Renal Responses to Long-Term Carotid Baroreflex Activation Therapy in Patients With Drug-Resistant Hypertension

Teba Alnima, Peter W. de Leeuw, Frans E.S. Tan, Abraham A. Kroon,
for the Rheos Pivotal Trial Investigators

Abstract—Carotid baroreflex activation has been demonstrated to provide enduring reductions in arterial blood pressure. The aim of this study was to investigate the effect of long-term therapy on renal function. A total of 322 patients were enrolled in the Rheos Pivotal Trial. Group 1 consisted of 236 patients who started baroreflex activation therapy 1 month after device implantation, whereas in the 86 patients from group 2 the device was activated 6 months later. Serum creatinine and urine albumin/creatinine ratio were collected at screening (before device activation), and at months 6 and 12. Multilevel statistical analyses were adjusted for various covariables. Serum creatinine increased from 78 to 84 μmol/L, and glomerular filtration rate decreased from 92 to 87 mL/min per 1.73 m^2 in group 1 at month 6 ($P<0.05$). These values did not change any further after 12 months of therapy. Patients with highest glomerular filtration rate showed the greatest decrease in glomerular filtration. Group 2 showed the same trends as group 1 even before device activation at month 6. Systolic blood pressure reduction seemed to be significantly related to the change in glomerular filtration rate in both groups. Albumin/creatinine ratio did not change in both groups during follow-up. In conclusion, baroreflex activation therapy in hypertensive patients is associated with an initial mild decrease in glomerular filtration rate, which may be considered as a normal hemodynamic response to the drop in blood pressure. Long-term treatment does not result in further decrease in renal function, indicating baroreflex activation as a safe and effective therapy. **(*Hypertension*. 2013;61:1334-1339.)** ● **Online Data Supplement**

Key Words: albumin/creatinine ratio ■ carotid baroreflex activation ■ drug-resistant hypertension ■ glomerular filtration rate ■ renal function

Baroreflex activation therapy (BAT) has proved to be an effective tool to reduce arterial blood pressure (BP) in patients with drug-resistant hypertension.[1,2] In a recent study by Bakris,[3] responders to BAT showed an average fall in systolic and diastolic pressure of 35/16 mm Hg after a follow-up period of 22 to 53 months with 55% of them at goal BP (<140 mm Hg or <130 mm Hg in renal disease and diabetes mellitus).

Because the kidneys are known to play a critical role in long-term BP regulation,[4] it is important to determine the impact of prolonged BAT on renal function. Only a few studies have reported on the effect of BAT on the kidney. Scheffers[1] observed a significant increase in serum creatinine in 22 patients after 1 year of continuous BAT. Nevertheless, information on other aspects of renal function, such as estimated glomerular filtration rate (eGFR) and urine albumin/creatinine ratio (ACR), is still very limited, and the long-term renal response to BAT has not been sufficiently investigated in human thus far.

The current article provides renal results from the phase III randomized Rheos Pivotal Trial in 322 subjects with resistant hypertension up to 12 months of follow-up.[2] Participants received either immediate BAT or deferred BAT (6 months later). The aim of this study was to investigate the renal response to prolonged BAT in patients with drug-resistant hypertension. To this end, we analyzed serum creatinine, eGFR, and urine ACR within and between the trial groups. Regarding the findings by Scheffers,[1] we hypothesized a mild decrease in renal function mainly as a result of significant BP reduction by BAT.

Methods

Study Design

The multicenter, randomized, double-blind Rheos Pivotal Trial (NCT00442286) was designed to assess the efficacy and safety of the Rheos system in patients with resistant hypertension. The ethics committee at each participating institution approved the protocol, and the investigation conformed to the principles outlined in the Declaration of Helsinki and Title 45, US Code of Federal Regulations, Part 46, Protection of Human Subjects, Revised November 13, 2001, effective December 13, 2001. All subjects provided written informed consent before the start of the study.

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From the Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands (T.A., P.W.d.L., A.A.K.); and Department of Methodology and Statistics, University of Maastricht, Maastricht, The Netherlands (F.E.S.T.).

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Correspondence to Abraham A. Kroon, Department of Internal Medicine, Maastricht University Medical Centre, P. Debyelaan 25, 6229 HX, Maastricht, The Netherlands. E-mail aa.kroon@mumc.nl

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Study Subjects

The Rheos Pivotal Trial included patients aged 21 to 80 years, who had an office cuff BP of ≥160/80 mm Hg, despite maximal tolerated therapy with ≥3 antihypertensive medications, including a diuretic. This measurement was obtained using a standardized automated device (BpTRU, VSM Medtech Ltd, Vancouver, Canada) within 30 days before the implant procedure. In addition, patients needed to have a 24-hour ambulatory systolic BP (SBP) of ≥135 mm Hg to be included. The main exclusion criteria were significant carotid atherosclerosis, inappropriate surgical candidate, and severe chronic kidney disease with eGFR ≤30 mL/min per 1.73 m^2. An extensive description of the inclusion and exclusion criteria has been provided elsewhere by Bisognano.[2]

Study Protocol

All eligible subjects were implanted with the Rheos system, which consisted of a pulse generator and 2 carotid leads. Device characteristics and the implant procedure have been described previously.[5,6] A total of 322 patients participated in the current investigation, and all procedures followed were in accordance with study guidelines. Participants were randomized in a 2:1 allocation 1 month after implantation of the device. Group 1 consisted of 236 patients who started immediately with BAT (immediate BAT). This group also included 57 patients, who were not randomized (open label). The remaining 86 patients in group 2 started therapy 6 months later (deferred BAT). Modification of antihypertensive drugs was allowed during the study. BP measurements were obtained in a sitting position with the patient's arm supported at the level of the heart. The cuff size was determined by a prior measurement of upper arm circumference. Office BP assessments were done at the same time (±2 hours) for every visit by BpTRU, which was programmed to take 6 measurements at 1-minute intervals. The mean of the last 5 readings was used as the office cuff pressure. In this study, we selected the BPs obtained at month 0 (1 month after device implantation but still before device activation) to be the baseline BPs. For further detailed explanation of the BP measurement method and Pivotal study protocol, we refer to the main article by Bisognano.[2]

Blood and urine samples were collected at screening (within 30 days before device implantation), and at month 6 and month 12 of follow-up. All samples were processed by a single reference laboratory. The blood was assayed for serum creatinine, and a morning clean catch urine was assayed for ACR. In addition, eGFR was calculated via the chronic kidney disease epidemiology collaboration equation (CKD-EPI).[7]

For a more detailed specification of the eGFR change, we divided the eGFR data at screening into the categories, low, intermediate, and high eGFR as follows: eGFR≤60, 60<eGFR≥90, and eGFR>90 mL/min per 1.73 m^2. In each eGFR category, we analyzed changes in eGFR during follow-up compared with baseline screening values.

Statistical Analyses

Results are expressed as mean±SD or as median and range for continuous variables, and as number with percentage for categorical variables. Various patient characteristics between groups were compared by an independent *t* test or a χ^2 test, where appropriate. Individual values for ACR were transformed into a logarithmic scale (base-10) for analysis. A mixed model analysis[8] was performed to compare the values of serum creatinine, eGFR, and urine ACR between groups 1 and 2 at screening, month 6, and month 12. We also used mixed model design to analyze the within group longitudinal trends in the above mentioned variables and accounted for the repeated measures in each group separately. The within group models were adjusted for multiple covariables, which seemed to be significant in a univariate analysis: age, sex, race, body mass index, antihypertensive therapeutic index (ATI),[9] net SBP reduction, dyslipidemia, diabetes mellitus type 2, coronary artery disease, duration of hypertension in the history, smoking, and obstructive sleep apnea. To determine the effect of various antihypertensive medication classes on the change in renal function, we performed post hoc analyses and tested the effect of each separate class on eGFR in both groups. The eGFR categories were analyzed by a dependent *t* test, which compared follow-up values at month 6 and month 12 to baseline screening values.

Statistical analyses were performed using SPSS 18.0 for Windows. *P* values <0.05 were considered statistically significant.

Results

Baseline characteristics and medications were equal between patients in groups 1 and 2, as shown in Tables 1 and 2. Mean office SBPs were 169±27 mm Hg in group 1 and 168±24 mm Hg in group 2 at month 0 (*P*=0.788). ATI averaged 32±18 and 35±21 for groups 1 and 2, respectively (*P*=0.328).

Change in Arterial Pressure

In group 1 (immediate BAT) SBP fell to 151±31 mm Hg (*P*<0.001) and 143±29 mm Hg (*P*<0.001) at month 6 and month 12, respectively (Table 2). Group 2 (deferred BAT) demonstrated a moderate but still significant SBP decrease to 160±26 mm Hg (*P*=0.013) at month 6, which became considerably larger at month 12 when the device had been continuously activated for 6 months (143±28 mm Hg; *P*<0.001). Comparing the SBPs between groups 1 and 2, there was a significant difference in the group means at month 6 (*P*=0.018), which was not present anymore at month 12 when both groups had been receiving BAT (*P*=0.833). Fairly similar results were obtained for diastolic BP and heart rate (Table 2).

Change in eGFR

Mean follow-up values of serum creatinine concentration and eGFR for both groups are presented in Table 3 and the Figure. Mean eGFR was significantly reduced after 6 months of BAT in group 1 (β=−2.954; 95% confidence interval [CI], −4.983 to −0.925; *P*=0.004). Group 2 also exhibited reduction in eGFR

Table 1. Baseline Characteristics

Characteristic	Group 1 (n=236)	Group 2 (n=86)	*P* Value
Demographics			
Sex, male	146 (62)	46 (55)	0.237
Age, y	54±10	53±10	0.306
Race, white	186 (79)	59 (70)	0.149
Body mass index, kg/m^2	33±5	32±6	0.426
Smoker	42 (18)	13 (16)	0.417
Medical history			
Diabetes mellitus type 2	67 (29)	27 (32)	0.531
Coronary artery disease	46 (20)	18 (21)	0.716
Antihypertensive medication			
Number	5±2	5±2	0.864
ACE inhibitor/AT II blocker	208 (88)	77 (90)	0.728
β-Blocker	200 (85)	72 (84)	0.822
α-Blocker	30 (13)	16 (19)	0.181
Calcium-channel blocker	152 (64)	62 (72)	0.196
Thiazides	146 (62)	53 (62)	0.969
Loop diuretic	83 (35)	29 (34)	0.809
Other diuretic	74 (31)	25 (29)	0.694
Sympatholytic	102 (43)	45 (52)	0.147

Values are n (%) or mean±SD. ACE indicates angiotensin-converting enzyme; and AT II, angiotensin II receptor.

Table 2. Changes in Blood Pressure and Antihypertensive Medication

Parameter	Time Point	Group 1 (n=236)	Group 2 (n=86)	*P* Value
SBP (mean±SD), mm Hg	Month 0	169±27	168±24	0.788
	Month 6	151±31 †	160±26 *	0.018
	Month 12	143±29 †	143±28 †	0.833
DBP (mean±SD), mm Hg	Month 0	100±18	100±14	0.731
	Month 6	90±18 †	95±15 †	0.032
	Month 12	87±18 †	87±15 †	0.796
HR (mean±SD), bpm	Month 0	79±14	79±17	0.959
	Month 6	72±14 †	75±15 *	0.096
	Month 12	71±14 †	72±15 †	0.679
ATI±SD	Screening	32±18	35±21	0.328
	Month 6	31±19	32±20	0.888
	Month 12	29±19 †	31±19 *	0.944

Values are mean±SD. SBP, DBP, and HR were measured at month 0, which is 1 month after device implantation but still before device activation. ATI indicates antihypertensive therapeutic index; DBP, diastolic blood pressure; HR, heart rate; and SBP, systolic blood pressure. Analyses performed by mixed models. **P*<0.05; †*P*<0.001 vs screening.

Table 3. Results of Creatinine, eGFR, and ACR Up to 1-Year Follow-Up

Parameter	Time Point	Group 1 (n=236)	Group 2 (n=86)	*P* Value
Creatinine (mean±SD), µmol/L	Screening	78±24	81±28	0.313
	Month 6	84±29 *	88±33 *	0.325
	Month 12	86±40 ‡	88±35 †	0.859
eGFR (mean±SD), mL/min per 1.73 m^2	Screening	92±20	91±22	0.601
	Month 6	87±22 †	85±23 *	0.589
	Month 12	85±24 †	86±24 *	0.786
ACR median (range), mg/mmol	Screening	1.8 (0.2–925)	3.2 (0.2–921)	<0.001
	Month 6	1.6 (0.1–410)	2.4 (0.1–836)	0.348
	Month 12	1.7 (0.2–537)	2.5 (0.2–289)	0.095

Values are mean±SD or median (range). ACR data were log transformed before performing mixed model analysis because of non-normal distribution. ACR indicates albumin/creatinine ratio; and eGFR, estimated glomerular filtration rate. Analyses were adjusted for multiple aforementioned covariables and performed by a mixed model design. **P*<0.05; †*P*<0.01; ‡*P*<0.001 vs screening.

at month 6 (β=−3.227; 95% CI, −6.185 to −0.269; *P*=0.033). In both groups, eGFR had significantly fallen at month 12 (β=−4.047; 95% CI, −6.461 to −1.634; *P*=0.001 for group 1; β=−4.680, 95% CI, −8.402 to −0.957; *P*=0.014 for group 2). In addition, levels of eGFR between both groups were not significantly different, neither at month 6 nor at month 12.

SBP reduction was significantly related to the fall in eGFR in group 1 (β=−0.115; 95% CI, −0.159 to −0.071; *P*<0.001) and in group 2 (β=−0.160; 95% CI, −0.237 to −0.083; *P*<0.001). ATI, which was significantly reduced at month 12, did not seem to be a significant predictor in the change in eGFR in both groups (β=−0.057; 95% CI, −0.147 to 0.032; *P*=0.208 for group 1; β=−0.054; 95% CI, −0.213 to 0.150; *P*=0.505 for group 2).

The categorized eGFR data in Table 4 indicate that patients in the highest eGFR category showed the largest decrease in eGFR during follow-up in group 1 and group 2. Patients in the intermediate eGFR category showed only a significant change at month 12 in group 1 (*P*=0.044). In the low eGFR category, no significant changes in eGFR occurred in either group.

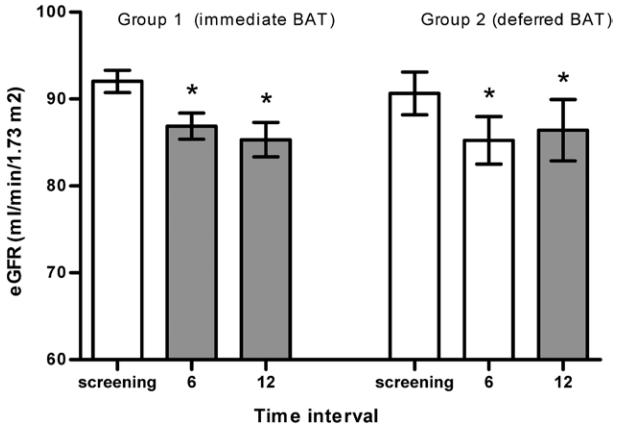

Figure. Bars represent the mean value of estimated glomerular filtration rate (eGFR) with the SE of the mean for each group at the different time intervals. Gray bars indicate baroreflex activation therapy (BAT) ON and white bars indicate BAT OFF. **P*<0.05 compared with screening.

Change in Urine ACR

Table 3 illustrates a wide spread in ACR values in both groups. Mixed model analysis demonstrated a significant difference in urine ACR between groups 1 and 2 at screening, which disappeared at month 6 and month 12 (*P*<0.001 at screening, *P*=0.348 at month 6, and *P*=0.095 at month 12).

Urine ACR values in group 1 remained almost unaffected after 6 months (logarithmic β=0.033; 95% CI, −0.018 to 0.084; *P*=0.205) and 12 months (logarithmic β=0.059; 95% CI, −0.003 to 0.121; *P*=0.063) of treatment. Group 2 showed the same trends at month 6 (logarithmic β=−0.046; 95% CI, −0.124 to 0.033; *P*=0.252) and month 12 (logarithmic β=−0.070; 95% CI, −0.170 to 0.031; *P*=0.175).

Table 4. eGFR in Low, Medium, and High eGFR Categories Up to 1-Year Follow-Up

	Time Point			
Group	Screening	Month 6	Month 12	n
Group 1				
eGFR≤60	49±8	49±13	43±13	18
60<eGFR≤90	78±8	76±16	74±16 *	75
eGFR>90	105±10	99±16 ‡	97±17 ‡	140
Group 2				
eGFR≤60	49±7	45±12	43±16	9
60<eGFR≤90	76±9	75±15	71±16	26
eGFR>90	107±10	100±13 †	101±16 †	47

eGFR (in mL/min per 1.73 m^2) categories are set by low, medium, and high eGFR at screening. Values are mean±SD. eGFR, estimated glomerular filtration rate. **P*<0.05; †*P*<0.01; ‡*P*<0.001 vs corresponding screening.

SBP reduction was a significant covariable in the estimation of urine ACR in group 1 (logarithmic β=−0.002; 95% CI, −0.003 to −0.001; $P<0.001$), but not in group 2 (logarithmic β=−0.002; 95% CI, −0.004 to 0.001; $P=0.127$).

Change in Antihypertensive Medication

As indicated in Table 2, ATI decreased significantly in both groups only after 1 year of follow-up (29±19; $P=0.004$ for group 1 and 31±19; $P<0.050$ for group 2). Nevertheless, mean ATI was still not significantly different between the groups at all time points. The number of patients treated with different drug classes during follow-up is presented in Table S1 in the online-only Data Supplement.

To test the effect of changes in medication on eGFR, post hoc analyses were performed on each antihypertensive drug class. Only calcium-channel blockers (CCBs) seemed to have a significant effect on eGFR. Patients with a CCB at screening in group 1 had a significantly higher eGFR than patients without a CCB (β=4.690; 95% CI, 0.075–9.304; $P=0.046$). However, this effect disappeared after receiving BAT at months 6 and 12 (β=0.697; 95% CI, −4.091 to 5.485; $P=0.775$; and β=0.779; 95% CI, −4.417 to 5.975; $P=0.769$, respectively). Group 2 demonstrated the same differences in eGFR values between subjects with and without a CCB (at screening, β=8.580; 95% CI, 1.047 to 16.113; $P=0.026$; at month 6, β=4.420, 95% CI, −3.173 to 12.013; $P=0.252$; and at month 12, β=7.519, 95% CI, −1.954 to 16.992; $P=0.119$). The drop in SBP in patients with and without a CCB was not significantly different (data not shown). Table S2 additionally specifies that the change in use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, thiazides, and loop diuretics did not influence the change in renal function during follow-up.

Discussion

In the present study, we evaluated the effect of prolonged BAT on the kidneys in a large patient population implanted with Rheos system for therapy-resistant hypertension. Long-term BAT resulted in a significant decrease in eGFR and no change in urine ACR in group 1 after 6 months and 1 year of continuous BAT. However, these responses were not progressive and relatively mild after 1 year of therapy. Group 2, which started BAT 6 months later than group 1, demonstrated similar renal responses at month 6 and month 12. This change in renal function can be explained in both groups by the drop in BP. Changes in antihypertensive medication were of no influence. Additional analyses revealed the decrease in eGFR was most apparent in subjects with baseline eGFR>90 mL/min per 1.73 m^2. Thus, the change in renal function during BAT may be explained by the physiological response to this therapy, which resulted in a profound BP fall attributable to inhibition of the sympathetic nervous system.

It is widely known that the kidneys play a dominant role in long-term BP regulation.[4,10] A key feature is the ability of the kidneys to alter renal excretion of salt and water by pressure natriuresis, which is impaired in all forms of hypertension.[11,12] Three effector target structures in the kidney contribute to BP control: the vasculature, the tubules, and the juxtaglomerular granular cells.[13] These systems regulate renal vascular resistance, sodium reabsorption, and renin release, respectively, by various factors, including renal sympathetic nerve activity.[14,15] Arterial baroreflexes are thought to affect renal excretory function, in part, by controlling renal sympathetic nerve activity with incomplete resetting even in the long term.[16,17] Potential mechanisms for the sustained BP lowering by BAT include inhibition of central sympathetic outflow (and renal sympathetic nerve activity).[18–21] In this study, both groups showed an obvious BP fall of ±15% with BAT at month 12. This has been presented in earlier work[2,3] and strongly confirmed in animal experiments[19,22] and human studies.[1]

The main finding of our study was the mild eGFR decrease with long-term BAT. Very few studies have addressed the renal response to BAT, and these were mainly animal studies. Lohmeier[23] explored the effects of suppression of sympathetic activity by 7 days of carotid baroreflex activation in obesity-induced hypertension in 6 dogs. They found a modest decrease in GFR associated with a sustained increase in fractional sodium excretion during carotid sinus stimulation. These values returned to prestimulation levels after terminating baroreflex activation. Iliescu[24] investigated the renal responses to baroreflex activation (for 2 weeks) in 6 normotensive dogs and found, along with a substantial BP reduction, about 10% and 20% decrease in GFR and renal blood flow, respectively, and no change in renal vascular resistance during the activation period. Lohmeier and Iliescu[23,24] explained the decrease in GFR by attenuation of tubular sodium reabsorption attributable to suppression of renal sympathetic nerve activity. This leads to increased sodium chloride delivery to the macula densa, which is expected to result in constriction of afferent arteriole by tubuloglomerular feedback and a concomitant GFR reduction. In our view, the decrease in eGFR during BAT could also be explained alternatively. In chronic hypertension in human endothelial dysfunction with impaired vasodilatation, the afferent arteriole gradually progresses into hyaline arteriosclerosis, myointimal hyperplasia, and vessel stiffness.[25,26] Afferent arteriolar hypertrophy and stiffness impair the ability of the arteriole to dilate in response to a fall in BP, resulting in a decrease in GFR attributable to a reduction in intraglomerular pressure. This indicates that it may be the inadequate ability of the afferent arteriole to dilate rather than the tubuloglomerular feedback-mediated constriction, which resulted in a decrease in GFR by BAT in these chronic hypertensive patients.

When dividing the subjects into groups of low, intermediate, and high eGFR according to screening values, the greatest decrease in eGFR was observed mainly in the high eGFR category (eGFR >90 mL/min per 1.73 m^2). These findings might be interpreted as deterioration in renal function by BAT. On the contrary, it is not uncommon for serum creatinine and GFR to increase and decrease, respectively, as the BP is lowered.[27,28] The exact mechanism behind this phenomenon is not entirely understood yet, but it may be drug-induced or by BP decrease.[28] Moreover, the observed mild, nonprogressive increase in serum creatinine along with the improvement in BP control in this study population could be considered as a successful reduction in the intraglomerular pressure.[29] Increases in serum creatinine up to 30%, which remain stable, should not be taken as an argument to withdraw from treatment.[30,31]

Our results lend further support to the evidence that a limited rise in creatinine may follow any form of antihypertensive treatment.[31] Interestingly, Mahfoud[32] recently demonstrated a 5% nonsignificant decrease in cystatin C as marker of GFR 6 months after renal denervation. The rate of decrease in eGFR is largely comparable with our findings after BAT but still needs further investigation. As long as both therapies have not been formally compared, it is difficult to draw conclusions about possible differences regarding their effects on the kidney. So far, we are inclined to believe that the mild change in renal function after BAT can be seen as a normal hemodynamic response to the fall in BP and not as a sign of renal injury.

To our knowledge, this is the first study that reports on the effect of long-term BAT on urine ACR. Microalbuminuria is a known risk factor for cardiovascular disease, which may be reversible by aggressive BP reduction.[33] However, our results did not demonstrate significant changes in ACR for both groups, despite the achieved BP fall at month 12. Only recently, this has also been shown for renal denervation.[32] This may be attributed to multiple factors. First of all, the acquired BP reduction in this study may not be large enough to realize a change in ACR within the specified follow-up period. In addition, the median ACR values in both groups were already below the limit of microalbuminuria, which may hinder the detection of a genuine effect of BAT on microalbuminuria. Moreover, adequate diagnosing of microalbuminuria requires 2 of 3 consecutive samples.[34] The current trial obtained only 1 baseline measurement of urine ACR at inclusion. Finally, about 90% of the study population used an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker at inclusion, which are known to be effective in attenuating albuminuria.[35] This may have masked a possible effect of BAT on the progression of proteinuria.

Antihypertensive medications have an important effect on overall renal function. Iliescu[24] found that baroreflex activation combined with amlodipine resulted in an even greater BP decrease but no change in GFR compared with only baroreflex activation. Our results do not entirely support this observation. Although there was a significantly higher eGFR in patients with a CCB than without a CCB at screening, this difference disappeared in both groups at months 6 and 12, which indicates that patients with a CCB also demonstrated a fall in eGFR along with BP decrease. These results show the complexity to predict a change in renal function in patients known with hypertension and other comorbidities for many years.

The main limitation of the present study is the lack of multiple baseline screening measurements of serum creatinine and urine ACR. This may have introduced a regression to the mean effect during follow-up. However, a regression to the mean effect is reduced in the between-group analyses by the randomized design. In addition, longer-term follow-up measurements are required to state the stability in renal function.

Perspectives

A mild, nonprogressive increase in serum creatinine and fall in eGFR occurred during 1 year of continuous BAT, which was mainly in patients with baseline eGFR >90 mL/min per 1.73 m^2. This response may in part be hemodynamic in nature and may even reflect long-term renal stability and protection.

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Novelty and Significance

What Is New?

- This is the first study presenting the effect of long-term baroreflex activation therapy on the kidney in a large human cohort, showing modest reduction in estimated glomerular filtration rate associated with blood pressure reduction.

What Is Relevant?

- Baroreflex activation therapy already demonstrated a successful blood pressure reduction in patients with drug-resistant hypertension. The kidney function seems to be preserved during this therapy.

Summary

Baroreflex activation therapy showed, next to blood pressure reduction, no adverse effects on the kidney. The mild reduction in estimated glomerular filtration rate probably reflects the hemodynamic decrease in systemic pressure rather than renal injury.