatinine	10 (43%)	7 (30%)	0.043	4 (19%)	7 (33%)	0.57
Macroalbuminuria, >300 mg/g creatinine	5 (22%)	4 (17%)		4 (19%)	3 (14%)	
Renin-aldosterone axis						
Aldosterone, pg/ml	95.0 (74.0–153.0)	107.0 (76.0–199.0)	0.32	n.a.	n.a.	
Renin, μIU/ml	35.4 (11.4–143.0)	30.3 (8.9–125.6)	0.90	n.a.	n.a.	
Aldosterone-renin-quotient	5.12 (1.40–15.35)	7.82 (1.61–23.81)	0.39	n.a.	n.a.	
Excretory renal function, n	22	22		21	21	
Serum creatinine, mg/dl	1.35±0.75	1.39±0.86	0.66	1.35±0.51	1.55±0.75	0.04
eGFR-MDRD, ml/min	63.6±27.8	63.1±29.1	0.82	62.8±25.0	54.5±23.4	<0.01
Cystatin C, mg/l	1.51±0.69	1.37±0.63	0.10	n.a.	n.a.	
CKD-EPI creatinine equation, ml/min	55.4±27.5	55.4±28.7	0.98	n.a.	n.a.	
CKD-EPI cystatin C equation, ml/min	53.6±22.7	60.4±26.1	0.02	n.a.	n.a.	
CKD-EPI creatinine–cystatin C equation, ml/min	57.1±23.5	60.3±26.1	0.11	n.a.	n.a.	
Urinary sodium excretion, n	22	22				
24-h Sodium excretion, mmol/day	116.61±63.93	134.94±47.29	0.13	n.a.	n.a.	
Sodium excretion/CKD cystatin C equation, mmol/day/ml/min	2.66±1.65	3.00±2.71	0.39	n.a.	n.a.	
Sodium excretion/CKD creatinine equation, mmol/day/ml/min	2.13 (1.32–3.97)	2.68 (1.44–4.54)	0.10	n.a.	n.a.	
Fractioned sodium excretion, %	0.85 (0.38–1.68)	1.33 (0.67–1.96)	0.12	n.a.	n.a.	

Values described by absolute and percentage proportions, mean ± SD or median (IQR). CKD-EPI = Chronic kidney disease epidemiology collaboration; GFR = glomerular filtration rate; serum creatinine in mg/dl to mol/l, ×88.4.

Impact of Baseline CKD Stage on BAT Effects

ANOVA analysis for CKD stage I–V revealed no effect on the change of SBP reduction ($p = 0.28$), whereas the percentage reduction of proteinuria is affected by the CKD stage I to IV ($p = 0.02$) (stage VD was excluded from analysis). Proteinuria only decreased in CKD stages III and IV (–42.5 ± 44.2%) ($p < 0.01$) (fig. 1). Therefore, the percentage proteinuria decrease correlated with baseline CKD-EPI cystatin C equation with $r = 0.454$ ($p = 0.03$).

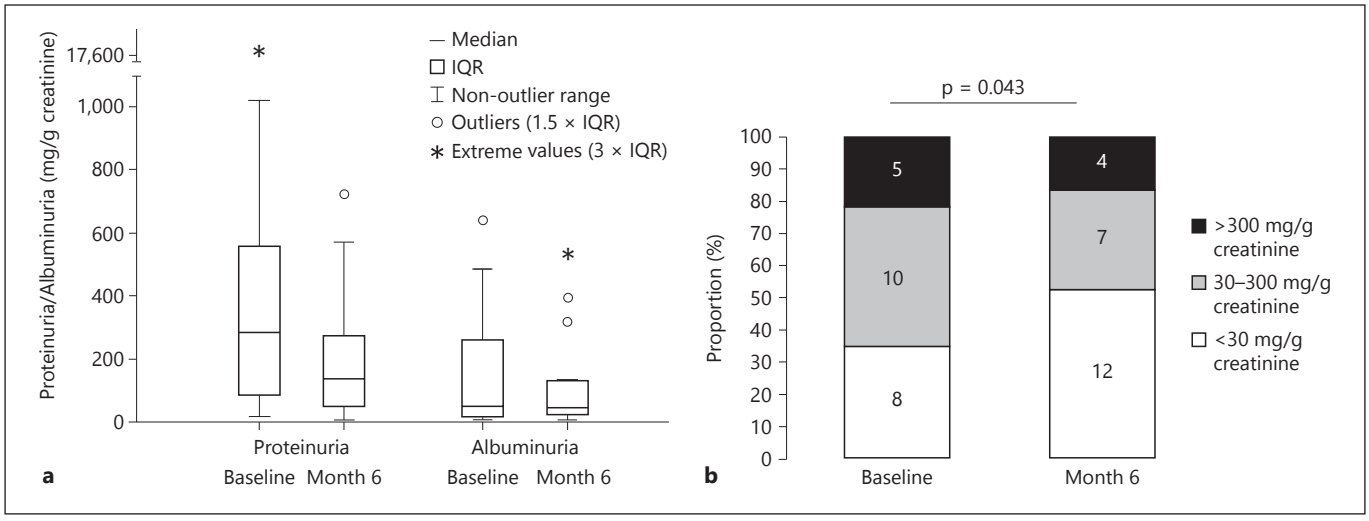
Discussion

This is the first prospective study on BAT for the treatment of resistant hypertension in CKD patients. Our study has three major findings:

1. BAT significantly lowers office BP in therapeutic-resistant hypertensive patients with CKD. 2. BAT reduces proteinuria/albuminuria BP-dependent and independently in patients with CKD. 3. The anticipated decrease in renal excretory function did not occur after 6 months of BAT.

Treatment of resistant hypertension in CKD is difficult. Nearly 40% of patients with CKD have an uncontrolled BP (in patients with macroalbuminuria up to 80%) [28] and almost the same proportion presents difficulties in the optimization of BP, needing 4 or more antihypertensive drugs in everyday conditions [29].

Actually, the amount of proteinuria [30, 31] and its reduction by treatment are predictive of renal outcome [31]. A therapeutic reduction of proteinuria by 20 to 50% or more than 50% after half a year reduces the risk



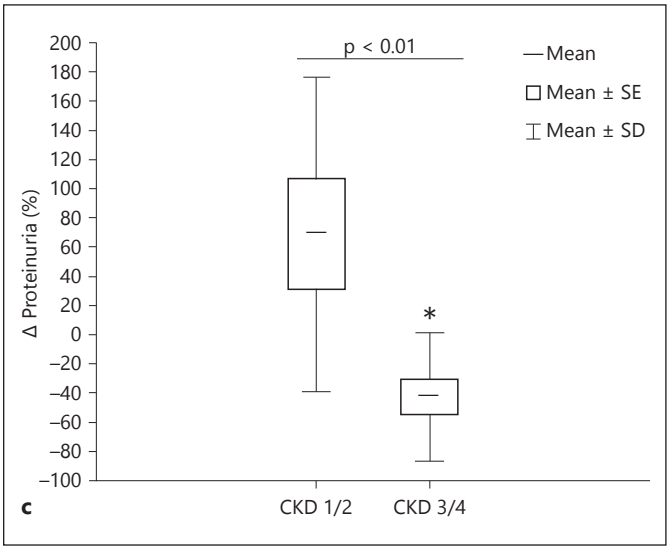


Fig. 1. Baroreflex activation therapy (BAT) significantly reduces proteinuria and albuminuria. **a** proteinuria baseline: 283.9 mg/g creatinine (83.5–555.1) month 6: 136.5 mg/g creatinine (47.6–274.3); albuminuria baseline: 47.7 mg/g creatinine (16.9–261.6) month 6: 45.0 mg/g creatinine (22.9–130.9) (both $p < 0.05$). **b** BAT influences albuminuria – distribution of albuminuria degree at baseline and at months 6 after starting BAT in patients with resistant hypertension and chronic kidney disease (CKD), n = 23. **c** Changes of proteinuria depends on CKD stage – Δ Proteinuria (%) in patients with CKD stage I and II (69.0 ± 43.0%) (n = 8) compared to patients with CKD III and IV (–44.5 ± 44.2%) (n = 14), $p < 0.01$.

of ESRD by nearly 50 or 75%, respectively [31]. Patients with therapeutic-resistant hypertension and CKD are considered high-risk patients for ESRD and cardiovascular events, but the treatment is challenging as many drugs as well as some interventional procedures (e.g., renal denervation) are contraindicated in this patient population. Our study shows, that BAT in this patient population is not only safe, but has the potential to decrease BP as well as proteinuria in this high-risk patient population. Hence, our study has immediate clinical consequences given the rising numbers of this patient population. We found a significant median reduction of proteinuria by 29.2%, which in subgroup analyses showed to be confined to patients with CKD stage III and IV. Potential antiproteinuric mechanisms might have been based on the improvement of renal hemodynamic and non-hemodynamic effects such as local RAAS activation and inhibition of sympathetic activity within the kidney [13, 32]. Obviously, SBP and albuminuria response in antihypertensive trials does not always run in parallel [33, 34]. Though cardiovascular risk is strongly correlated to BP, there is also a clear dependence on the achieved albuminuria regardless of the level of SBP. With regard to renal function, the residual level of albuminuria in patients who had reached SBP target was strongly associated with the risk of ESRD [35]. Thus, it is of importance to improve cardiovascular outcome and preserve renal function to perform a dual approach of lowering both BP and albuminuria [33]. The study does not exclude the well-established correlation between BP and proteinuria reduction, but suggests that BAT might additionally contribute to cardiovascu-

lar risk reduction by improving proteinuria also BP-independently. Elevated sympathetic nervous activity is suggested to constitute an important mechanism contributing to the onset and maintenance of renal injury. Therefore, inhibition of the sympathetic nervous system might aid in the prevention and treatment of renal injury, CKD, and ESRD [36].

In fact, sympathetic overdrive shows an inverse relationship with GFR [37]. Of note, in our study there is a significant correlation between baseline proteinuria and ambulatory SBP reduction as well as a pronounced antiproteinuric effect in higher CKD stages. On the basis of the AASK trial [31] an annual GFR decrease of 2.95 ml/min and a 1.1% rate of ESRD could be anticipated in our cohort. This was corroborated by data achieved in controls refusing BAT. Depending on the applied GFR estimation formula, the excretory renal function remained at least unchanged in our cohort with a non-significant decrease of 0.5 ml/min in eGFR (MDRD) formula, while other equations showed a trend toward improvement up to a maximal, significant increase of 6.8 ml/min in all patients using the CKD-EPI cystatin C equation. Notably, cystatin C-based CKD equations have been shown to have a greater accuracy and precision [25]. This is in contrast to extended data in the Rheos pivotal trial, which showed an eGFR decrease of 5 ml/min after 6 and of 11 ml/min after 12 months. Interestingly, eGFR-reduction was restricted to patients with a baseline eGFR >60 ml/min [15].

Therapeutic strategies for patients with arterial hypertension and CKD are mainly based on interventions in the RAAS-system as well as in volume homeostasis. There are no prospective studies or evidence-based guidelines to date on how to optimize antihypertensive regimen in CKD patients with uncontrolled BP even under a treatment with 6 to 7 antihypertensive drugs as in our cohort.

Our study has some potential limitations. It is a single center, nonrandomized trial and the sample size is small, which is the consequence of the current availability of the method as well as ethical reasons to withhold an efficacious therapy from high-risk patients with resistant hypertension. As shown for several interventional hypertension trials including the recent Symplicity-3 trial, the use of sham group is critical in defining real outcomes [38]. Though being aware of the potential confounding factors of an absent randomized control group, the present pilot trial was not designed to be an interventional study, which can be performed only with a great afford in a multicenter design. As a reasonable compromise to investigate Hawthorne effect by treating patients in a center for hypertension as well as regression to the mean on the investigated parameters, 21 patients meeting the inclusion criteria but refusing BAT served as a control group. Because of the relative small number of patients, minor differences between the treatment group and the control group might not have reached statistical significance. Though renoprotective effects are ascribed to most antihypertensive medications, the withdrawal might also have influenced functional renal data. For analysis of the eGFR decline, the duration of the observation period is relatively short and a longer follow-up is foreseen. However, this study was performed in a difficult-to-treat class of patients with severe hypertension were antihypertensives therapy can impact renal function in a negative way. Since sympathetic overactivity contributes to increased CV risk and progression of renal disease, via BP-dependent as well as BP-independent mechanisms, our data provide evidence that BAT might protect individuals with CKD and resistant hypertension, which are supposed to have increased levels of sympathetic nerve activity. In conclusion, BAT might represent in future, in addition to its use in resistant hypertension, an adequate therapy for CKD patients. The present study shows, that BAT reduces proteinuria and albuminuria and leads to a stabilization of CKD progression, indicating that BAT might be a potential factor to decelerate the progress of renal failure. The cohort in our study does not allow the analysis of clinical outcome. Precise evaluation of potential nephroprotective effects of BAT in patients with resistant hypertension and CKD will also need randomized controlled trials using sham procedures to respect the double blind design.

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Disclosure Statement

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