

Vascular and Renal Hemodynamic Changes after Renal Denervation

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Summary

Background and objectives Renal denervation (RDN) has been shown to be effective in reducing BP in treatment-resistant hypertension. Measurement of the renal and sympathetic activity revealed a decrease in sympathetic drive to the kidney and small resistance vessels after RDN. However, the consequences on renal perfusion and renal vascular resistance (RVR), as well as central hemodynamics, are unknown.

Design, setting, participants, & measurements Nineteen patients with treatment-resistant hypertension (office BP $\geq 140/90$ mmHg, despite at least three antihypertensive drugs [including a diuretic], and diagnosis confirmed by 24-hour ambulatory BP monitoring) underwent RDN between January and October 2011. Renal perfusion and RVR were noninvasively assessed by magnetic resonance imaging with arterial spin labeling, and renal function was assessed by estimating GFR before (day -1), after (day $+1$), and again after 3 months of RDN. Central hemodynamics was assessed using pulse wave analysis at day -1 and after 6 months of RDN.

Results Peripheral office BP (systolic, 158 ± 26 versus 142 ± 23 mmHg, $P=0.002$; diastolic, 83 ± 13 versus 76 ± 9 mmHg, $P=0.02$) and mean systolic 24-hour ambulatory BP (159 ± 17 versus 152 ± 17 mmHg, $P=0.02$) were significantly reduced 6 months after RDN. Renal perfusion was not statistically different between day -1 and day $+1$ (256.8 [interquartile range (IQR), $241-278$] versus 263.4 [IQR, $252-277$] ml/min per 100 g; $P=0.17$) as well as after 3 months (256.8 [IQR, $241-278$] versus 261.2 [IQR, $240-285$] ml/min per 100 g; $P=0.27$) after RDN. RVR dropped (432.1 [IQR, $359-525$] versus 390.6 [IQR, $338-461$] AU; $P=0.02$), whereas renal function was not statistically different at any time point. Central systolic BP (145 ± 31 versus 131 ± 28 mmHg; $P=0.009$), diastolic BP (85 ± 18 versus 80 ± 14 mmHg; $P=0.03$), and central pulse pressure (61 ± 18 versus 52 ± 18 mmHg; $P=0.02$) were significantly reduced 6 months after RDN. Central augmentation index (24 ± 8 versus $20 \pm 8\%$; $P=0.02$) was decreased 6 months after RDN.

Conclusion The data indicate that RDN significantly reduced peripheral and central BP. Despite reduced systemic BP, renal perfusion and function did not change after RDN.

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Introduction

Arterial hypertension is the most important risk factor for cardiovascular morbidity and mortality. The Symplicity Clinical Trial Program has recently suggested that catheter-based renal denervation (RDN) is a safe approach to substantially reduce BP in patients with resistant hypertension. Moreover, the findings of the extended long-term follow-up (comprising a series of nonrandomized studies involving >150 patients) suggest that BP reduction is sustained after RDN, at least up to 2 years (1). However, several unresolved issues need further exploration, such as the less clear effect of RDN on renal hemodynamics. Increased renal sympathetic nerve activity is well known to affect renal vasculature, resulting in decreased renal blood flow due to vasoconstriction *via* stimulation of α_{1A} -adrenoreceptors (2). However, no published data have analyzed the effect of RDN on renal perfusion immediately after the procedure or later on. Renal

perfusion can be measured by magnetic resonance imaging with arterial spin labeling (MRI-ASL) without contrast agents, such as iodine or gadolinium. Therefore, repeated measurements can be obtained without dye-related risks to the patient. Previously, we compared MRI-ASL with para-aminohippuric acid plasma clearance (the gold standard of renal perfusion measurements) and found a close relationship ($r=0.58$; $P<0.001$), indicating that this technique can approximate kidney perfusion (3,4).

Sensory afferent signaling originating from the kidneys modulates increased central sympathetic outflow toward other organs, including the heart and peripheral vasculature (5–7). However, data on central hemodynamics and arterial function (*e.g.*, pulse wave reflection) after RDN are lacking. Therefore, the aim of our study was to elucidate the effect of RDN on systemic and renal hemodynamics more precisely.

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Material and Methods

Study Cohort and Design

This investigator-initiated prospective observational analysis included 19 adults with treatment-resistant hypertension, defined as BP \geq 140/90 mmHg despite use of at least three antihypertensive drugs in full doses from different classes (including a diuretic) according to the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (8) and European Society of Hypertension/European Society of Cardiology guidelines (9,10); hypertension was confirmed by 24-hour ambulatory BP measurement, and patients were receiving a stable drug regimen and underwent RDN. Patients were treated between January and October 2011. In line with the recent position paper of the European Society of Hypertension (11), the main exclusion criterion was renal artery anatomy that is ineligible for treatment. Additional exclusion criteria were myocardial infarction, unstable angina pectoris, or a cerebrovascular accident within the last 6 months and widespread atherosclerosis, with documented intravascular thrombosis or unstable plaques and any contraindications for MRI.

The study protocol was approved by the local ethics committee, and the study was performed according to Declaration of Helsinki and "good clinical practice" guidelines. Written informed consent was obtained from all patients before study entry.

Brachial Office BP and 24-hour Ambulatory BP Monitoring

Brachial office BP and heart rate were measured after 5 minutes of rest in a sitting position with an oscillometric device (Dinamap Pro100V2; Criticon, Norderstedt, Germany); the last three measurements were averaged. In addition, ambulatory 24-hour BP measurements were obtained with an automatic portable device (Spacelabs No. 90207, Issaquah, Washington).

Catheter-based RDN

For RDN, the femoral artery was accessed with standard endovascular technique. The Simplicity catheter (Medtronic Ardian Inc., Palo Alto, CA) was advanced in each renal artery by angiography. As described previously in detail (12,13), at least four radiofrequency ablations (up to 120 seconds), controlled and regulated by a radiofrequency generator, were applied within the lengths of each renal artery. To obtain an activated clotting time of $>$ 250 seconds, all patients were given 5000 IU heparin. Diffuse visceral pain during the procedure was managed with anxiolytics and narcotics.

Renal Perfusion Measured with ASL

As previously reported from our group in detail (4), renal perfusion was measured with MRI on a 1.5-T scanner (Magnetom Avanto, Siemens, Erlangen, Germany) in supine position with dedicated surface coils using the flowing blood spins as natural "contrast media." All MRI-ASL images were analyzed by the same radiologist (J.R., with $>$ 10 years of experience in MRI and 3 years of experience in MRI perfusion techniques), who was blinded to the date of the examinations and the clinical data of the study participants.

In prior evaluations by our study group comprising 80 measurements, the intraobserver coefficient of variation

was 2.7%. Moreover, as a measure of reproducibility and accuracy, a high correlation was found between two separate measurements on the same day in 10 healthy persons ($r=0.84$, $P<0.01$; unpublished data). In addition, Artz *et al.* (14) published excellent repeatability and accuracy using the MRI-ASL technique.

Renal vascular resistance (RVR) was calculated as mean arterial pressure (mmHg) divided by renal perfusion measured by MRI-ASL (ml/min per 100 g kidney tissue) and therefore given in arbitrary units (AU).

The same procedure was applied at the examination at day -1 , day $+1$, and 3 months after RDN.

Pulse Wave Analysis

Brachial BP was recorded on the dominant arm with an oscillometric device (Dinamap Pro 100V2; Criticon, Norderstedt, Germany), and the last three measurements were averaged. Radial artery waveforms were sampled in the same arm by noninvasive technique, calibrated to the measured average brachial BP, using the SphygmoCor System (AtCor Medical, Sydney, Australia) as previously reported (15). Corresponding central (aortic) waveforms were then automatically synthesized from the radial artery waveform by a built-in validated transfer function (16–18). From the derived central waveforms, data are given for central systolic, diastolic BP, pulse pressure, and augmentation pressure (defined as the difference between the second and the first systolic peaks).

Central augmentation index (cAIx) is defined for a central waveform as the ratio of augmentation pressure to pulse pressure. cAIx is also reported as normalized to a heart rate of 75 beats per minute (cAIx@75). A good agreement between noninvasive and invasive assessed BP has been repeatedly shown (15,17,19,20). All recordings were of high quality, defined as quality index $>$ 80% (based on an in-device algorithm).

Biochemistry

Routine methods were used for the determination of serum concentrations of cystatin C (nephelometry) and creatinine (modified Jaffé method). Estimated GFR was calculated using Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD), and CKD-Epidemiology Collaboration (CKD-EPI) formulas (21–23).

Statistical Analyses

All analyses were performed using SPSS software, version 19.0 (SPSS, Inc., Chicago, IL). Normal distribution of data was confirmed by Kolmogorov-Smirnov tests before further analyses. Normally distributed data were compared by paired *t* tests and are expressed as mean \pm SD. Nonparametric data are presented as median and interquartile range (IQR). A two-sided *P* value $<$ 0.05 was considered to represent a statistically significant difference. In addition, a general linear model was applied to adjust for the possible effect of both clinical variables at baseline and the change in BP and heart rate due to RDN on the change in cAIx@75.

Results

Clinical and Peripheral BP Data

We included 19 patients in this open-label study. The clinical characteristics of the study population are given in

Table 1. Most of the middle-aged patients were men and were overweight. Although patients were treated with 5.6 ± 1.3 antihypertensive drugs on average, office systolic BP was 158 ± 26 mmHg and office diastolic BP was 83 ± 13 mmHg. Compared with day -1 , peripheral (brachial) office BP was significantly reduced 3 months and 6 months after RDN (Table 2). Baseline systolic BP was correlated with the reduction of systolic BP due to RDN ($r = -0.49$; $P = 0.04$). Furthermore, average 24-hour BP derived from ambulatory BP monitoring was reduced from day -1 to 6 months after RDN (Table 2). Heart rate did not differ at any time point (Table 2).

Patients and physicians were instructed not to change antihypertensive medication during the study period. However, the antihypertensive drug regimen was reduced in five patients: in four patients because of confirmed BP levels below respective target BP and in one patient according to the recommendation not to combine aliskiren with another renin-angiotensin system-acting drug in patients with CKD and diabetes. In two patients, antihypertensive doses were increased.

Renal Hemodynamics and Function

Renal perfusion was not statistically different between day -1 and day $+1$ (256.8 [IQR, 241–278] versus 263.4 [IQR, 252–277] ml/min per 100 g; $P = 0.17$) after RDN. In addition, there was no significant change between day -1 and 3 months (256.8 [IQR, 241–278] versus 261.2 [IQR, 240–285] ml/min per 100 g; $P = 0.27$) after RDN, as well as between day $+1$ and 3 months ($P = 0.57$) after RDN (Figure 1). In contrast, RVR was significantly reduced (432.1 [IQR, 359–525]) versus 390.6 [IQR, 338–461] AU; $P = 0.02$) 3 months after RDN. Renal function, irrespective of whether assessed by cystatin C or serum creatinine, was not

statistically different at any point (Table 3). Accordingly, there was no significant difference in estimated GFR (eGFR) measured using Cockcroft-Gault, MDRD, and CKD-EPI formulas at any point. No patients developed a doubling of serum creatinine or even a 25% or more reduction of eGFR (CKD-EPI formula) after RDN at any point.

Central Hemodynamics

Central systolic and diastolic BP were significantly reduced 6 months after RDN, respectively. The decrease in central systolic BP was not statistically different from the decrease in peripheral brachial systolic BP (-14 ± 20 mmHg versus -17 ± 20 mmHg; $P = 0.29$). Central pulse pressure and augmentation pressure reflecting arterial stiffness of large arteries were significantly reduced 6 months after RDN (Table 2), and in parallel compared with day -1 cAIx@75 decreased at 6 months after RDN ($24\% \pm 8\%$ versus $20\% \pm 8\%$; $P = 0.02$) (Figure 2). According to general linear models, age, peripheral office systolic BP at baseline, body mass index, and eGFR did not have a significant association with cAIx@75; only the change in systolic BP due to RDN was a confounder on the change of cAIx@75 ($P = 0.02$).

Discussion

Sympathetic overactivity plays a crucial pathogenetic role in the development, maintenance, and aggravation of arterial hypertension. A meta-analysis of long-term trials has shown a linear correlation between deterioration in renal function over time and BP (24). Moreover, muscle sympathetic nerve activity (assessed by microneurography) was significantly and inversely correlated with eGFR in hypertensive patients (25). In the Symplicity HTN-2 trial renal function (assessed by serum creatinine, eGFR [MDRD], and cystatin C concentrations) did not change from baseline to 6 months of RDN (13). The extended long-term follow-up of the Symplicity HTN-1 trial demonstrated a stable maintenance of eGFR (-2.9 [95% CI, -6.2 to 0.3] ml/min per 1.73 m²) after 1 year ($n = 64$). Only limited data ($n = 10$) are available on 2 years of follow-up, showing a change of eGFR of -16.0 ml/min per 1.73 m², which seems to be related to excessive diuretic therapy (1). Nevertheless, concerns have been raised because of the limited follow-up data on whether RDN might negatively influence renal function (1,26).

Our study could confirm published data on unchanged renal function, regardless of which laboratory measure or formula to calculate eGFR was used (21–23) (Table 3), but eGFR stability cannot be claimed because follow-up was only 3 months. To our knowledge, ours is the first study to measure renal perfusion using MRI-ASL before, immediately, and again 3 months after RDN. One of our major findings is that despite reduced systemic BP, renal blood flow did not change after RDN, either immediately or 3 months after RDN (Figure 1). In addition to laboratory data on estimating GFR, we applied imaging techniques to determine renal perfusion after RDN and found no alteration of renal blood flow. Our data give additional insight into the regulation of renal perfusion after RDN. It is well established that among others, stimulation of the renal sympathetic nerves causes a reduction of renal blood

Table 1. Clinical characteristics

| Characteristic | Value |
|---|----------------|
| Age (yr) | 62.3 ± 9.2 |
| Men/women (<i>n/n</i>) | 14/5 |
| Height (cm) | 172 ± 11 |
| Weight (kg) | 92.1 ± 15 |
| Body mass index (kg/m ²) | 30.4 ± 4.1 |
| Waist (cm) | 107 ± 9.1 |
| Number of antihypertensive agents | 5.6 ± 1.3 |
| Types of antihypertensive agents (<i>n</i>) | |
| Angiotensin-converting enzyme inhibitors | 7 |
| Angiotensin-receptor blockers | 14 |
| Direct renin inhibitors | 13 |
| Calcium-channel blockers | 17 |
| β -blockers | 14 |
| Diuretics | 14 |
| Central sympatholytics | 16 |
| Aldosterone antagonists | 2 |
| Vasodilators | 9 |
| Coronary heart disease (%) | 32 |
| Type 2 diabetes mellitus (%) | 63 |
| Hypercholesterolemia (%) | 37 |

Values expressed with a plus/minus sign are the mean \pm SD.

| Measure | Day -1 | 3 Months | 6 Months | P Value | |
|------------------------------|--------|----------|----------|------------------------|------------------------|
| | | | | Day -1 versus 3 Months | Day -1 versus 6 Months |
| Peripheral (brachial) | | | | | |
| Office SBP (mmHg) | 158±26 | 144±22 | 142±23 | 0.001 | 0.002 |
| Office MAP (mmHg) | 110±17 | 99±12 | 99±12 | 0.002 | 0.003 |
| Office DBP (mmHg) | 83±13 | 75±8 | 76±9 | 0.005 | 0.02 |
| Office HR (beats/min) | 68±14 | 70±15 | 66±12 | 0.13 | 0.45 |
| Central (aortal) | | | | | |
| SBP (mmHg) | 145±31 | NA | 131±28 | NA | 0.009 |
| DBP (mmHg) | 85±18 | NA | 80±14 | NA | 0.03 |
| Pulse pressure (mmHg) | 61±18 | NA | 52±18 | NA | 0.02 |
| AP (mmHg) | 19±9 | NA | 14±8 | NA | 0.01 |
| 24-hour ABPM | | | | | |
| Mean SBP (mmHg) | 159±17 | NA | 152±17 | NA | 0.02 |
| Mean DBP (mmHg) | 84±13 | NA | 80±8 | NA | 0.14 |

Values expressed with a plus/minus sign are the mean ± SD. SBP, systolic BP; MAP, mean arterial pressure; DBP, diastolic BP; HR, heart rate; NA, not applicable; AP, augmentation pressure; ABPM, ambulatory BP monitoring.

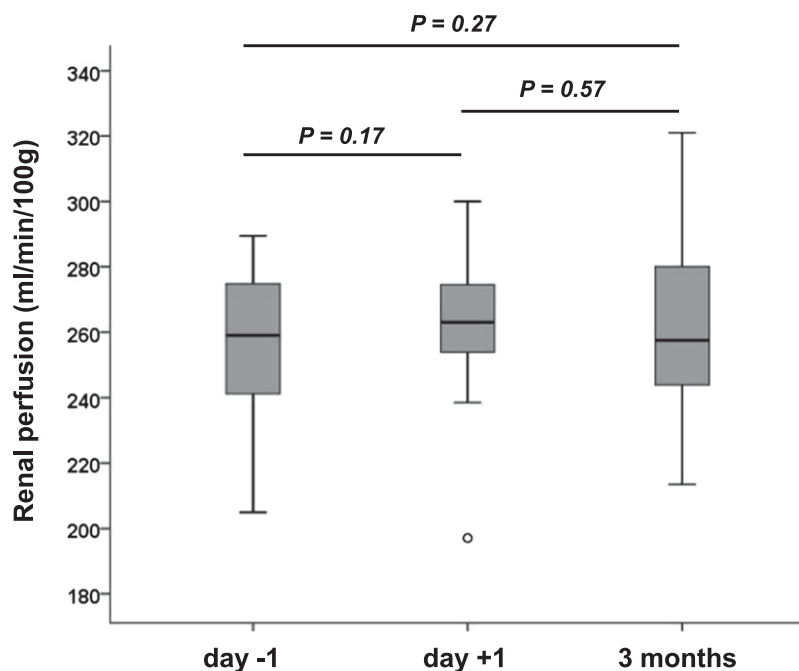


Figure 1. | Renal perfusion measured by 1.5-T magnetic resonance imaging with arterial spin labeling before (day -1), after (day +1), and after 3 months of renal denervation. Medians, interquartile ranges, minimum and maximum, and outlier are shown.

flow (27,28). Indeed, a case report has shown that RDN was attended by an increase in renal plasma flow (29), but these data come from a single patient. In our study cohort, calculated RVR (using renal perfusion assessed by MRI-ASL and brachial mean arterial pressure) was significantly reduced 3 months after RDN, indicating reduced resistance in renal vascular bed. These data are in accordance with another report relying on duplex ultrasonography that found a decreased renal resistive index after 6 months of RDN, indicating reduced intraparenchymal resistance (30). Thus, in this study we observed that renal perfusion

did not change acutely or after 3 months of RDN (Figure 1). This indicates that autoregulation of renal perfusion did not appear to be adversely effected, despite substantially reduced systemic BP after RDN, and confirms the absence of hyperfiltration after RDN in all patients, including those with diabetes. Moreover, the preserved renal perfusion in the presence of reduced systemic BP may partly explain the preserved renal function seen after RDN as opposed to diuretic medication (31).

In addition to the changes in renal hemodynamics, we assessed central hemodynamics. The second major finding

| Variable | Day -1 | Day +1 | 3 Months | P Value | |
|--|----------|----------|----------|----------------------|------------------------|
| | | | | | |
| | | | | Day -1 versus Day +1 | Day -1 versus 3 Months |
| Serum creatinine (mg/dl) | 1.25±0.7 | 1.19±0.6 | 1.25±0.8 | 0.18 | 0.99 |
| Cystatin C (mg/dl) | 1.08±0.4 | NA | 1.09±0.4 | NA | 0.64 |
| eGFR (ml/min per 1.73 m ²) | | | | | |
| CKD-EPI | 69.5±26 | 70.4±24 | 71.5±26 | 0.69 | 0.26 |
| MDRD | 72.6±29 | 74.5±29 | 73.9±28 | 0.46 | 0.62 |
| Cockcroft -Gault | 90.1±42 | 92.3±42 | 91.2±42 | 0.43 | 0.68 |

Values are expressed as mean ± SD. NA, not applicable; eGFR, estimated GFR; CKD-EPI, CKD-Epidemiology Collaboration; MDRD, Modification of Diet in Renal Disease.

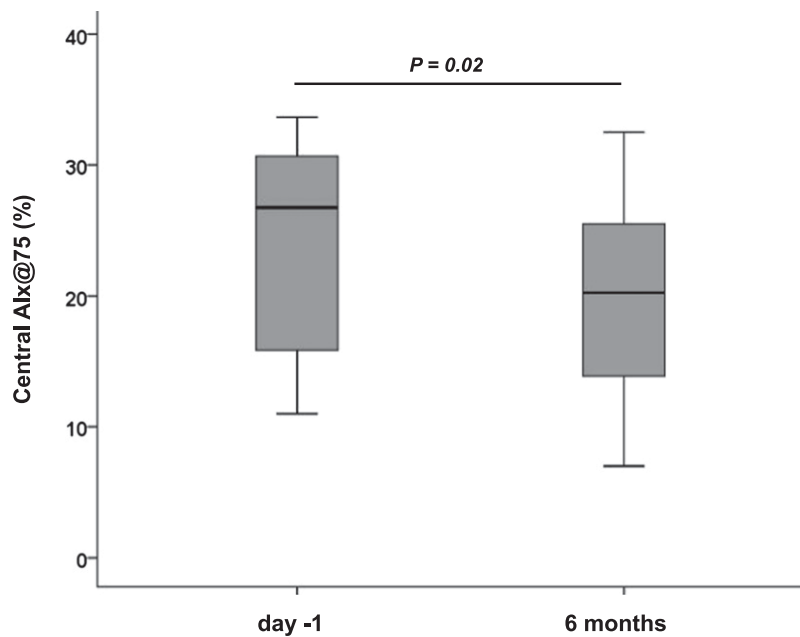


Figure 2. | Central augmentation index normalized to a heart rate of 75 beats per minute (cAIx@75) before (day -1) and after 6 months of renal denervation. Medians, interquartile ranges, minimum and maximum are shown.

of this study is that RDN significantly reduces central BP, central pulse pressure, and central augmentation pressure and cAIx@75. Central hemodynamics more precisely assess the pressure load on the cardiovascular system in arterial hypertension. Recently, it was found that central BP more accurately predicts all-cause and cardiovascular mortality compared with peripheral BP (32). Moreover, evidence suggests that central BP has an independent predictive value for cardiovascular events (33,34). Studies have also shown substantial differences in the ability of antihypertensive drugs to affect central in contrast to peripheral hemodynamics and related cardiovascular risk (35,36). The level of central BP is influenced by several variables, including arterial stiffness and pressure wave reflection. However, the predominant role is a matter of debate (37). Exemplary findings from a twin study suggested that the increase in central BP was mainly associated with increased pulse wave reflection due to arterial dimensions or

peripheral large artery tone, rather than arterial stiffness (38). Sensory afferent signaling arising from the kidneys leads to increased sympathetic outflow, resulting in vasoconstriction of small resistance vessels, and thereby represents one neural mediated way, which leads to elevated BP (39,40). In the past, cAIx was partly considered to be a surrogate measure of arterial stiffness. However, cAIx is a composite measure of the magnitude (*e.g.*, vasoconstriction of peripheral blood vessels, which is under control of sympathetic system) and the timing of wave reflection, which itself is affected by an earlier return of the pulse wave as a result of an increased pulse wave velocity due to arterial stiffness. Moreover, central pulse pressure, the physiologic pulsatile component of BP and the simplest measure of large arterial stiffening, was reduced 6 months after RDN. Hence, these findings may indicate that RDN affects pulse wave reflection *via* a reduction in peripheral resistance, also resulting in a reduction of central BP.

In contrast to prior studies of RDN (12,13), we included patients with treatment-resistant hypertension, whose office BP was only $\geq 140/90$ mmHg despite use of at least three antihypertensive drugs in full doses from different classes (including a diuretic); these patients had confirmed persistent hypertension, not white coat hypertension or pseudo-resistant hypertension. This patient population more realistically approximates a large population of sub-optimally treated hypertensive patients in whom RDN significantly reduced peripheral systolic and diastolic BP, as well as results on 24-hour ambulatory BP monitoring (Table 2). As expected, the magnitude of BP reduction is less than previously reported as the entry BP criteria in our study were comparably less. Since baseline BP emerged as the only determinant of BP decrease after RDN (12,13), we related the lower BP decrease in the study to the lower baseline BP. In accordance with prior studies, we also found a correlation between baseline systolic BP and the reduction of systolic BP due to RDN ($r = -0.49$; $P = 0.04$).

In conclusion, our data indicate that RDN reduces central BP, which may improve cardiovascular prognosis. Despite reduced perfusion pressure of the kidney, renal perfusion and function did not change immediately or 3 months after RDN.

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Disclosures

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