BLOOD PRESSURE RESPONSE TO RENAL DENERVATION IS CORRELATED WITH BASELINE BLOOD PRESSURE VARIABILITY: A PATIENT-LEVEL META-ANALYSIS

Short title: Blood Pressure Variability and Renal Denervation

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Abstract

Background: Sympathetic tone is one of the main determinants of blood pressure (BP) variability and treatment-resistant hypertension (rHT). The aim of our study was to assess changes in BP variability after renal (RDN). Additionally, on an exploratory basis, we investigated whether baseline BP variability predicted the BP changes after RDN.

Methods: We analyzed 24-h BP recordings obtained at baseline and 6 months after RDN in 167 rHT patients (40 % women; age, 56.7 years; mean 24-h BP, 152/90 mmHg) recruited at 11 expert centers. Blood pressure variability was assessed by weighted standard deviation (SDiw), average real variability (ARV), coefficient of variation (CV) and variability independent of the mean (VIM).

Results: Mean office and 24-h BP fell by 15.4/6.6 mmHg and 5.5/3.7 mmHg, respectively ($P<0.001$). In multivariable-adjusted analyses, systolic /diastolic SDiw and VIM for 24-h systolic/diastolic BP decreased by 1.16/0.63 mmHg ($P\leq 0.01$) and 0.85/0.43 mmHg ($P\leq 0.05$), respectively, whereas no significant changes in ARV or CV occurred. Furthermore, baseline SDiw ($P=0.0006$), ARV ($P=0.012$) and VIM ($P=0.04$) predicted the decrease in 24-h diastolic - but not 24-h systolic - BP after RDN.

Conclusions: RDN was associated with a decrease in BP variability independent of the BP level, suggesting that responders may derive benefits from the reduction in BP variability as well. Furthermore, baseline diastolic BP variability estimates significantly correlated with mean diastolic BP decrease after RDN. If confirmed in

younger patients with less arterial damage, in the absence of the confounding effect of drugs and drug adherence, baseline BP variability may prove a good predictor of BP response to RDN.

Keywords: ■ renal denervation ■ resistant hypertension ■ blood pressure variability ■ ambulatory blood pressure measurement

Condensed abstract

We analysed different blood pressure variability estimates in 167 patients with drug-resistant hypertension recruited in 11 European expert centres from the ENCOReD network. Weighted standard deviation (SDiw) and variability independent of the mean (VIM) derived from 24-h ambulatory blood pressure decreased significantly after renal denervation. Furthermore, baseline diastolic SDiw and VIM correlated with blood pressure changes after renal denervation. Our results suggest that (i) responders to renal denervation may derive ancillary benefits from reduction in blood pressure variability; (ii) baseline blood pressure variability may predict blood pressure response to renal denervation.

Introduction

Blood pressure (BP) variability is the result of complex interactions between extrinsic environmental and behavioral factors and intrinsic cardiovascular regulatory mechanisms, both humoral and neural [1,2]. The influence of these different factors is difficult to disentangle. However, it is generally accepted that central sympathetic drive is one of the main determinants of BP variability [1,3] and treatment-resistant hypertension [4,5]. In particular, studies implementing microneurographic traffic recordings from peroneal nerves, showed a direct relation between 24-h BP variability and muscle sympathetic nerve activity (MSNA) [6]. We hypothesized that an intervention targeting to reduce renal sympathetic nerves activity, such as renal denervation (RDN), might decrease BP variability, which if confirmed in the long-run might decrease cardiovascular risk [7]. However, previous studies testing this hypothesis were usually small, monocentric [2,7,8], and applied indices of BP variability that were heavily dependent on the BP level [2,7-9]. These studies did therefore not allow to prove or disprove that RDN influenced BP variability. None of the aforementioned studies tested whether BP baseline variability predicted the BP response to RDN over and above baseline BP.

Furthermore, in view of the modest BP benefits of RDN performed with the unipolar Symplicity catheter [10,11], the identification of responders to RDN is a central issue in the field [12,13]. As patients with higher baseline sympathetic tone may respond better to RDN, the identification of an easy-to-determine, non-invasive

index of baseline sympathetic activity, likely to predict the BP response to RDN, is a top research priority [12,13].

In this study, we took advantage of the collaboration within the European Network Coordinating research on Renal Denervation (ENCOReD) [14]. We assessed changes in 24-hour ambulatory BP variability in response to RDN and investigated whether baseline BP variability predicted the 6-month BP changes induced by RDN. We used ambulatory monitoring as the state-of-the-art technique for the assessment of BP.

Methods

Patients

Following the fifth ENCOReD network meeting, held in Leuven on 31 January 2014, 11 centers volunteered to contribute anonymised data for analysis. The eligibility criteria for RDN at the participating centers complied with the European consensus [15] and have been described previously [14]. Briefly, eligibility criteria for RDN included: (i) optimized treatment with 3 or more antihypertensive drug classes at the maximal tolerated dose, preferably including a diuretic; (ii) a systolic office BP of at least 140 mmHg; (iii) a daytime or 24-h systolic BP of at least 135 or 130 mmHg, respectively; (iv) an estimated glomerular filtration rate (eGFR) of 30 ml/min/1.72 m2 or higher; (v) systematic exclusion of secondary hypertension; (vi) suitable anatomy of the renal arteries (diameter ≥ 4 mm, length ≥ 20 mm, absence of stenosis ≥ 50% or renal artery stent. All patients who underwent at least two 24-h BP measurements of sufficient quality, one at baseline and the second at follow-

up and in whom the unedited BP recordings could be made available were eligible for inclusion in this analysis. Ambulatory BP recordings were reviewed for 222 consecutively enrolled patients. Of those, we excluded 52, due to missing readings during 3 consecutive hours on ambulatory BP monitoring, either at baseline or at follow-up. Three additional patients were discarded, because the number of daytime or nighttime readings was less than 10 or 5, respectively. The total number of patients eligible for inclusion in the current analysis was therefore 167. All participating centers received approval from the competent Institutional Review Board. Patients provided written informed consent except in centers where RDN is part of routine clinical care.

Blood Pressure Measurement

In the current RDN studies, office BP was measured either by validated oscillometric devices (ten centers) or auscultation of the Korotkoff sounds (one center). The number of office readings averaged per visit ranged from 2 to 5. All participating centers used validated portable monitors to measure the ambulatory BP according to the guidelines of the European Society of Hypertension [16]. Across centers, the intervals between daytime and nighttime readings ranged from 15 to 30 minutes and from 30 to 60 minutes, respectively. The recordings were sparsely edited, removing only readings labelled with an error code or with lower systolic than diastolic BP level. We computed the daytime and nighttime BP as the within-individual mean of the readings between 10 AM and 8 PM (daytime) and 12 PM to 6 AM (nighttime) respectively, weighted for the interval between readings. These short

definitions of daytime and nighttime eliminate the transition periods in the morning and the evening during which BP changes rapidly in most people and result in daytime and nighttime BP levels that approximate within 1-2 mmHg to the wakeful and asleep BP recorded by the diary method [18].

Blood Pressure Variability

We assessed reading-to-reading 24-hour BP variability using different estimates, both dependent (weighted standard deviation, average real variability) and independent of the mean (coefficient of variation, variance independent of the mean). Weighted standard deviation (SDiw) is the standard deviation (SD) over 24 hours weighted for the time interval between consecutive readings[19-20] . Average real variability (ARV) [21] is the average of the absolute differences between consecutive BP measurements. It has the advantage of accounting for the order of the BP measurements. Standard deviation weighted according to Bilo et al.(SDtw) [22] is the average of daytime and nighttime SD weighted for the duration of the daytime and nighttime interval. It allows to get rid of the influence of nocturnal BP fall . However, it remains dependent to some extent of mean BP. Coefficient of variation (CV) is SD divided by the mean. Finally, variance independent of the mean (VIM) [23] is calculated as the SD divided by the mean to the power x and multiplied by the population mean to the power x. The power x is obtained by fitting a curve through a plot of SD against mean using the model $SD = a \times mean^{x}$, where *x* was derived by non-linear regression analysis as implemented in the PROC NLIN procedure of the SAS package.

Statistical Methods

We used SAS, version 9.4, for database management and statistical analysis. We applied Student's *t*-tests to compare unadjusted means and to determine the significance of unadjusted within-group BP and BP variability changes (follow-up measurement subtracted from baseline) and the χ^2 –statistic to compare proportions. To estimate baseline predictors of changes in BP variability, we applied a generalization of the standard linear model, as implemented in the PROC MIXED procedure of the SAS package. In multivariable-adjusted analyses, we considered as covariables: sex, age, body mass index, mean arterial pressure, pulse pressure, baseline night-day mean BP ratio, glomerular filtration rate (eGFR; estimated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula) [24], smoking and drinking, and a history of diabetes mellitus or cardiovascular disease. In mixed models, we also adjusted for baseline and we accounted for center as a random effect. Significance was a two-tailed α level of 0.05 or less.

Results

Baseline Characteristics

Twenty-four hour ambulatory BP measurements were analyzed in 167 patients (mean age 56.7 years; 40.1% women; mean baseline office and 24-h ambulatory BP: 172/98 and 152/90 mmHg, respectively). The median number of ambulatory blood pressure readings at baseline was 58 (IQR: 45-64; 5^{th}-95^{th} percentile: 33-78) over 24 hours, 28 (IQR: 20-31; 5^{th}-95^{th} percentile: 16-40) during daytime and 12 (IQR: 7-13; 5^{th}-95^{th} percentile: 6-18) during nighttime. Corresponding numbers at

follow-up were 58 (IQR: 46-65; 5^{th}-95^{th} percentile: 31-77) over 24 hours, 27 (IQR: 21-30; 5^{th}-95^{th} percentile: 13-39) during daytime and 12 (IQR: 7-13; 5^{th}-95^{th} percentile: 6-18) during nighttime. **Table 1** lists the baseline characteristics of the patients across tertiles of 24-h systolic BP (<143 mmHg; 143-159 mmHg, ≥ 159 mmHg). The proportion of smokers was higher in the second (20.7%) and third (20.4%) tertiles compared to the first (3.6%) tertile of systolic BP (*P*=0.016). Mean age tended to be higher in the first (59.5 years) compared to the second (54.7 years) and third (56.1 years) tertiles (*P*=0.053). 24-h ambulatory heart rate increased significantly across tertiles of 24-h systolic and diastolic BP (p<0.029). Otherwise, the groups did not differ with regard to body mass index, eGFR, prevalence of diabetes or previous cardiovascular diseases. SDtw and ARV derived from systolic BP slightly increased with higher category of 24-h systolic BP (SDtw: 13.1±4.6; 14.6±4.3; 15.2±4.4 mmHg; *P*=0.041; ARV: 12.0±3.1; 13.2±4.2; 13.7±4.2mmHg; *P*=0.06), whereas no trend was observed for SDiw, CV or VIM derived from systolic BP. SDiw, SDtw and ARV derived from diastolic BP significantly increased across tertiles of diastolic BP (SDiw: 11.6±3.6; 13.0±4.3; 14.8±4.3; *P*=0.0004; SDtw: 8.9±2.4; 10.2±2.8; 11.8±4.2; *P*<0.0001; ARV: 8.6±2.6; 9.6±3.1; 10.8±4.1; *P*=0.002). No trend was observed for CV or VIM derived from diastolic BP. Notably, after exclusion of 68 patients with less than 20 daytime and 7 nighttime BP readings [25], these findings remained virtually unchanged (data not shown).

Renal sympathetic denervation

Experienced interventional specialists performed all procedures. Symplicity catheters were used in most cases (Symplicity: 72%, Symplicity Flex: 8%, Symplicity Spyral: 0.5%). Other catheters used were 6F short IMA catheters (13%), Vessix (4%), St Jude EnlighHTN (2%) and Covidien OneShot (0.5%) catheters.

Experienced changes in Blood Pressure level after RDN

The systolic/diastolic BP reductions between baseline and follow-up (6.7 ± 2.5 months after RDN) averaged 15.4/6.6 mmHg for office BP, and 5.5/3.7 mmHg (**Table 2**), 6.3/4.1 mmHg, and 4.5/2.9 mmHg for 24-h, daytime and nighttime ambulatory BP, respectively (*P*<0.001 for all). The 24-h ambulatory heart rate decreased from baseline to follow-up with -1.12 (95%CI: -2.17 to -0.08) beats per minute (p= 0.035 after multivariable adjustment). The number of drug classes decreased from 4.8±1.5 at baseline to 4.3±1.7 at follow-up (*P*<0.001).

Changes in Blood Pressure variability after RDN

Changes in ARV derived from systolic or diastolic 24-h ambulatory BP did not reach statistical significance (-0.20, *P*=0.49; -0.31, *P*=0.29, respectively). Similarly, decreases in CV were not significant (-0.45, *P*=0.12; -0.39, *P*=0.28, for 24-h systolic and diastolic BP, respectively). SDiw, SDtw and VIM derived from 24-h systolic BP decreased by -1.29 mmHg (95%CI: -2.17 to -0.42; P=0.004), -0.78 mmHg (95%CI: --1.43 to -0.12; P=0.02) and -1.11 mmHg (95%CI: -1.92 to -0.30; P=0.007), respectively. Decreases in SDiw and VIM derived from systolic BP (-1.18 mmHg, 95%CI: -

1.84 to -0.51; P=0.0006 and -0.86 mmHg, 95%CI: -1.45 to -0.27; P=0.005, respectively) remained significant in multivariable-adjusted analyses and were paralleled by similar changes for 24-h diastolic BP (-0.63 mmHg, 95%CI: -1.12 to -0.13; P=0.014 and -0.42 mmHg, 95%CI: -0.86 to -0.01; P=0.054, respectively) (**Table 2**).

Relation between Baseline BP Variability and Ambulatory BP Changes after RDN

We also tested the relations of BP variability indices at baseline with changes in ambulatory BP level after RDN, expressed as the difference of 24-ambulatory BP at baseline minus follow-up (6.7±2.5 months after RDN).While the relation between baseline SDw derived from 24-ambulatory systolic BP and change in 24-h systolic ambulatory BP after RDN was borderline significant (P=0.057), no relation was found between other BP variability estimates at baseline and 24-h ambulatory systolic BP response to RDN (P=0.35, 0.97 and 0.25, for baseline ARV, CV and VIM, respectively). In contrast, baseline SDiw (P=0.0006), ARV (P=0.01) and VIM (P=0.04) - but not CV (P=0.22) - derived from 24-h diastolic BP were significantly related with changes in 24-h diastolic BP level after RDN. After adjustment for baseline BP, correlations with SDiw (*P*=0.028) and VIM (*P*=0.030) - but not ARV (*P*=0.17) - remained statistically significant, while the correlation with CV reached statistical significance (*P*=0.031) (Figure 1). Finally, we attempted to determine the optimal threshold value of the different BP variability estimates for predicting diastolic BP decrease after RDN. Diastolic BP response was defined as a mean 24-hour diastolic BP change > 10 mmHg after RDN. Thresholds were determined by maximizing the Youden index (maximum of sensitivity plus specificity minus 1). The opti-

mal thresholds for each baseline variability estimate, the proportion of patients correctly or incorrectly classified as responders or non-responders, as well as the corresponding sensitivity, specificity and predictive values are indicated in Table 3.

Discussion

The two key findings of this new analysis of the ENCOReD database are the following: (i) RDN decreases not only BP level, but BP variability as well; (ii) diastolic BP variability at baseline is correlated with 24-h diastolic BP changes in response to RDN.

Several studies [2,7-9] proposed that RDN might decrease BP variability, as captured by the unadjusted [2,7-9] or adjusted [2] standard deviation of mean 24-h ambulatory BP, time-rate of 24-h ambulatory BP variation (mean of the absolute ratios of the difference between successive BPs and the minutes between them) [8], ARV [2,9] and CV of 24-h ambulatory BP [2,9]. However, most of these analyses [2,7,8] were performed in small, single centre cohorts (sample sizes ranging from 11 to 31). The effect of RDN on the indices of BP variability was not always consistent between studies, and some of the indices chosen, such as unadjusted standard deviation of the mean or ARV, are strongly related with mean BP [26]. In all studies [2,7,9] but one [8], RDN was performed using the Symplicity unipolar catheter. Finally, none of these studies assessed VIM, which is considered to be a particularly robust index of BP variability independent of the mean [23].

In contrast with the publication by Miroslawska et al. [2], performed in a small subset (n=23) of truly adherent patients with resistant hypertension, in the ENCOReD database, RDN was not followed by a significant decrease in ARV or CV. Notably however, in the recent study by Ewen et al. [9] including 84 patients, changes in these measurements were only borderline significant 6 months after RDN (P=0.054 and 0.071, respectively). We nevertheless documented a significant

decrease in VIM of 24-h systolic and diastolic BP. The decrease in VIM of 24-h systolic - but not diastolic - BP remained significant in a fully adjusted model (Table 2). While most BP variability indices, including CV [23] may be influenced by mean BP values, VIM includes an additional coefficient derived from curve fitting which makes it truly independent of the mean [23,26]. Along the same lines, standard deviation weighted according to Bilo et al.(SDtw) [22], which allows to get rid of the influence of nocturnal BP fall, also decreased after RDN, though significance was lost after full adjustment . However, it remains dependent to some extent of mean BP. Overall, our results strongly suggest that RDN decreases BP variability over and above its effect on BP level. The lack of decrease in visit-to-visit VIM in the Syst-Eur randomised controlled trial in the placebo and active-treatment arms [27] further supports the hypothesis that decreased BP variability documented after RDN is not entirely explained by reduction of BP level or regression to the mean, but at least partly reflects the sympatholytic effects of the intervention *per se* [1,3]. Besides a decrease in BP and BP variability, RDN was also associated with a decrease in heart rate. These findings are not unexpected in view of the influence of sympathetic system on heart rate and are in agreement with previous studies [28,29].

Whether decreased BP variability after RDN may contribute to improve cardiovascular prognosis over and above mean BP decrease remains to be demonstrated. First, the possible benefits of RDN in terms of “hard” cardiovascular endpoints remain unsubstantiated. Second, both changes in BP level [14] and BP variability after RDN using the Symplicity system are modest and highly variable among indi-

vidual patients. Last but not least, most studies have been performed using BP variability indices that are highly correlated with mean BP [26]. VIM was used in few studies, mostly to assess visit-to-visit BP variability rather than 24-h ambulatory BP variability as in the present study. In the ASCOT study, Rothwell et al. [23] found a strong relation between VIM derived from office BP (visit-to-visit BP variability) - but not ambulatory BP - and cardio- and cerebrovascular events. In contrast, in multivariable-adjusted analyses, BP variability indices including VIM were not independent predictors of cardiovascular morbidity or mortality, either in the Syst-Eur randomized controlled trial [27] or in a population-based sample representative of the general Flemish population [30].

Another key finding of our study is that baseline diastolic SDiw, ARV and VIM correlated with diastolic - but not systolic -BP response to RDN (Figure 2). From a pathophysiologic perspective, these results are meaningful. Indeed, the steady component of BP reflected by mean or diastolic BP is a measure of peripheral vascular resistance [31], which in its turn is dependent on sympathetic tone [32] and decreases after renal sympathetic nerve ablation [33]. Several lines of evidence suggest that increased vascular resistance, a hallmark of diastolic hypertension in young patients with sympathetic overactivity [34] is due to narrowing of pre-capillary arterioles, and that these changes precede BP elevation [35]. In contrast, systolic BP and pulse pressure predominantly reflect the degree of stiffness of conductance vessels [36], increase with the accumulation of aged-related structural damage and are less likely to be influenced by the autonomic system. This may explain the lack of predictive value of baseline systolic BP variability on systolic BP changes after

RDN, and more generally the modest BP-lowering effects of RDN in patients with isolated systolic hypertension [37]. Along the same lines, it is worth noting that in the recent randomized controlled study DENERVHTA comparing the BP lowering efficacy of RDN with that of 50 mg of spironolactone in patients with resistant hypertension, the decrease in BP variability was limited to the RDN arm and significant only for diastolic - not systolic - BP [38]. Notably, the BP reduction associated with RDN precedes and seems to be independent of decrease in sympathetic nerve system activity assessed by MSNA [39]. Hence, the larger BP decrease observed after RDN in patients with a higher baseline BP variability - and possibly a higher baseline sympathetic activity - may not be due to a larger decrease in sympathetic nerve system activity. Our results are partly consistent with those obtained by Tsioufis et al. [8] in a cohort of 31 patients denervated using the EnligHTN multielectrode ablation catheter. Nevertheless, comparison is difficult, as the latter used a different BP variability estimate, namely time rate, defined as the first derivative of the BP values against time (mean of the absolute ratios of the differences between successive BPs and the minutes between them).

Our study should be interpreted within the context of its limitations. The most important is the absence of control group, which makes it vulnerable to the Hawthorne effect and other patient-and physician-related bias [40]. However, this limitation is mitigated by the use of BP variability estimates derived from 24-hour ambulatory blood pressure variability, which is blinded by definition, rather than visit-to-visit BP variability, and inclusion of VIM, which is independent of BP level, and may thus be even less influenced by placebo and white-coat effects. Second, most pa-

tients (>80%) were denervated using the first-generation unipolar Symplicity catheter. Hence, our results cannot be extrapolated to more performant, second-generation catheters, which might produce more efficient RDN and therefore larger effects on BP variability. Third, in the absence of procedural endpoint [41], the completeness of RDN could not be assessed. Finally, while the number of prescribed antihypertensive drug classes was documented both at baseline and 6 months after RDN, details on medications and posology were not systematically recorded, and drug adherence was not assessed in most centers [14]. In the absence of the confounding effect of drugs change, the predictive value of baseline BP variability on BP response to RDN may be even better. Still, with 167 patients from 11 European centers, our study is the largest performed on BP variability up to now. The mean 24-h BP decrease after RDN (-5 mmHg) is similar to that observed in our initial ENCOReD patient level meta-analysis [14] and in the highly standardized DENERHTN randomised controlled trial [42]. Finally, this study is the first to assess BP variability independent of the mean (VIM), and to look for the predictive value of baseline BP variability on BP outcome after RDN.

In conclusion, RDN using the unipolar Symplicity catheter was associated with a decrease in short-term BP variability at 6 months, over and above a modest decrease in BP level. Whether this would translate into additional benefits in terms of cardiovascular mortality and morbidity remains to be proven. Furthermore, baseline BP variability estimates were related with diastolic BP changes after RDN. This intriguing observation needs confirmation in randomized controlled studies using more efficient and reproducible RDN systems, and/or RDN guided by renal nerve

stimulation [39], including younger, ideally untreated patients with milder hypertension, a group considered as particularly suitable for upcoming RDN trials [11,13].

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Table 1 Baseline characteristics of 167 patients across tertiles of 24-h systolic or diastolic BP level

Baseline characteristics	24-h systolic BP				24-h diastolic BP			
	≤142 mmHg	143-158 mmHg	≥159 mmHg	P-value	≤83 mmHg	84-95 mmHg	≥96 mmHg	P-value
Number (%) with characteristic	55	58	54		54	56	57	
Women	19 (34.6)	20 (34.5)	28 (51.9)	0.10	19 (35.2)	22 (39.3)	26 (45.6)	0.53
Non-white ethnicity	1 (1.8)	1 (1.7)	4 (7.4)	0.19	0 (0)	2 (3.6)	4 (7.0)	0.14
Smokers	2 (3.6)	12 (20.7)‡	11 (20.4)	0.016	3 (5.6)	5 (8.9)	17 (29.8)†	0.0005
Drinking alcohol	25 (45.5)	22 (37.9)	14 (25.9)	0.10	25 (46.3)	20 (35.7)	16 (28.1)	0.14
Diabetes mellitus	17 (30.9)	11 (19.0)	18 (33.3)	0.19	23 (42.6)	15 (26.8)	8 (14.0)	0.003
Previous cardiovascular disease								
Coronary heart disease	8 (14.6)	11 (19.0)	9 (16.7)	0.82	13 (24.1)	8 (14.3)	7 (12.3)	0.21
Stroke	2 (3.6)	4 (6.9)	4 (7.4)*	0.66	3 (5.6)	3 (5.4)	4 (7.0)	0.92
Mean (SD) characteristic								
Age, y	59.5±11.6	54.7±9.6*	56.1±10.8	0.053	64.2±9.6	54.9±9.5‡	51.3±9.2*	<0.0001
Body mass index, kg/m^2	29.6±4.8	30.0±5.3	30.2±5.7	0.83	30.4±5.2	29.8±5.4	29.7±5.3	0.73
Serum creatinine, μmol/L	88.2±21.8	85.1±28.8*	84.3±25.2	0.70	86.2±19.5	87.3±29.8	84.2±25.9	0.81
eGFR, ml/min/1.73 m^2	78.8±18.0	84.2±19.7	82.0±19.5	0.33	76.4±16.9	82.3±19.6	86.2±19.7	0.025
24-hour ambulatory heart rate	67.5±10.9	70.5±10.2	72.8±9.7	0.029	65.4±9.4	70.8±10.5†	74.3±9.6	<0.0001
Office blood pressure								
Systolic BP, mmHg	159.9±19.1	171.6±30.1*	184.1±25.3*	<0.0001	167.9±26.3	168.1±24.6	179.1±28.9*	0.04
Diastolic BP, mmHg	91.9±11.4	98.3±18.1*	102.4±18.2	0.004	85.5±11.1	96.6±12.3‡	109.9±15.5‡	<0.0001
Blood pressure variability (SBP)								
SDiw, mm Hg	17.1±6.2	18.0±5.0	19.4±5.7	0.099	17.5±5.9	17.8±5.7	19.2±5.4	0.26
SDtw, mm Hg	13.1±4.6	14.6±4.3	15.2±4.4	0.041	13.3±3.9	14.1±4.7	15.4±4.7	0.045
ARV, mm Hg	12.0±3.1	13.2±4.2	13.7±4.2	0.060	12.6±3.9	12.4±3.5	13.8±4.3	0.12
CV, %	12.8±4.6	11.9±3.2	11.4±3.4	0.15	12.4±4.0	12.0±4.0	11.8±3.4	0.74
VIM, units	17.8±6.3	17.5±4.6	17.6±5.0	0.97	17.4±5.4	17.4±5.5	18.1±5.1	0.75
Blood pressure variability (DBP)								
SDiw, mm Hg	12.6±4.4	13.2±4.0	13.7±4.3	0.38	11.6±3.6	13.0±4.3	14.8±4.3*	0.0004

SDtw, mm Hg	9.5±3.1	10.5±3.9	11.0±3.2	0.066	8.9±2.4	10.2±2.8*	11.8±4.2*	<0.0001
ARV, mm Hg	9.1±3.2	9.6±3.7	10.3±3.3	0.066	8.6±2.6	9.6±3.1	10.8±4.1	0.002
CV, %	15.8±5.5	14.6±4.1	14.1±4.4	0.16	15.7±5.2	14.5±4.7	14.2±4.3	0.23
VIM, units	13.1±4.5	12.8±3.6	12.5±3.3	0.15	12.7±4.0	12.5±3.7	13.1±3.9	0.71

eGFR: glomerular filtration rate estimated from the serum creatinine concentration using CKD-EPI formula. P-values denote significance of the differences in prevalence rates or means across tertiles of 24-h systolic (SBP) or diastolic (DBP) blood pressure. SDiw: standard deviation over time weighted for the time interval between consecutive readings. SDtw: average of daytime and nighttime standard deviation weighted for the duration of the daytime and nighttime interval. ARV: average real variability. CV: coefficient of variation. VIM: variability independent of mean. Significance of the difference with the adjacent lower tertile: * $P \leq 0.05$; † $P \leq 0.01$; ‡ $P \leq 0.001$.

Table 2

Baseline values and 6-month changes (Δ) in 24-h BP level and variability indices

BP level and variability	24-h systolic Ambulatory BP	P-value	24-h diastolic Ambulatory BP	P-value
24-h BP level, mm Hg				
Baseline	151.6±16.8		89.6±13.4	
Unadjusted Δ	-5.48 (-8.12 to -2.85)	<0.0001	-3.72 (-5.38 to -2.07)‡	<0.0001
Adjusted Δ	-5.18 (-7.41 to -2.94)	<0.0001	-3.84 (-5.21 to -2.47)	<0.0001
SDiw, mm Hg				
Baseline	18.2±5.7		13.2±4.3	
Unadjusted Δ	-1.29 (-2.17 to -0.42)	0.004	-0.89 (-1.58 to -0.21)	0.011
Adjusted Δ	-1.18 (-1.84 to -0.51)	0.0006	-0.63 (-1.12 to -0.13)	0.014
SDtw, mm Hg				
Baseline	14.3±4.5		10.3±3.5	
Unadjusted Δ	-0.78 (-1.43 to -0.12)	0.020	-0.53 (-1.07 to 0.01)	0.055
Adjusted Δ	-0.43 (-0.92 to 0.06)	0.087	-0.22 (-0.64 to 0.20)	0.30
ARV, mm Hg				
Baseline	12.9±4.0		9.7±3.4	
Unadjusted Δ	-0.20 (-0.78 to 0.38)	0.49	-0.31 (-0.87 to 0.26)	0.29
Adjusted Δ	-0.38 (-0.77 to 0.01)	0.059	0.01 (-0.35 to 0.38)	0.94
CV, %				
Baseline	12.0±3.8		14.8±4.7	
Unadjusted Δ	-0.45 (-1.0 to 0.12)	0.12	-0.39 (-1.10 to 0.32)	0.28
Adjusted Δ	-0.51 (-0.94 to -0.08)	0.020	-0.37 (-0.92 to 0.18)	0.18
VIM, units				
Baseline	17.6±5.3		12.8±3.8	
Unadjusted Δ	-1.11 (-1.92 to -0.30)	0.007	-0.77 (-1.36 to -0.18)	0.011
Adjusted Δ	-0.86 (-1.45 to -0.27)	0.005	-0.42 (-0.86 to -0.01)	0.054

SDiw: standard deviation over time weighted for the time interval between consecutive readings. SDtw: average of daytime and nighttime standard deviation weighted for the duration of the daytime and nighttime interval. ARV: average real variability. CV: coefficient of variation. VIM: variability independent of mean. Changes are follow-up – baseline.

Table 3 Classification of 24-h diastolic BP level changes after RDN (Δ) by baseline BP variability indices

Blood pressure variability indices (threshold*)	Correctly classified		Incorrectly classified		Classification parameters			
	Responder	Non-responder	Responder	Non-responder	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
SDiw (11.8 mm Hg)	28	66	65	8	77.8	50.4	30.1	89.2
SDtw (8.7 mm Hg)	30	59	72	6	83.3	45.0	29.4	90.8
ARV (7.8 mm Hg)	30	55	76	6	83.3	42.0	28.3	90.2
CV (15.0%)	18	83	48	18	50.0	63.4	27.3	82.2
VIM (13.5 units)	17	94	37	19	47.2	71.8	31.5	83.2

* Optimal threshold values of the different BP variability indices for predicting diastolic BP changes after RDN were determined by maximizing the Youden index. Responder: mean 24-h diastolic BP decrease > 10 mm Hg after RDN (follow-up - baseline). Non-responder: mean 24-h diastolic BP decrease ≤ 10 mm Hg. SDiw: standard deviation over time weighted for the time interval between consecutive readings. SDtw: average of daytime and nighttime standard deviation weighted for the duration of the daytime and nighttime interval. ARV: average real variability. CV: coefficient of variation. VIM: variability independent of mean.

Legends of the Figures:

Figure 1: relation between baseline BP variability indices dependent (SDiw, ARV) and independent (CV, VIM) of the mean derived from 24-h diastolic BP (X-axis) and baseline-adjusted changes in 24-h diastolic BP after RDN (Δba 24-h DBP) (Y-axis). BP: blood pressure. The dotted lines on both sides of the regression line represent the 95% confidence interval.