ORIGINAL PAPER

Relationship Between Short-Term Blood Pressure Variability and Subclinical Renal Damage in Essential Hypertensive Patients

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The authors aimed to analyze the relationship between subclinical renal damage, defined as the presence of microalbuminuria or an estimated glomerular filtration rate (eGFR) between 30 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2 and short-term blood pressure (BP) variability, assessed as average real variability (ARV), weighted standard deviation (SD) of 24-hour BP, and SD of daytime and nighttime BP. A total of 328 hypertensive patients underwent 24-hour ambulatory BP monitoring, 24-hour albumin excretion rate determination, and eGFR calculation using the Chronic Kidney Disease Epidemiology Collaboration equation. ARV of 24-hour systolic BP (SBP) was significantly higher in patients with subclinical renal damage (*P*=.001). This association held (*P*=.04) after adjustment for potential confounders. In patients with microalbuminuria, ARV of 24-hour SBP, weighted SD of 24-hour SBP, and SD of daytime SBP were also independently and inversely related to eGFR. These results seem to suggest that in essential hypertension, short-term BP variability is independently associated with early renal abnormalities. *J Clin Hypertens (Greenwich).* 2015;17:473–480. © 2015 Wiley Periodicals, Inc.

Since the pioneering observations of Stephen Hales during the 18th century it has been recognized that blood pressure (BP) is not a constant parameter; rather, it shows marked spontaneous oscillations over short-term (minutes to hours) and long-term (days to months) periods. Far from being a "background noise" that hindered assessment of "true BP," short-term BP variability (BPV) seems to be relevant to the pathophysiology of target organ damage and to the incidence of clinical events, as suggested by studies performed in humans by invasive continuous 24-hour BP measurements[1,2] and as clearly shown by investigations conducted in sinoaortic-denervated rats.[3–6] Although the precise quantification of short-term BPV requires beat-to-beat BP recording,[7] its assessment is also possible, even if less accurately, through the use of intermittent noninvasive 24-hour ambulatory BP monitoring (ABPM). However, studies in which short-term BPV was estimated by ABPM yielded conflicting results.[8–32]

Short-term BP variability has been usually estimated by 24-hour, daytime, or nighttime standard deviation (SD) of average BP. However, the limitations of the SD as a measure of short-term BPV have stimulated the search of more refined BPV estimates.[6,7,10,13,20,21]

One of these is the average real variability (ARV) of 24-hour BP, ie, the average of the absolute differences of consecutive measurements.[20] This statistical parameter is sensitive to the individual BP measurement order and less sensitive to low sampling frequency of ABPM.[21] Some studies suggest that ARV better predicts cardiovascular (CV) risk in comparison to the traditional SD.[20,22,23]

Another new index of short-term BPV is the "weighted" SD of the 24-hour mean value, ie, the average SD of daytime and nighttime BP, each weighted for the duration of the day and night periods, respectively. This in order to mathematically remove any potential interference of the magnitude of the day-night BP difference, regarded as a "beneficial" component of 24-hour BP variability from the quantification of overall 24-hour SD.[10]

Chronic kidney disease (CKD), since the earliest stages, is associated with a high risk of premature CV events.[33,34] It could be hypothesized that an enhanced short-term BPV in patients with early renal abnormalities may help to explain in part their increased CV risk.

Only a few studies explored the relationship between short-term BPV and markers of early renal damage, with conflicting results.[11–13,29,30] In particular, little is known about the association of early renal abnormalities with ARV of 24-hour BP and with weighted SD (wSD) of 24-hour BP.[30]

Our study aimed to analyze, in a group of untreated essential hypertensive (EH) patients, the relationship between subclinical renal damage and short-term BPV.

METHODS

The study population was selected from the hypertensive patients consecutively attending our hypertension center. Most of them had been referred to our institution by their general practitioners for specialist advice.

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Exclusion criteria were age younger than 18 years and older than 70 years; renovascular, malignant, endocrine hypertension, or hypertension associated with obstructive sleep apnea syndrome; known proteinuria and hematuria; estimated GFR (eGFR) <30 mL/min/1.73 m^2; previous known nephritic diseases and hereditary renal diseases; heart failure; history or clinical signs of ischemic heart disease or cerebrovascular diseases; major non-CV diseases; and unreliable 24-hour urine collection

Endocrine and renovascular hypertension were ruled out, as previously described.[35,36] Persons who reported smoking cigarettes regularly during the past year were considered current smokers.

Written informed consent was obtained from each patient. The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the local review board.

Study Design

In all patients, careful clinical history and physical examination were performed. Furthermore, 24-hour ABPM was carried out. Additionally, a 24-hour urine sample was collected to evaluate albumin excretion rate (AER).

Measurements

The 24-hour AER was assayed by a solid-phase enzyme immunoassay (Microalbumin-ELISA; DRG Diagnostics, Marburg, Germany). Further details about the assay characteristics and the precautions taken for the urine collection procedures are reported elsewhere.[36] Microalbuminuria was defined as an AER of 20 μg/min to 200 μg/min, which is equivalent to a range of 30 mg/d to 300 mg/d.[34]

Creatinine was measured using the Creatinine Plus standardized enzymatic assay (Roche Diagnostics). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[37]

In line with the 2013 European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension,[38] subclinical (asymptomatic) renal organ damage was defined by the presence of microalbuminuria or eGFR between 30 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2.

A portable, noninvasive SpaceLabs 90207 recorder (Redmond, WA) was used to perform 24-hour ABPM. BP was recorded automatically at 15-minute intervals during the day and at 20-minute intervals during nighttime resting. Only records with more than 80% of valid data were accepted. Moreover, ABPM with no consecutive hours without valid readings and ≤3 hours without valid readings were also discarded. If the patient agreed, in case of poor-quality recordings, ABPM was repeated within 1 week of the first evaluation. Further details regarding the procedures for ABPM were published previously.[35,36]

Short-term BPV was estimated with the following parameters: (1) SD of daytime (systolic and diastolic) BP; (2) SD of nighttime BP; (3) wSD 24-hour BP, defined as the mean of daytime and nighttime BP SD weighted by the duration (in number of hours) of each time period[10]; and (4) average real variability of 24-hour BP, calculated using the following formula:

$$\mathrm{ARV} = \frac{1}{N-1}\sum_{k=1}^{N-1} |\mathrm{BP}_{k+1} - \mathrm{BP}_k|$$

where k ranges from 1 to n−1, and n is the number of BP readings.[20]

Statistics

Normal distribution of the continuous variables was assessed by the Kolmogorov-Smirnov test and the assumption of satisfactory Gaussian distribution was not met for the following variables: AER, triglycerides, and all the indices of short-term BPV evaluated in the present study. They were expressed as median and interquartile range and transformed to natural logarithm to better satisfy distributional assumptions before parametric tests were used.

Differences between groups were evaluated using the independent-sample Student t test for continuous variables and the chi-square test for the categorical variables. Adjustment for potential confounding factors was carried out by analysis of covariance (ANCOVA).

Univariate associations between the indices of short-term BPV, AER, eGFR, and other variables were assessed by simple linear regression analyses and Pearson correlation coefficients.

To investigate the multivariate association of short-term BPV with preclinical renal damage, multiple stepwise logistic regression analyses were performed by calculating odds ratios (ORs) and their 95% confidence limits on the basis of various models in which the presence or absence of renal damage was considered as a dependent variable and each index of short-term BPV (separately included) regarded as explanatory variable along with the corresponding average BP value, age, sex, diabetes, and waist circumference.

Multiple linear regression analyses were also used to evaluate the independent correlates of (log) AER and eGFR, including the indices of short-term BPV (separately from each other) into the models as explanatory variables and all the parameters associated with the markers of renal dysfunction and with the indices of short-term BPV in univariate analyses. The potential influence of microalbuminuria on the relationship between short-term BPV and eGFR was tested by also including into the multivariate models the multiplicative two-way interaction term index of short-term BPV × microalbuminuria. The null hypothesis was rejected at a two-tailed $P<.05$.

Statistical analyses were performed using the SYSTAT DATA software package, version 12 (Systat, San Jose, CA).

RESULTS

We enrolled 328 untreated essential hypertensive patients. Of these, 309 (94%) had never been treated for hypertension, whereas 19 (6%) had received antihypertensive treatment in the past but not during the 3 months before the study.

No sign of renal dysfunction was detected in 232 patients, while the remaining 96 patients were considered to have subclinical renal damage. Eighteen patients had an eGFR ≤60 mL/min/1.73 m^2 and 93 had microalbuminuria. Table I presents the clinical and demographic characteristics of the patients.

Body mass index (BMI), waist circumference, (log) serum triglycerides, serum uric acid (serum uric acid), and (log) AER and the proportion of patients with type 2 diabetes were significantly higher and the eGFR lower in the group with subclinical renal damage than in those without renal dysfunction. High-density lipoprotein cholesterol tended to be lower and the percentage of men tended to be greater in the former group when compared with the latter, albeit these differences did not attain statistical significance.

As shown in Table II, the patients with subclinical renal damage exhibited higher values of clinic, 24-hour, daytime, and nighttime systolic BP (SBP), as well as of 24-hour diastolic BP (DBP), in comparison to those with normal kidney function.

The two groups did not differ with respect to the indices of short-term BPV (Table II), except for ARV of 24-hour SBP (9.9 [8.6–11.2] mm Hg vs 9.1 [8–10.2] mm Hg; *P*=.001) (Figure 1) and ARV of 24-hour DBP (8 [7–9.6] mm Hg vs 7.5 [6.9–8.9] mm Hg; *P*=.03), which were higher in patients with subclinical renal damage. The difference regarding ARV of 24-hour SBP, but not that regarding ARV of 24-hour DBP, held (*P*=.02) even after adjustment by ANCOVA for age, sex, 24-hour mean SBP, waist circumference, serum uric acid, and diabetic status. All the indices of short-term BPV were not significantly different between smokers and nonsmokers (all *P*>.12; data not shown).

The correlation between short-term BPV indices and markers of subclinical renal damage with each other and with other variables in the whole population are shown in Table III.

eGFR was significantly related in an inverse manner to SD of daytime SBP, wSD of 24-hour SBP, and ARV of 24-hour SBP. These relationships were driven by the close correlations observed between these variables in the subset of patients with microalbuminuria, whereas there was no significant correlation in those without microalbuminuria (Figures 2–4). The other significant univariate correlates of eGFR in the overall population were age, (log) AER, serum uric acid, serum glucose, total cholesterol, BMI, waist circumference, and clinic, 24-hour, and nighttime SBP. Among the indices of short-term BPV, only ARV of 24-hour SBP was significantly related to (log) AER, whereas the relationships of AER with SD of daytime SBP and with wSD of 24-hour SBP did not reach statistical significance (*P*=.096 and *P*=.093, respectively). Albumin excretion rate was also positively associated with serum uric acid, BMI, waist circumference, (log) triglycerides, clinic SBP, and 24-hour, daytime, and nighttime SBP and DBP and inversely associated with HDL cholesterol.

The logistic multiple regression analysis revealed that the presence of subclinical renal damage was independently associated with (log) ARV of 24-hour systolic BP (OR per unit increase, 4.2 [1.07–15.8]; *P*=.04), along with 24-hour mean SBP (OR per 1-mm Hg increase, 1.03 [1.01–1.05]; *P*=.02), waist circumference (OR per 1-cm increase, 1.04 [1.01–1.07; *P*=.004]), serum uric acid (OR per 1-mg/dL increase, 1.4 [1.13–1.75]; *P*=.003), and diabetes (yes=1; no=0; OR, 2.16 [1.08–4.3]; *P*=.03). When the ARVs of 24-hour SBP and DBP were replaced by wSD of 24-hour SBP and DBP in the same model, neither the former nor the latter were related to subclinical renal damage. Similarly, SD of

TABLE I. Clinical and Demographic Characteristics of Hypertensive Patients With Subclinical Renal Damage and Without Kidney Damage

	Subclinical Renal Damage (n=96)	No Kidney Damage (n=232)	*P* Value
Age, y	47.0±14.0	45.7±11.9	.394
Men, No. (%)	63 (65.6)	129 (55.6)	.086
Smokers, No.(%)	31 (32.3)	66 (28.4)	.429
Type 2 diabetes, No. (%)	18 (18.8)	23 (9.9)	.02
Serum glucose, mg/dL	97.0±22.1	95.6±21.1	.590
Body mass index, kg/m^2	28.8±4.8	27.3±3.9	.003
Waist circumference, cm	98.6±12.5	92.9±11.0	<.001
Total cholesterol, mg/dL	206.5±42.0	212.8±40.4	.205
HDL cholesterol, mg/dL	45.8±11.1	48.2±10.2	.059
Serum triglycerides, mg/dL	136.0 (93.0–193.0)	118.5 (78.5–160.5)	.008
Serum uric acid, mg/dL	5.7±1.7	4.8±1.3	<.001
Albumin excretion rate, μg/min	37.7 (27.0–123.9)	7.2 (4.6–12.1)	<.001
Estimated GFR, mL/min/1.73 m^2	89.4±15.5	99.5±15.3	<.001

Abbreviations: GFR, glomerular filtration rate; HDL, high-density lipoprotein.

TABLE II. Clinic and Ambulatory BP Data of Hypertensive Patients With Subclinical Renal Damage and Without Kidney Damage

	Subclinical Renal Damage (n=96)	No Kidney Damage (n=232)	*P* Value
Clinic systolic BP, mm Hg	157±20	152±17	.022
Clinic diastolic BP, mm Hg	98±19	95±16	.145
24-h systolic BP, mm Hg	140±12	134±12	<.0001
24-h diastolic BP, mm Hg	88±11	85±10	.017
24-h heart rate, beats per min	74±10	74±9	.985
Daytime systolic BP, mm Hg	144±12	138±12	<.0001
Daytime diastolic, mm Hg	91±11	89±10	.111
Nighttime systolic BP, mm Hg	131±15	125±13	<.0001
Nighttime diastolic BP, mm Hg	81±11	80±8	.359
SD of daytime systolic BP, mm Hg	12.4 (9.7–14.8)	11.9 (9.7–14.1)	.489
SD of daytime diastolic BP, mm Hg	10.4 (8.2–12.9)	10.2 (8.8–12.3)	.928
SD of nighttime systolic BP, mm Hg	12.1 (9.4–15.1)	11.9 (9.7–14.3)	.589
SD of nighttime diastolic BP, mm Hg	10.8 (8.6–13.1)	10.8 (9.0–12.8)	.710
Weighted SD of 24-h systolic BP, mm Hg	12.2 (10.2–14.2)	11.5 (9.7–14.4)	.597
Weighted SD of 24-h diastolic BP, mm Hg	11.1 (9.3–12.9)	10.8 (9.1–12.0)	.190

Abbreviations: BP, blood pressure; SD, standard deviation.

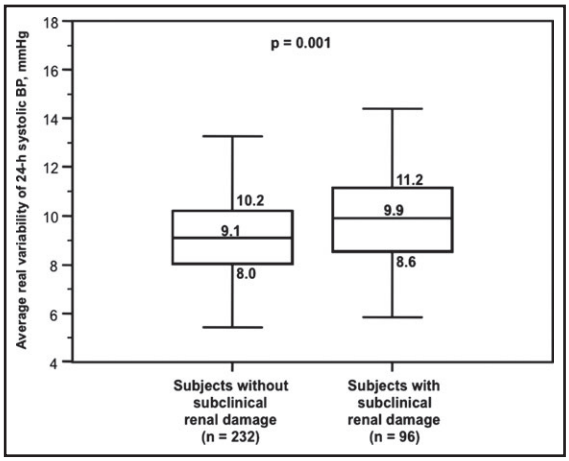

FIGURE 1. Box plots showing average real variability of 24-hours systolic blood pressure in hypertensive patients with subclinical renal damage and in those without it. In the box-and-whisker plots, the central boxes represent the values from the lower to upper quartile (25–75 percentile). The middle lines represent the medians. Lower and upper whiskers extend to 5th and 95th percentiles. This difference remained significant (*P*=.02), even after adjustment by analysis of covariance for age, sex, 24-hour mean systolic BP, waist circumference, serum uric acid, and diabetic status.

daytime SBP and DBP and SD of nighttime SBP and DBP were independently associated with subclinical renal damage when included in the multivariate model in lieu of ARV of 24-hour SBP and DBP, along with the corresponding daytime or nighttime mean BP values. Analogous conclusions were reached when the mean values of ambulatory BP readings were replaced by clinic BPs; when diabetes, as a dichotomous variable, was replaced by serum glucose; or when BMI was introduced into the model instead of waist circumference.

When we explored the independent correlates of eGFR by a stepwise linear multiple regression analysis, we found that none of the indices of short-term BPV were related to the outcome variable. However, along with age (β=−0.59; *P*<.001) and serum uric acid (β=−0.17; *P*=.002), the interaction term ARV of 24-hour SBP × microalbuminuria was inversely associated with eGFR (β=−0.21; *P*<.001). Similar results were obtained when the interaction term ARV of 24-hour SBP × microalbuminuria was replaced in the multivariate model by the term wSD of 24-hour SBP × microalbuminuria (β=−0.19; *P*<.001) or by the term SD of daytime SBP × microalbuminuria (β=−0.20; *P*<.001).

When we repeated multiple regression analysis considering (log) AER as the outcome variable, we observed that serum glucose (β=0.15; *P*=.04), serum uric acid (β=0.16; *P*=.01), waist circumference (β=0.16; *P*=.015), eGFR (β=−0.17; *P*=.01), 24-hour mean SBP (β=.17; *P*=.004), and ARV of 24-hour SBP (β=0.14; *P*=.03) were independently associated with AER. When the other indices of short-term BPV replaced ARV of 24-hour SBP in the multivariate model, none of these indices showed a significant relationship with (log) AER.

DISCUSSION

The main finding of our study was the identification of a significant association between the combination of early renal abnormalities configuring subclinical renal damage and the ARV of 24-hour SBP in a cohort of untreated hypertensive patients. This association was weakened but still significant after adjustment for potential confounding factors such as age and average level of 24-hour SBP. It was driven chiefly by the positive relationship we also observed between ARV of 24-hour SBP and AER. In contrast, inverse associations between eGFR with ARV of 24-hour SBP, wSD of

TABLE III. Correlations of Short-Term BP Variability Indices and Renal Parameters With Each Other and With Other Variables in the Whole Study Population

			SD of Daytime BP		SD of Nighttime BP		Weighted SD of 24-H BP		ARV of 24-Hours BP	
	eGFR	(Log) AER	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic	Systolic	Diastolic
	r	*r*	*r*	*r*	*r*	*r*	*r*	*r*	*r*	*r*
Estimated GFR	–	−0.168[a]	−0.124[b]	−0.019	−0.090	0.067	−0.140[b]	0.05	−0.145[e]	0.027
(Log) AER	−0.168[a]	–	0.092	0.033	0.066	0.049	0.093	0.020	0.169[a]	0.090
Serum uric acid	−0.175[c]	0.268[d]	−0.020	−0.050	−0.034	−0.086	−0.034	−0.088	−0.101	−0.005
Age	−0.596[d]	0.033	0.299[d]	0.079	0.135[b]	−0.017	0.296[d]	0.049	0.302[d]	0.016
Body mass index	−0.225[d]	0.150[e]	0.112[b]	0.139[b]	0.131[b]	0.048	0.163[a]	0.110[b]	0.169[a]	0.183[c]
Waist circumference	−0.187[c]	0.190[c]	0.049	0.093	0.109[b]	0.040	0.101	0.063	0.122[b]	0.115[b]
Glycemia	−0.123[b]	0.127[b]	0.044	0.087	0.053	0.044	0.093	0.110[b]	0.037	0.024
Total cholesterol	−0.183[c]	−0.005	0.123[b]	0.074	0.005	0.014	0.105	0.088	0.056	0.016
HDL cholesterol	0.089	−0111[b]	0.001	−0.061	−0.124[b]	0.136[b]	−0.043	−0.087	0.003	−0.048
(Log) triglycerides	−0.100	0.126[b]	0.081	0.104	0.087	0.131[b]	0.157[a]	0.141[b]	0.005	0.001
Clinic systolic BP	−0.206[f]	0.133[b]	0.250[d]	0.244[d]	0.137[b]	0.136[b]	0.257[d]	0.247[d]	0.103	0.094
Clinic diastolic BP	−0.007	0.087	0.083	0.161[a]	0.137[b]	0.136[b]	0.078	0.171[a]	0.057	0.061
24-h systolic BP	−0.113[b]	0.226[d]	0.183[c]	0.136[b]	0.222[d]	0.157[a]	0.216[d]	0.141[b]	0.264[d]	0.118[b]
24-h diastolic BP	0.035	0.134[b]	0.039	0.031	0.035	0.062	0.067	0.021	0.050	0.030
Daytime systolic BP	−0.042	0.215[d]	0.229[d]	0.153[e]	0.204[f]	0.164[a]	0.217[d]	0.151[e]	0.270[d]	0.109[b]
Daytime diastolic BP	0.049	0.118[b]	0.018	0.014	0.016	0.102	0.012	0.018	0.030	0.069
Nighttime systolic BP	−0.163[a]	0.184[c]	0.163[a]	0.105	0.123[b]	0.060	0.146[e]	0.071	0.212[f]	0.095
Nighttime diastolic BP	0.005	0.121[b]	0.046	0.074	0.023	0.001	0.104	0.082	0.042	0.060

Abbreviations: AER, albumin excretion rate; BP, blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; SD, standard deviation.
[a]*P*<.005. [b]*P*<.05. [c]*P*<.001. [d]*P*<.0001. [e]*P*<.01. [f]*P*<.0005.

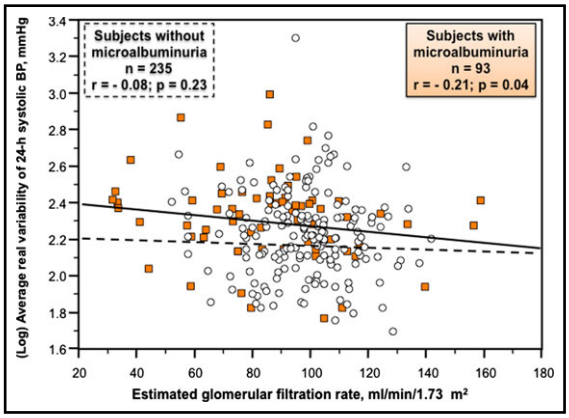

FIGURE 2. Scattergram showing the relationship between average real variability of 24-hours systolic blood pressure (transformed as a logarithm for its skewed distribution) and estimated glomerular filtration rate in hypertensive patients with microalbuminuria (filled squares) and without microalbuminuria (open circles). The calculated regression lines for microalbuminuric (solid line) and normoalbuminuric (broken line) subjects are also shown.

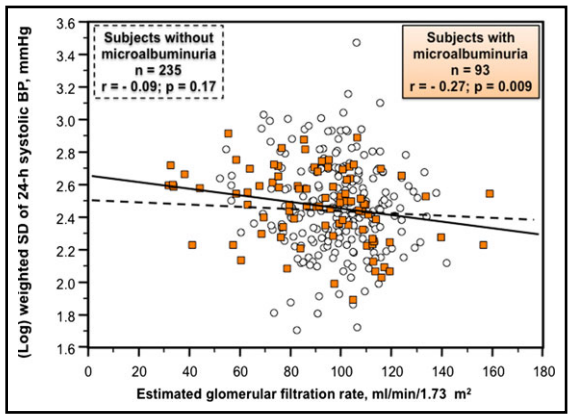

FIGURE 3. Scattergram showing the relationship between weighted standard deviation (SD) of 24-hours systolic blood pressure (transformed as a logarithm for its skewed distribution) and estimated glomerular filtration rate in hypertensive patients with microalbuminuria (filled squares) and without microalbuminuria (open circles). The calculated regression lines for microalbuminuric (solid line) and normoalbuminuric (broken line) subjects are also shown.

24-hour SBP, and SD of daytime SBP were observed only in univariate analyses carried out in the overall study population, but they lost statistical significance after taking into account the effect of some covariates in multiple regression analyses. These relationships again became significant in the presence of microalbuminuria. Indeed, when the interaction terms ARV of 24-hour SBP × microalbuminuria, wSD of 24-hour SBP × microalbuminuria, and SD of daytime SBP × microalbu-

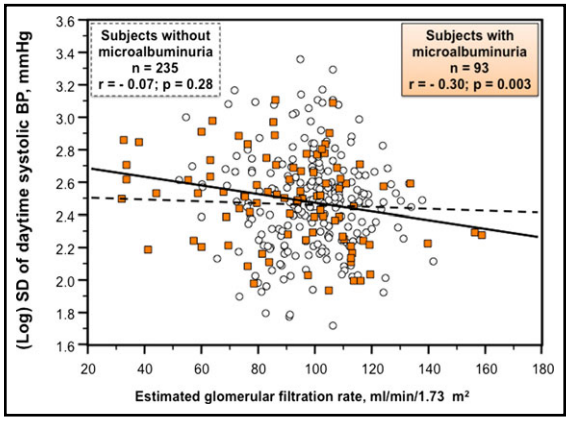

FIGURE 4. Scattergram showing the relationship between standard deviation (SD) of daytime systolic blood pressure (transformed as a logarithm for its skewed distribution) and estimated glomerular filtration rate in hypertensive patients with microalbuminuria (filled squares) and without microalbuminuria (open circles). The calculated regression lines for microalbuminuric (solid line) and normoalbuminuric (broken line) subjects are also shown.

minuria were included alternatively into the multiple regression models with the outcome variable eGFR, all the corresponding *P* values were <.001.

Limited and conflicting data exist regarding the relationship between short-term BPV and early markers of kidney damage.[11–13,29,30] Several hypotheses can be offered to explain discrepant conclusions of these studies, including the present investigation. One putative reason may be the different number of valid BP readings or the difference in the interval of BP recordings during which short-term BPV was assessed, which was generally shorter in our study (every 15 minutes during daytime and every 20 minutes during nighttime) when compared with other studies. It is well-known that the accuracy of the estimates of short-term BPV, obtained by intermittent recordings, is heavily dependent on the frequency and/or number of BP readings.[39]

Other potential reasons for inconsistent findings may be the different methods used to assess short-term BPV and measure AER as well as the wide variability in microalbuminuria assay.

To the best of our knowledge, the present study was the first to evaluate the relationship of ARV and wSD of 24-hour BP with AER and eGFR in the same participants. Manios and colleagues[13] addressed the relationship between a novel index of short-term BPV, the rate of 24-hour BP variation, and GFR estimated by the abbreviated MDRD study equation in 803 untreated hypertensive patients. This parameter, which is the first derivative of BP values against time and therefore a measure of the speed of BP fluctuations, is similar to ARV.[13,40] It was higher in patients with eGFR <60 mL/min/1.73 m^2 than in those with greater value of eGFR.[13] However, our study presents many different findings compared with those of Manios and colleagues. In this study, eGFR was not used as a continuous variable because the MDRD formula has not been validated for eGFRs >60 mL/min per 1.73m^2. In contrast, we used the eGFR with CKD-EPI equation, which is more accurate than the MDRD formula, when the GFR is >60 mL/min per 1.73m^2.[37] By using the CKD-EPI equation it is possible to report eGFR across the entire range of values without substantial bias. Furthermore, the patients enrolled in our study were about 9 years younger than those in the study by Manios and colleagues.[13]

Unlike the study by Manios and associates, we found no independent association with any of the indices of short-term BPV and the eGFR in the overall population, even though the negative relationship between short-term BPV and eGFR became strongly significant in microalbuminuric patients. A putative explanation of our finding may be that microalbuminuria interacts synergistically with an increased short-term SBP to impair the glomerular filtration process. In other words, an enhanced short-term BPV may adversely affect the glomerular filtration only in the presence of a sign of early kidney injury, such as microalbuminuria, which may be an expression of impaired autoregulation of glomerular blood flow.[34] It may be assumed that when autoregulation is disturbed the glomerular vascular bed may become more vulnerable to the mechanical insults derived from wide BP fluctuations.

For the cross-sectional nature of the present study this explanation remains speculative and needs to be tested in future investigations. Similarly, it is important to recognize that the association between short-term BPV and microalbuminuria do not imply causality and it is possible that short-term BPV elevation may be the product, rather than the cause, of early renal damage.

It is entirely possible that heightened short-term BPV, from whatever cause, leads to renal damage by afferent arteriolar barotraumas. It is also conceivable that the relationship between short-term BPV and AER is not direct but is mediated by an increased large artery stiffness, resulting from the traumatic effect of wider BP swings on the walls of conduit arteries. This, in turn, may determine increased urinary excretion of albumin.

In this regard, it is interesting to note that in sinoaortic-denervated rats, an experimental model of high short-term BPV without hypertension, Miao and Su demonstrated that a chronic increase in BPV produces aortic hypertrophy after 2 weeks of the surgical intervention and left ventricular hypertrophy after at least 10 weeks. In contrast, histological kidney damage was evident after only 16 weeks.[4,5] This lends support to the view that aortic hypertrophy induced by enhanced BPV may lead to an impaired arterial distensibility, thereby increasing left ventricular load and, in turn, favoring left ventricular hypertrophy and subsequently renal damage.

However, it is also entirely possible that aortic stiffness, which is closely associated with microalbuminuria, may induce wider fluctuations in SBP. This is

because rigid carotid and aortic walls determine a reduced stimulation of arterial baroreceptors located in these vascular areas by pulsatile BP, with a consequent impaired sensitivity of the baroreflex and its resulting reduced ability in buffering BP oscillations. Therefore, microalbuminuria could simply represent an epiphenomenon of arterial stiffness and systemic endothelial dysfunction, without a causative pathogenetic role in this context.

It is noteworthy that a close association between short-term BPV and aortic stiffness has been documented by Schillaci and colleagues.[14] In this investigation, the relationship between aortic PWV and ARV of 24-hour SBP (the only index of short-term BPV associated with microalbuminuria in our study) was stronger than that with SD of 24-hour, daytime, or nighttime SBP.[14]

It is also worth noting that our results were obtained in a select population of untreated young and middle-aged Caucasian patients with mild to moderate essential hypertension, without severe renal functional impairment and free of CV diseases. Therefore, the conclusions of our study cannot be extrapolated to non-white populations and caution is needed when applying the results of our investigation to treated hypertensive patients or to those with more advanced degrees of kidney or CV damage.

CONCLUSIONS

Our study showed an independent, albeit modest, association between early renal abnormalities and some indices of short-term BPV in untreated patients with essential hypertension. This may help to explain the elevated CV risk associated with enhanced short-term blood pressure (STBP) variability and with both microalbuminuria and mild to moderate reduction in GFR.

Further longitudinal studies are needed to understand the causal link between increased short-term BPV and subclinical renal damage. Future studies are also needed to determine whether medications able to reduce short-term BPV would be of clinical benefit in the prevention or treatment of early renal damage.

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