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ORIGINAL PAPER

Effect of baroreflex activation therapy on renal sodium excretion in patients with resistant hypertension

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Abstract

Objective Activation of the sympathetic nervous system increases sodium retention in resistant hypertension. Baroreflex activation therapy (BAT) is an interventional method to reduce sympathetic overactivity in patients with resistant hypertension. This study aimed to assess the effect of BAT on urinary sodium excretion.

Methods From 2012 to 2015, consecutive patients with resistant hypertension and blood pressure (BP) above target despite polypharmacy strategies were consecutively included in this observational study. BAT was provided with the individual adaption of programmed parameters over the first months. 24-h urinary sodium excretion (UNa) was estimated at baseline and after 6 months using the Kawasaki formula in patients undergoing BAT. Additionally, the fractional sodium excretion, plasma renin activity, and aldosterone levels were assessed.

Results Forty-two patients completed the 6-month follow-up period. Office systolic and ambulatory 24-h systolic BP at baseline were 169 ± 27 mmHg and 148 ± 16 mmHg despite a median intake of 7(3–9) antihypertensive drugs. After 6 months of BAT, systolic office BP decreased to 150 ± 29 mmHg ($p < 0.01$), 24-h systolic BP to 142 ± 22 mmHg ($p = 0.04$) and 24-h UNa increased by 37% compared to baseline (128 ± 66 vs. 155 ± 83 mmol/day, $p < 0.01$). These findings were accompanied by a significant increase in fractional sodium excretion (0.74% [0.43–1.47] to 0.92% [0.61–1.92]; $p = 0.02$). However, in contrast to the significant BP reduction, eGFR, plasma sodium, renin activity and aldosterone levels did not change during BAT. The increase in sodium excretion was correlated with the change in eGFR ($r = 0.371$; $p = 0.015$).

Conclusion The present study revealed a significant increase of estimated 24-h UNa which may contribute to the long-term BP-lowering effects of this interventional method.

Keywords Resistant hypertension · Urinary sodium excretion · Kawasaki formula · Sympathetic nervous system · Baroreflex activation therapy

Abbreviations

BAT	Baroreflex activation therapy
BMI	Body mass index
BP	Blood pressure
eGFR	Estimated glomerular filtration rate
HTN	Arterial hypertension
IQR	Inter-quartile range
MRA	Mineralocorticoid receptor antagonists
UNa	24-h urinary sodium excretion (UNa)
RAAS	Renin–angiotensin aldosterone system
SD	Standard deviation

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Introduction

Arterial hypertension (HTN) belongs to one of the most relevant risk factors for cardiovascular diseases. Appropriate treatment is mandatory to prevent complications like myocardial infarction, stroke or chronic kidney disease. Besides

a variety of pharmacological possibilities, novel approaches have been established for the treatment of HTN. Baroreflex activation therapy (BAT) is an interventional method to reduce sympathetic overactivity in patients with resistant HTN. BAT is not only capable of reducing blood pressure (BP) efficiently, [1] but may also reduce fasting glucose, [2] reduce arterial stiffness, [3] and exert nephroprotective effects [4].

In randomized Rheos pivotal trial, BP reduction at month 6 in comparison to pre-implant BP values was significantly larger in the activated BAT group compared to the deactivated BAT group, but the predefined endpoint (proportion of subjects that achieve at least a 10 mmHg drop in SBP at Month 6 compared with post-implant baseline values, with a superiority margin of 20%) was missed, potentially due to unexpected large BP reduction within the BAT off group after implantation of the BAT device [5].

However, exact mechanisms on how BAT effectively reduces BP is not yet fully understood. Though BAT is able to reduce BP up to 6 years, underlying mechanisms contributing to this sustained BP control are unknown [6]. In hypertensive patients, increased levels of sympathetic nervous system activity as well as increased tissue sodium content have been reported [7–14]. Besides other mechanism, activation of the sympathetic nervous system increases sodium retention and consecutive plasma volume expansion and thereby contributes to the pathophysiology of HTN [15]. In a preclinical setting, the sympathicoinhibitory BAT decreased sodium retention and increased renal sodium excretion [16]. Sodium homeostasis contributes to the pathophysiology of HTN, [17, 18] and changes in systolic BP align with changes in sodium excretion, [19] so it is of special interest to investigate renal sodium excretion in patients undergoing BAT. Therefore, this study aims to assess the effect of BAT on urinary sodium excretion in a clinical setting.

Methods

Patients, BAT and study protocol

Patients with resistant HTN [20] and BP above target (ESH/ESC Guidelines [21, 22]) despite polypharmacy strategies including life-style behaviours and optimal therapy for secondary reasons were consecutively included into this observational study. Inclusion of patients receiving BAT was performed consecutively from 2012 to January 2015. For BAT, the Barostim neo™ (CVRx, Minneapolis, USA) was used as described previously [23, 24]. The BAT device consists of a lead sutured directly onto the carotid sinus and a pulse generator implanted in an infraclavicular position in a minimally invasive procedure that includes intraoperative testing for optimal lead placement for BP response [23, 24]. BAT was initiated 4 weeks after implant and the stimulation was individually increased by adaption of programmed parameters during monthly follow-up visits. Study visits, which included collecting blood samples, asking for medication adherence and medical history, performing a physical examination, reviewing medication and assessing vital signs, were performed before and 6 months after BAT activation. Modification of antihypertensive medication by the treating physician based on the individual office and/or self-measured BP was allowed during the observation period. In particular, antihypertensive medication was reduced if ≥ 1 of the following criteria were fulfilled: (1) BP was below individual target, (2) BP was above target and severe symptoms associated with BP reduction (eg, dizziness) developed and (3) occurrence of typical side effects (e.g. hyperkalaemia using aldosterone antagonist) [25]. All patients provided informed consent before the initiation of protocol-mandated procedures. Patients with GFR < 15 ml/min, patients on hemodialysis and patients who did not complete the 6 month follow-up visit were excluded from the present analysis.

Patients showing a reduction of systolic BP of ≥ 10 mmHg in office-based measurements were defined as responders to BAT [26]. 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).

Routine analyses and estimation of sodium excretion

Plasma sodium, creatinine and urine sodium were analyzed by standard methods. CKD-EPI creatinine, CKD-EPI cystatin C and CKD-EPI creatinine–cystatin C were calculated using formulas described previously [27]. Serum aldosterone concentration, plasma sodium concentration and plasma renin activity were analyzed using commercial tests from IBL International (Hamburg, Germany) and Diasorin Deutschland GmbH (Dietzenbach, Germany) according to the protocols provided by the manufacturer. 24-h urinary sodium excretion was estimated from a fasting morning sample using the Kawasaki-formula which has been evaluated as a reliable estimation of 24-h sodium excretion in patients with HTN treated with antihypertensive drugs [28–30]. To prevent interference due to changes in renal function during follow-up, 24-h sodium excretion was adjusted for the CKD-EPI cystatin C, CKD-EPI creatinine and CKD-EPI creatinine cystatin C equations. Fractioned sodium excretion was calculated by the formula: (Urine sodium $\times$ plasma creatinine)/(Plasma sodium $\times$ urine creatinine). At baseline, BP was measured at each arm, and the arm with the higher BP was used for all subsequent readings. Brachial BP of the arm was recorded after 10 min of supine rest using a semiautomatic oscillometric device [Bosch + Sohn GmbH (Juningen, Germany)] two times within a 3-min interval.

The mean values out of these two measurements were averaged. Ambulatory BP measurement was performed using an oscillometric Spacelabs Model 90207 Recorder (Spacelabs Healthcare, Nürnberg, Germany) with readings taken every 15 min in daytime and every 30 min at nighttime. Ambulatory blood pressure readings were averaged for 24 h, daytime (7 am–10 pm), and nighttime (10 pm–7 am).

Statistical analysis

The data were evaluated using the statistical Software Statistica 13. To analyze the potential differences between baseline and follow-up in the investigated variables, either a paired 2-sided t-test or a Wilcoxon matched pair test were used, depending on the distribution of the data. A Shapiro–Wilk-test was used to test if data were normally distributed. The Pearson's correlation coefficient was used to describe the relationship between two metric variables. Unpaired two-sided *t* test was performed to investigate differences in sodium excretion between subgroups of patients. ANOVA was performed to analyze differences in the change of 24 h-UNa after 6 months in different subgroups. The threshold for statistical significance was chosen to be $p < 0.05$. Data are presented as mean ± standard deviation (SD), median [interquartile range (IQR)] or median (range), as indicated for baseline and 6-months values.

Results

Patients at baseline

A total number of 42 patients receiving BAT were analyzed. The gender ratio was almost equal with 20 males and 22 females included in the study. With an average BMI of 34 ± 7 kg/m^2, the majority of patients ($n = 29$; 69%) were obese. Taking a closer look at the relevant concomitant diseases, most patients presented with multiple cardiovascular risk factors. A number of 32 patients (76%) presented with dyslipoproteinemia, 28 patients (67%) had a history of smoking and 15 patients (36%) suffered from diabetes mellitus. Nearly one-third of the patients were already diagnosed with coronary heart disease and 88% had documented chronic kidney disease ≥ CKD stage 1 with 36% ≥ CKD stage 3. Detailed baseline characteristics are demonstrated in Table 1.

Table 1 Patients' characteristics at baseline

N	42
Female *n* (%)	22 (52%)
Age (years)	57 ± 12
BMI (kg/m^2)	34 ± 7
Relevant concomitant diseases	
Congestive heart failure	6 (14%)
Coronary heart disease	12 (29%)
Diabetes mellitus	15 (36%)
Dyslipoproteinemia	32 (76%)
History of smoking	28 (67%)
Chronic kidney disease ≥ CKD stage 1	37 (88%)
Chronic kidney disease ≥ CKD stage 3	15 (36%)
Prior renal denervation	15 (36%)

Values are mean ± SD, *n* (%), or median (range), chronic kidney disease (CKD), body mass index (BMI), estimated glomerular filtration rate (eGFR), modification of diet in renal disease (MDRD)

BAT increases renal sodium excretion

At baseline, the office BP was 169 ± 27/90 ± 18 mmHg despite a median intake of 7 (range 3–9) antihypertensive drugs. At the 6 month follow-up visit, BAT reduced systolic and diastolic office BP to 150 ± 29 mmHg and 82 ± 18 mmHg, respectively ($p < 0.01$), while the number of antihypertensive medication was numerically reduced to a median of 6 (range 3–9) ($p = 0.08$) without reaching statistical significance. Accordingly, average ambulatory 24-h BP decreased after 6 months as follows: average 24-h BP (from 148 ± 16/83 ± 13 mmHg to 142 ± 22/75 ± 15 mmHg, $p = 0.04/0.03$), daytime BP (from 151 ± 16/86 ± 13 mmHg to 145 ± 24/81 ± 16 mmHg, $p = 0.04/0.02$) and nighttime BP (from 141 ± 18/85 ± 13 to 133 ± 23/72 ± 15 mmHg, $p = 0.01/0.03$) (Table 2).

A number of 27 patients (64%) were classified as responders to BAT. There were no differences in the change of 24-h UNa after 6 months ($p = 0.43$), number of antihypertensive medication at baseline ($p = 0.47$) and months 6 ($p = 0.55$), type of antihypertensive medication nor within the programming parameters of BAT between responders and non-responders (Supplemental table 1). The 24-h UNa calculated by the Kawasaki formula increased 37% compared to baseline (128 ± 66 vs. 155 ± 83 mmol/day, $p < 0.01$) (Fig. 1). In 28 patients (67%), an increase in 24-h UNa was observed. Thirteen patients (31%) showed a decrease of > 10% in 24-h UNa, while 23 patients (55%) showed an increase of > 10% in 24-h UNa. In concordance with change in 24-h UNa, a number of 28 patients (67%) showed increased fractional sodium excretion, while fractional sodium excretion was decreased in 14 patients (33%). Subgroup analysis revealed no significant differences related to change in 24-h UNa: responders $p = 0.43$; CKD ≥ 3 $p = 0.90$; age > 60 years $p = 0.88$, female $p = 0.57$, prior renal denervation $p = 0.09$, diabetes mellitus $p = 0.79$. In accordance to the changes in 24-h UNa, a significant increase occurred in the fractional sodium excretion from 0.74% (0.43–1.47) to 0.92% (0.61–1.92) ($p = 0.02$) after 6 months of BAT,

Table 2 Office BP, estimated sodium excretion, parameter of RAAS, renal function and antihypertensive drugs at baseline and 6 months after initiating of BAT

	Baseline	6 months BAT	*p*
N	42	42	
Office BP			
Systolic (mmHg)	169 ± 27	150 ± 29	< 0.01
Diastolic (mmHg)	90 ± 18	82 ± 18	< 0.01
Mean (mmHg)	121 ± 20	109 ± 21	< 0.01
Heart rate (bpm)	72 ± 13	70 ± 11	0.20
24-h ambulatory BP[#]			
Mean systolic (mmHg)	148 ± 16	142 ± 22	0.04
Mean diastolic (mmHg)	83 ± 13	78 ± 15	0.03
Daytime systolic	151 ± 16	145 ± 24	0.04
Daytime diastolic	86 ± 13	81 ± 16	0.02
Nighttime systolic	141 ± 18	133 ± 23	0.01
Nighttime diastolic	77 ± 13	72 ± 15	0.03
Estimated sodium excretion			
Plasma sodium (mmol/l)	140.8 ± 2.4	140.5 ± 2.8	0.46
Fractioned sodium excretion (%)	0.74 (0.43–1.47)	0.92 (0.61–1.92)	0.02
By Kawasaki formula (mmol/day)	128 ± 66	155 ± 83	< 0.01
Adj. for cystatin C (mmol/day/ml/min)	2.06 (1.29–3.53)	2.16 (1.45–3.61)	0.02
Adj. for creatinine (mmol/day/ml/min)	1.61 (1.05-3.00)	2.02 (1.40–3.20)	0.03
Adj. for creatinine-cystatin C (mmol/day/ml/min)	1.84 (1.13–3.55)	1.96 (1.45–3.34)	0.03
Urine creatinine (mg/dl)	101 ± 65	81 ± 63	0.07
Hematocrit (%)	41.3 ± 4.5	41.2 ± 4.5	0.93
Body weight (kg)	97.5 ± 23.6	97.6 ± 24.8	0.87
Parameters of RAAS			
Serum aldosterone (pg/ml)*	99 (78–151)	109 (78–150)	0.21
Plasma renin activity (µIU/ml)*	34 (11–104)	30 (9-126)	0.24
Aldosterone/Renin-quotient*	6.2 (1.9–15.0)	7.4 (2.1–17.4)	0.96
Excretory renal function			
CKD-EPI creatinine equation (ml/min)	70 ± 29	72 ± 31	0.53
CKD-EPI cystatin C equation (ml/min)	61 ± 26	62 ± 27	0.51
CKD-EPI creatinine–cystatin C equation (ml/min)	65 ± 28	66 ± 29	0.43
Number of antihypertensive drugs	7 (3–9)	6 (3–9)	0.08
Increase (number of patients)		8 (19%)	
Decrease (number of patients)		12 (28%)	
Patients receiving (drug classes)			
ACE-inhibitor	19 (45%)	16 (38%)	
AT1-blockers	24 (57%)	25 (60%)	
Aldosterone receptor antagonist	14 (33%)	14 (33%)	
Direct renin inhibitors	7 (17%)	6 (14%)	
Beta-blockers	34 (81%)	35 (83%)	
Calcium-channel blockers	33 (79%)	31 (74%)	
Loop diuretics	20 (48%)	23 (55%)	
Thiazide diuretics	32 (76%)	29 (69%)	
Alpha-1 receptor blockers	31 (74%)	26 (62%)	
Alpha-2-adrenergic agonists	34 (81%)	29 (69%)	
Direct vasodilators	25 (60%)	24 (57%)	

Values described by absolute and percentage proportions, mean ± SD or median (IQR) except for number of antihypertensive drugs: median (range), as indicated. Blood pressure (BP); angiotensin-converting enzyme (ACE); Angiotensin II receptor antagonists (AT1-blockers); CKD-EPI (Chronic kidney disease epidemiology collaboration); GFR (glomerular filtration rate); RAAS (renin–angiotensin aldosterone system) serum creatinine in mg/dl to µmol/l, × 88.4. *$n = 41$. [#]ABPM data were available in 40 patients

whereas plasma concentration of sodium (140.8 ± 2.4 vs. 140.5 ± 2.8 mmol/l, p = 0.46), hematocrit (41.3 ± 4.5 vs. 41.2 ± 4.5%, p = 0.93) and body weight (97.5 ± 23.6 vs. 97.6 ± 24.8, $p = 0.87$) remained unchanged. Within a non-predefined additional analysis, the present cohort of therapy-resistant HTN patients displayed decreased renal sodium excretion at baseline (128 ± 66 mmol/day) compared to a population-based dataset from a meta-analysis investigating 24-h sodium excretion in normotensive controls (153 ± 3 mmol/day) (p < 0.01) [31]. In the overall cohort, the increase in renal sodium excretion remained significant after adjustment for cystatin C [from 2.06 mmol/day/ml/min (1.29–3.53) to 2.16 mmol/day/ml/min (1.45–3.61) ($p = 0.02$)], creatinine (from 1.61 mmol/day/ml/min (1.05–3.00) to 2.02 mmol/day/ml/min (1.40–3.20) ($p = 0.03$)) and creatinine-cystatin C (from 1.84 mmol/day/ml/min (1.13–3.55) to 1.96 mmol/day/ml/min (1.45–3.34)), respectively. Detailed numbers are outlined in Table 2. Correlation analysis revealed a significant correlation between change in estimated glomerular filtration rate (eGFR) and change in estimated 24-h sodium excretion ($r = 0.371$; $p = 0.015$) (Fig. 2). No correlation was observed between baseline eGFR and change in estimated 24-h sodium excretion after 6 months ($r = 0.217$; $p = 0.16$).

Correlation of sodium excretion and BP reduction

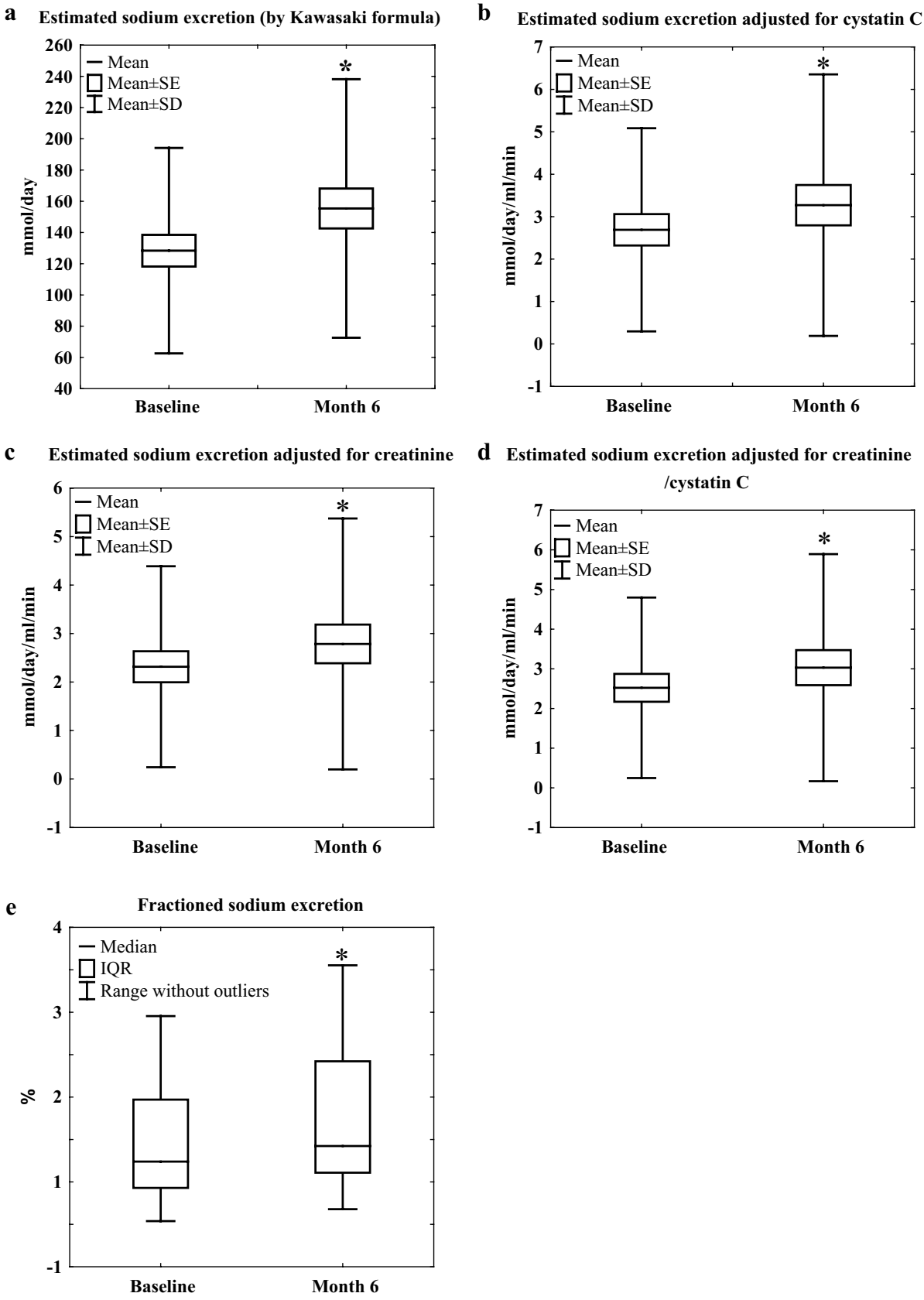
There was no correlation between systolic office or average ambulatory BP-reduction and increase in urinary sodium excretion after 6 months of BAT (office BP $r = 0.0873$, $p = 0.58$; ambulatory BP $r = 0.0316$, $p = 0.85$). There was a numerically higher increase of 24-UNa in patients with prior renal denervation without reaching statistical significance (+48 ± 63 vs. + 15 ± 55 mmol/day, $p = 0.09$).

BAT does not change parameters of the RAAS

Renal sodium excretion is closely related to the renin angiotensin aldosterone system (RAAS). Therefore changes in the concentrations of plasma renin activity (PRA) and aldosterone between baseline and after 6 months of BAT were analyzed. Despite the marked fall in BP, PRA and serum aldosterone levels did not increase during sustained activation of the baroreflex (Table 2).

Influence of antihypertensive medication

In 12 patients (29%) antihypertensive medication was reduced due to BP reaching levels below the individual target, medication side effects or symptoms of hypotension. In eight patients (19%) who remained above BP target during follow-up, antihypertensive medication was increased. Because antihypertensive medication changed in several patients during follow-up, we analyzed the change in urinary sodium excretion separately according to the change in antihypertensive medication after 6 months of BAT. Regarding change in 24-h UNa at month 6, there was no statistically significant differences between patients with reduced number of antihypertensive medication(+ 50 ± 66 mmol/day, $n = 12$), unchanged medication status (+ 13 ± 58 mmol/day, n = 22) and patients with increased number of antihypertensives (+ 31 ± 47 mmol/day, $n = 8$) ($p = 0.21$). Because diuretics and MRA directly affect sodium excretion, the number of prescribed diuretics was analyzed, showing no difference in the number of diuretics or MRA between baseline and month 6 (Table 2). With a detailed view to change in diuretic therapy during follow-up, the use of thiazids was abandoned in three patients, whereas the use of loop diuretics were initiated in three patients before follow-up visit. These three patients with initiated loop diuretic therapy showed change in 24-h UNa of − 18 ± 40 mmol/day, indicating that this slightly increase in the use of loop diuretics did not have influence on results of 24-UNa. Whereas 21 patients (50%) took less than two diuretics, 21 patients (50%) were on combined diuretic treatment (two or more different diuretic classes). Patients with combined diuretic intake compared to patients with single diuretic use did not show differences in 24-UNa at baseline and change in 24-UNa after 6 months, respectively (Supplemental Table 2). To further exclude a bias induced by antihypertensive medication, a sub-analysis was performed investigating sodium excretion in patients according to the intake of agents with relevant effects on urinary sodium excretion, namely thiazides, loop diuretic and MRAs. At baseline, 32 (76%) patients were treated with thiazide diuretics, 20 (48%) were treated with loop diuretics and 14 (33%) were treated with MRAs. Notably, neither sodium excretion at baseline nor the observed increase after 6 months was different in patients taking MRAs or diuretics (Supplemental table 2). None of the patients took SGLT1-inhibitors at baseline and follow-up. Because antihypertensive medication changed in several patients during follow-up, we analyzed the change in urinary sodium excretion separately according to the change in antihypertensive medication after 6 months of BAT. Regarding 24-h UNa, there was no statistically significant difference between patients with reduced number of antihypertensive medication and patients with increased number of antihypertensives (+ 50 ± 66 mmol/day, $n = 12$ vs. + 31 ± 47 mmol/day, $n = 8$, $p = 0.36$). Moreover, ANOVA analysis with the status of antihypertensive medication change as group (increase, decrease, unchanged) did not reveal significant differences regarding 24-h UNa change after 6 months ($p = 0.21$).


a
Estimated sodium excretion (by Kawasaki formula)
mmol/day
Mean
Mean±SE
Mean±SD
Baseline
Month 6
b
Estimated sodium excretion adjusted for cystatin C
mmol/day/ml/min
c
Estimated sodium excretion adjusted for creatinine
d
Estimated sodium excretion adjusted for creatinine /cystatin C
e
Fractioned sodium excretion
%
Median
IQR
Range without outliers

◂**Fig. 1** Estimated sodium excretion calculated by the Kawasaki formula before and 6 months after BAT ($n=42$). **a** Estimated sodium excretion estimated by the Kawasaki formula was increased by a median of +37% (*$p<0.01$), **b** adjusted for Cystatin C, **c** adjusted for creatinine, **d** adjusted for cystatin/creatinine and **e** fractional sodium excretion

Discussion

Normal control of BP requires complex integration of regulatory mechanisms across multiple physiological systems. HTN is, therefore, a very nonspecific manifestation of a range of potential causative mechanisms. Based on the "Guytonian paradigm", renal control of extracellular fluid volume and BP is driven chiefly by three responses: (1) neurohumoral control of renal excretory function, (2) neurohumoral control of resistance vessels, and (3) pressure natriuresis [32].

It is known that activation of the sympathetic nervous system, an important mechanism in the development of therapy-resistant HTN [33, 34], intensifies sodium retention. Stimulation of both α1- and β1-receptors leads to increased reabsorption of sodium in renal tubule cells and increased basal release of renin [35].

Analyzing effects of sympathicoinhibition by BAT on renal BP-regulatory responses in therapy-resistant HTN patients resulted in the following major finding: BAT significantly improves estimated sodium excretion and fractioned sodium excretion after 6 months whereas parameters of the renin–angiotensin–aldosterone system remain unchanged. At first glance, this seems to contradict the paradigms mentioned above. Chronic inhibition of the sympathetic nervous system, however, leads to a shift in pressure-natriuresis towards a lower BP threshold [16], that is in accordance to the present results. This might explain, at least in part, the missing correlation between BP reduction and increase in urinary sodium excretion in the present study. Of note, after 6 months of BAT there was no difference in the sodium excretion in the present cohort compared to the previously mentioned population-based normotensive dataset (155 ± 66 mmol/day; $p=0.70$). To date, only a few preclinical studies have evaluated the effect of sympathicoinhibition on renal sodium excretion [6, 36, 37]. Herein, chronic electrical stimulation of the carotid sinus resulted in an increase in fractional sodium excretion in a canine model, and an increase in fractional sodium excretion was observed in patients undergoing renal denervation [38]. The exact mechanism in which BAT leads to an increase of natriuresis is not clear. A potential mechanism might be based on the hypothesis that hypertensive patients have higher sodium retention in the skin and muscle compared to normotensives [39, 40]. It is conceivable that the normalization of BP along with increased natriuresis will lead to redistribution of sodium from the interstitium into the intravascular compartment. This would explain unchanged serum sodium despite increased natriuresis. However, this concept remains a hypothesis and cannot be confirmed by the present data due to the lack of technical preconditions necessary to prove such a hypothesis.

In the present study, office BP reductions were more pronounced than the reduction in 24-h ABP. This might be because inclusion of patients were based on office values and ABPM was performed after inclusion. Thereby, postinclusion ABP change during this study is not because of regression to the mean, which might have influenced office BP change. However, the phenomena of different BP reduction between office and ABP has been consistently demonstrated in serval antihypertensive trials and could be demonstrated accurately in a meta-analysis including 44 studies, showing that reduction in 24-h SBP was 36.5% less than the reduction in the office SBP [41]. Furthermore, it needs to be discussed if the difference might be partially mediated by a suppression of the white-coat effect, which is associated with increased sympathetic activity and resistant hypertension [42].

Despite lowering BP, there was no significant change in eGFR during BAT, but a correlation between sodium excretion and change in eGFR was observed. This contradicts the concept that reduced arterial BP results in decreased excretory renal function. However, it indicates that BAT mediates sustained effects to promote urinary sodium excretion in patients with resistant HTN. Thus, the reduction of BP throughout 6 months along with increased sodium excretion suggests persistent effects of BAT to enhance renal excretory function.

Another interesting finding was a stable level of PRA despite the distinct decrease in BP, which would usually result in an increase in PRA levels. The present observation suggests inhibitory effects of BAT on renin secretion, which is in accordance with the preexisting experimental data [37, 43–45]. As the RAAS exerts powerful long-term effects on both renal excretory function and BP, baroreflex-mediated suppression of renin secretion through inhibition of renal adrenergic activity may contribute to the long-term BP-lowering effects of this interventional method [43, 46].

As body weight and haematocrit were unchanged during follow-up, it is tempting to speculate whether a consecutive blood volume reduction was achieved or not. As sodium is at least in part distributed in the interstitium of e.g. skin a re-distribution of sodium seems conceivable although this has to be proofed.

The present study has potential limitations. Due to the challenge in defining a comparable patient cohort, in which further conservative treatment would be advised, there was no control group, so potential bias with regard to sodium excretion and BP change due to placebo and

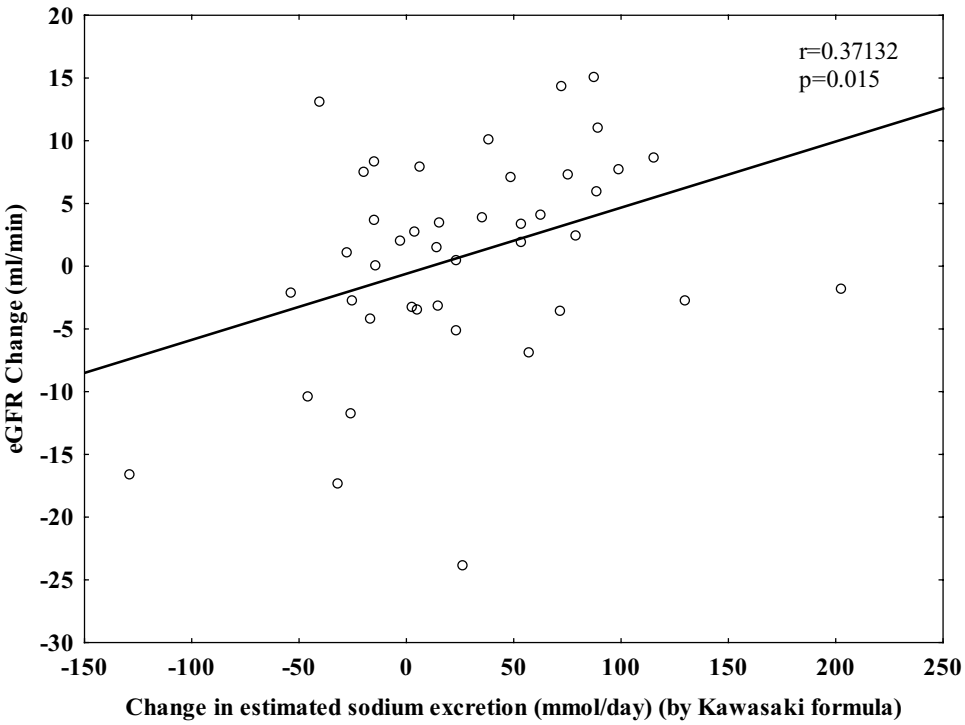


Fig. 2 Correlation between change in estimated glomerular filtration rate (eGFR) and estimated 24-h sodium excretion. eGFR was calculated by the CKD-EPI-creatinine equation. Estimated sodium excretion was calculated by the Kawsaki formula

Hawthorne effect cannot be excluded. While it is of interest to assess daily sodium intake, there are no data available on individual sodium intake. Though 24-h urine collection was not performed, the Kawasaki formula to estimate 24-h sodium excretion has been validated in patients with HTN taking antihypertensive medications and represents a reliable method, and effects of diuretics therapy could be excluded [29, 30]. In interpreting the present findings, it is important to consider that sodium excretion was estimated 6 months after activation of BAT and not during the first days after activation as was done in preclinical studies. Antihypertensive medication was not stable during follow-up. However, censoring for post-procedural medication changes did not affect the change in urinary sodium excretion after BAT, suggesting that a relevant influence of antihypertensive treatment changes is unlikely. As 15 patients (36%) had a CKD stage 3 or higher a prominent proportion of patients were primarily not treated only with thiazide but loop diuretics or combined diuretic therapy. Therefore, the group of patients without thiazide intake includes patients taking loop diuretics and/or MRA, so that the apparent numerically lower urinary sodium excretion at baseline in the thiazide group is at least partly explained. In patients with resistant hypertension adherence for antihypertensive drug treatment is poor, and especially poor for diuretic therapy [47]. Though patients were instructed to be adherent during the study, we could not exclude the influence of non-adherence or change in adherence on the present results.

Conclusion

In addition to a reduction of BP 6 months after initiating BAT, a significant increase in renal sodium excretion was observed in the present study. Further randomized trials in which sodium intake is documented are needed to confirm increased sodium excretion by BAT and to investigate if additional sodium restriction provides additive BP-lowering effects.

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Compliance with ethical standards

Conflict of interest MW and MK declare lecture fees and/or funding of CVRx. Research program, Faculty of Medicine, Georg-August-University Göttingen, to MW and a research grant from CVRx to MK and MW. ML, LYL, AKS, GM and SL declare that they have no conflict of interest.

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