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Abstract—Microalbuminuria is a known marker of subclinical organ damage. Its prevalence is higher in patients with resistant hypertension than in subjects with blood pressure at goal. On the other hand, some patients with apparently well-controlled hypertension still have microalbuminuria. The current study aimed to determine the relationship between microalbuminuria and both office and 24-hour ambulatory blood pressure. A cohort of 356 patients (mean age 64 ± 11 years; 40.2% females) with resistant hypertension (blood pressure ≥ 140 and/or 90 mm Hg despite treatment with ≥ 3 drugs, diuretic included) were selected from Spanish hypertension units. Patients with estimated glomerular filtration rate < 30 mL/min/1.73 m² were excluded. All patients underwent clinical and demographic evaluation, complete laboratory analyses, and good technical-quality 24-hour ambulatory blood pressure monitoring. Urinary albumin/creatinine ratio was averaged from 3 first-morning void urine samples. Microalbuminuria (urinary albumin/creatinine ratio ≥ 2.5 mg/mmol in males or ≥ 3.5 mg/mmol in females) was detected in 46.6%, and impaired renal function (estimated glomerular filtration rate < 60 mL/min/1.73 m²) was detected in 26.8%. Bivariate analyses showed significant associations of microalbuminuria with older age, reduced estimated glomerular filtration rate, increased nighttime systolic blood pressure, and elevated daytime, nighttime, and 24-hour diastolic blood pressure. In a logistic regression analysis, after age and sex adjustment, elevated nighttime systolic blood pressure (multivariate odds ratio, 1.014 [95% CI, 1.001 to 1.026]; $P=0.029$) and reduced estimated glomerular filtration rate (multivariate odds ratio, 2.79 [95% CI, 1.57 to 4.96]; $P=0.0005$) were independently associated with the presence of microalbuminuria. We conclude that microalbuminuria is better associated with increased nighttime systolic blood pressure than with any other office and 24-hour ambulatory blood pressure monitoring parameters. (*Hypertension*. 2011;57:00-00.) • **Online Data Supplement**

Key Words: resistant hypertension ■ microalbuminuria ■ urinary albumin/creatinine ratio ■ ambulatory blood pressure monitoring ■ night-systolic blood pressure ■ estimated glomerular filtration rate

In the last 2 decades, microalbuminuria has risen consistently as a reliable marker of subclinical target organ damage, both in diabetic and nondiabetic persons.¹⁻⁷ It has been shown that microalbuminuria is a risk factor with significant prognostic impact for both incident cardiovascular and renal diseases and for all cause-mortality^{1-4,6,8-17}. Current guidelines for the detection, prevention, and treatment of high blood pressure (BP) and chronic kidney disease have, therefore, included microalbuminuria as a determinant of cardiovascular and renal risk.^{18,19}

There is also some evidence of the association of high urinary albumin excretion (UAE) with elevated BP in subjects with resistant hypertension.²⁰ Until now, 24-hour ambulatory BP monitoring (ABPM) has been the best-known tool to identify patients with true resistant hypertension. The few surveys performed on this specific population have not

agreed to which of the ABPM parameters is best associated with target organ damage,²¹ although a recent prospective study pointed to nighttime systolic BP (SBP) as probably being the best prognostic risk marker for future cardiovascular morbidity and all-cause and cardiovascular mortalities.²² We aimed to evaluate which of the ABPM parameters is related to increased albuminuria in resistant hypertensives.

Methods

Study Population

Adult patients with clinical diagnosis of resistant hypertension^{18,23,24} (ie, office SBP and diastolic BP ≥ 140 mm Hg and/or ≥ 90 mm Hg, respectively, despite a prescribed therapeutic schedule with an appropriate combination of ≥ 3 full-dose antihypertensive drugs, including a diuretic), were recruited consecutively from specialized hypertension units spread throughout Spain (for the full list of investigators, please see the online data supplement, available at

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http://hyper.ahajournals.org). The study protocol was approved by the local institutional ethical committees, and written informed consent was obtained from all participants. The investigation conforms to the principles outlined in the declaration of Helsinki. Exclusion criteria were secondary hypertension, estimated glomerular filtration rate (eGFR), according to the Modification of Diet in Renal Disease study equation, <30 mL/min/1.73 m² of any etiology and terminal or inability disease, as well as those subjects on long-term corticosteroid or nonsteroidal anti-inflammatory therapies.

All patients submitted to a standard protocol, in which demographic and anthropometric characteristics as well as cardiovascular risk factors were recorded, and all subjects underwent laboratory examination and 24-hour ABPM.

Diabetes mellitus was diagnosed using medical history, if patients were under antidiabetic treatment, or when they had a minimum of 2 fasting plasma glucose determinations >7.0 mmol/L. All diabetic patients had type 2 diabetes. Dyslipidemia was considered when treatment with lipid-lowering drugs had been implemented, if total cholesterol was >5.0 mmol/L or LDL cholesterol (LDL-C) was >3.0 mmol/L or HDL-C was <1.0 mmol/L in men or <1.2 mmol/L in women, or if triglycerides were >1.7 mmol/L. Metabolic syndrome was defined according to the American Heart Association and National Heart, Lung, and Blood Institute Scientific definition.²⁵ Clinical history and physical and routine laboratory examinations were used to screen secondary hypertension. When any secondary cause was suspected, specific diagnostic procedures were carried out.

Office BP Measurement

Office BP was measured by trained nurses in all hypertension units according to current guideline recommendations. BP was assessed after 5 minutes of rest in the sitting position using appropriately sized cuffs between 8 and 10 AM before taking any antihypertensive drugs through validated oscillometric semiautomatic devices (Omron 705IT). We obtained 3 measurements spaced by 2 minutes in each of ≥ 2 separate visits, and the average of the last 2 BP measurements was considered as the final office BP values. When these 2 determinations were significantly different, additional measurements were taken.

Ambulatory BP Monitoring

All subjects underwent a 24-hour ABPM registration with validated Spacelabs-90207 or Spacelabs-90217 devices and suitably sized cuffs. The monitoring started between 8 and 10 AM of a working day, after office BP measurements had been registered, with ambulatory BP readings obtained at 20-minute intervals and 30-minute intervals throughout awake and asleep periods, respectively. The patients recorded their sleep and awake times during the monitoring. These times were used to define the awake and asleep periods. All patients were required to have a recording of good technical quality ($\geq 80\%$ of valid readings) to enter the study. Pseudoresistant hypertension was diagnosed if office BP was ≥ 140 and/or 90 mm Hg and 24-hour BP $<130/80$ mm Hg.

Urinary Albumin Excretion

UAE was determined as the average of the urinary albumin/creatinine ratio evaluated from 3 fresh first-morning void urine samples, obtained on separate days within a 1-month period. Microalbuminuria was defined according to the currently gender-specified thresholds accepted by the European Societies of Hypertension and Cardiology²⁴ (ie, a urinary albumin/creatinine ratio ≥ 2.5 mg/mmol and ≥ 3.5 mg/mmol in males and females, respectively).

Serum Creatinine and eGFR

Serum creatinine was measured by an enzymatic modified Jaffé reaction (CREA; Roche Diagnostics) using the Hitachi Modular System Analyzer (Roche Diagnostics), consistent with the current National Kidney Disease Education Program recommendations for standardizing serum creatinine measurement.²⁶ The intra-assay coefficient of variation was 2.3%. We estimated the eGFR by using the IDMS (isotope dilution mass spectrometry) traceable simplified Modification of Diet in Renal Disease equation.²⁷

Table 1. Comparison of Several Demographic and Clinical Parameters Between Patients With Microalbuminuria and Normoalbuminuric Patients

Variable	Normoalbuminuria n=190	Microalbuminuria n=166	P Value
Sex (males/females)	47.4/52.6	74.1/25.9	<0.0001
Age (y)	64.8 \pm 11.6	62.4 \pm 11.5	0.05
UAE* (mg/mmol)	0.83 (0.45; 1.36)	9.01 (4.02; 35.84)	<0.0001
Body mass index (kg/m ²)	30.9 \pm 4.9	30.6 \pm 5.7	0.60
Metabolic syndrome, %	61.6	60.6	0.85
Diabetes mellitus, %	31.1	39.8	0.09
eGFR ≤ 60 mL/min/1.73 m ² , %	16.0	32.5	0.0004
Renin-angiotensin system blockade, %	91.1	95.2	0.89

*Data are given as median (p25; p75). Remaining data are given as mean \pm SD or percentages.

Statistical Analyses

Ordinary statistical methods were performed with the statistical package SAS for Windows version 9.2. Briefly, normally distributed variables are summarized as mean \pm SD, and categorical data are presented as percentages. Bivariate comparisons between patients with microalbuminuria and patients with normoalbuminuria were performed by unpaired *t* tests or ANOVA in continuous data, by Wilcoxon-Mann-Whitney test in asymmetrically distributed data, and by χ^2 test in categorical data. Because of skewed distribution, values of urinary albumin/creatinine ratio were log transformed. Logistic regression analyses were performed to ascertain the independent factors associated with microalbuminuria, with microalbuminuria used as the dependent variable. To select variables to enter the multivariate analysis, a *P* value ≤ 0.20 in the bivariate analyses was required. Variables were introduced into the model by the stepwise-forward method. Multivariate odds ratios (ORs) and their 95% CIs were calculated for each independently associated variable.

Results

A total of 356 patients with clinical diagnosis of resistant hypertension were enrolled in the study. After 24-hour ABPM, 23.9% of them showed to have pseudoresistant hypertension according to the criterion defined above. Mean age \pm SD was 64 \pm 11 years, and 40.2% were females. The prevalence of other cardiovascular risk factors was as follows: 35.1% had type 2 diabetes mellitus, obesity (body mass index ≥ 30 kg/m²) was diagnosed in 51.8%, metabolic syndrome accounted for 61.1%, and 11.7% were current smokers. The prevalence of microalbuminuria and impaired renal function (eGFR <60 mL/min/1.73 m²) was 46.6% and 23.8%, respectively.

Bivariate analyses show the comparisons, with regard to several clinical parameters, between patients with normoalbuminuria and microalbuminuria (Table 1). Patients with microalbuminuria were predominantly males, whereas percentages of men and women with albuminuria in a normal range were similar. As for patients with impaired renal function, the prevalence was nearly double in subjects with microalbuminuria compared with those without. On the other hand, there were no statistically significant differences between both groups when referring to body mass index or to metabolic syndrome and diabetes percentages. With regard to

Table 2. Comparison of Office BP and 24-Hour ABPM Parameters Between Patients With Microalbuminuria and Normoalbuminuric Patients

Variable	Normoalbuminuria n=190	Microalbuminuria n=166	P Value
Office BP			
Office SBP (mm Hg)	160.1 ± 15.7	159.2 ± 15.1	0.62
Office DBP (mm Hg)	91.0 ± 11.3	90.5 ± 10.9	0.68
Office PP (mm Hg)	69.1 ± 16.5	68.8 ± 17.3	0.86
24-Hour ABPM			
Daytime SBP (mm Hg)	141.1 ± 17.7	144.1 ± 17.1	0.12
Daytime DBP (mm Hg)	81.1 ± 11.6	83.9 ± 12.7	0.034
Daytime PP (mm Hg)	60.0 ± 16.3	60.2 ± 15.6	0.92
Nighttime SBP (mm Hg)	133.3 ± 20.8	137.7 ± 19.3	0.047
Nighttime DBP (mm Hg)	73.2 ± 11.3	76.8 ± 12.7	0.006
Nighttime PP (mm Hg)	60.2 ± 17.3	60.9 ± 16.0	0.69
24-Hour SBP (mm Hg)	138.4 ± 18.0	141.7 ± 17.3	0.09
24-Hour DBP (mm Hg)	78.1 ± 11.0	81.2 ± 12.5	0.016
24-Hour PP (mm Hg)	60.4 ± 15.7	60.5 ± 15.5	0.95

Data are given as mean ± SD.

PP indicates pulse pressure; DBP, diastolic BP.

BP values, differences of office BP measurements and 24-hour ABPM parameters between normoalbuminuric patients and subjects with microalbuminuria are shown in Table 2. There were no differences in office BP measurements. As for 24-hour ABPM parameters, nighttime SBP and daytime, nighttime, and 24-hour diastolic BP were significantly higher in patients with microalbuminuria. Further on, a logistic regression analysis was performed to ascertain the parameters best associated with microalbuminuria in resistant hypertensive patients. The variables included were age, sex, reduced eGFR (<60 mL/min/1.73 m²), increased nighttime SBP and elevated daytime, nighttime, and 24-hour diastolic BP. Significant independent associations with microalbuminuria in the final model were reduced eGFR (OR, 2.79 [95% CI, 1.57 to 4.96]; *P*=0.0005) and elevated nighttime SBP (OR, 1.014 [95% CI, 1.001 to 1.026]; *P*=0.029).

Given the close association found between microalbuminuria and nighttime SBP, we performed additional analyses to better outline this relationship. We divided the whole cohort into 2 subgroups of patients: those with nighttime SBP ≥120 mm Hg (77%), and those with nighttime SBP below this value.¹⁸ We found that the percentage of subjects in the first group who had microalbuminuria was 51%, whereas the percentage of microalbuminuric patients with nighttime SBP <120 mm Hg was 33% (*P*=0.006).

Discussion

The main finding of this study is that a high nighttime SBP is more closely associated with subclinical target organ damage,

in terms of a higher UAE rate, than any other ABPM parameter in patients with resistant hypertension, whereas office BPs have no value. Further, we found that the eGFR correlates inversely with albuminuria in resistant hypertensives.

Resistant hypertensive subjects are a rather common subgroup of patients with a well-known high cardiovascular morbidity and mortality risk,^{28–30} although they have not been widely studied. There are very few but consistent studies reporting on the superiority of ABPM recordings over office BP in resistant hypertensives as predictors of adverse cardiovascular outcomes.^{22,28,29} To our knowledge, the relationship of the concrete ABPM measures with the markers of subclinical organ damage has not been reported. Microalbuminuria is believed to be one precursor of established cardiovascular disease. The knowledge of the main ABPM parameter associated with microalbuminuria in these patients might help to target the BP-lowering treatment earlier and more accurately, or at least indicate the timely administration of antihypertensive treatment.³¹

Our results add the body of evidence that nighttime SBP is the ABPM parameter that best associates with microalbuminuria. In addition, microalbuminuria accounted for more than half of the resistant hypertension patients whose nighttime SBP was above the normal range. In fact, there was a high percentage (>40%) of patients with daytime SBP within the normal range but with high nighttime SBP who had microalbuminuria (data not shown). Thus, it appears that over-ranged values of nighttime SBP could be responsible for more subclinical organ damage in resistant hypertensives.

This relationship between nighttime SBP and albuminuria has been reported previously in very few studies in other population subgroups but not in resistant hypertensives. Nighttime SBP was first reported to be related to UAE in a small study in type 2 diabetic patients.³² Two other studies showed the prognostic value of nocturnal BP elevation regarding albuminuria: Lurbe et al demonstrated that high nighttime SBP preceded microalbuminuria development in adolescents and young adults with type 1 diabetes mellitus,³³ and another prospective study showed that nighttime SBP rise was an independent predictor of progression of albuminuria in elderly people with type 2 diabetes.³⁴ Again in diabetic patients, the preliminary results of the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) study show a strong correlation for nighttime SBP and urinary albumin/creatinine ratio, better than with any other ABPM parameter.³⁵ Very few studies, mostly from the same investigator group, have reported on the relationship between ABPM and microalbuminuria in resistant hypertensives. A large cross-sectional study demonstrated that the parameters that showed a closer correlation with microalbuminuria were 24-hour pulse pressure and a nondipping pattern but not nighttime SBP.²¹ In contrast, the same authors showed recently that nighttime SBP was the measurement with a closer cardiovascular prognostic influence, but the relationship with albuminuria was not assessed in this cohort.²² In addition to the relationships between BP and albuminuria concerning ABPM parameters, the results of the present study show that office BP measurements are poorly correlated with

UAE in subjects with resistant hypertension, confirming the better performance of 24-hour ABPM over office BP readings to underscore subclinical target organ damage, as had been suggested previously in other subgroups of the population, such as type 2 diabetics³⁶ or subjects with moderate to high levels of hypertension plus left ventricular hypertrophy.³⁷

We also observed that nighttime diastolic BP was significantly higher in microalbuminuric patients, although this relationship was lost in the multivariate analysis. In this way, Bianchi et al showed this finding in a small cohort of nondipping patients with essential hypertension.³⁸ However, this fact has not been reported previously in resistant hypertension patients, nor does our study confirm its independent significance.

Finally, our results show that a low eGFR correlates independently with higher UAE. This finding was not surprising because it is thought that microalbuminuria reflects endothelial dysfunction and microvascular damage in different parts of the cardiovascular system and that the kidney is, for sure, one of the target organs. Therefore, the association of high UAE and impaired renal function seems reasonable. In any case, it is important to point to the repetitively proved assumption that both microalbuminuria and eGFR are predictors of cardiovascular risk independent of each other, probably providing complementary information.^{1,8,10} This highlights the significance of detecting elevated UAE in these patients, no matter which level of eGFR they have.

There are some limitations that need to be mentioned. This is a cross-sectional study, and certainly correlation does not necessarily imply causality. We cannot infer from our results that a poor control of nighttime SBP is responsible for a higher UAE, although it seems reasonable to think of microvascular damage linking both findings. A prospective study targeting nighttime SBP in those patients would clear up the question whether this therapeutic measure lowers both UAE and cardiovascular outcomes rates. Another question we have not been able to answer is whether high nighttime SBP is a special feature of resistant hypertension per se or whether it depends on antihypertensive treatment in some way. For ethical reasons, antihypertensive drugs could not be withdrawn in these high-risk patients. Because this is not a prospective study and patients were attended in so many centers, there was not a unique therapeutic schedule. However, most of them, 93%, received almost one renin-angiotensin system blocker, and all of them, by definition, had a diuretic in their treatment regimen. Despite the mentioned limitations, we must emphasize that one of the main strengths of the present study is that our data on urinary albumin/creatinine ratio are based on the measurement of albuminuria in 3 morning spot urines, which confers a high accuracy to the results.

In conclusion, our data suggest that in patients with resistant hypertension, nighttime SBP above normal levels is associated independently with higher rates of UAE, no matter which office BP levels they have, suggesting that more efforts should be addressed to elicit such insufficient BP control and to optimize the treatment.

Perspectives

This study discloses some features from a not yet well-known subgroup of hypertensive subjects (ie, those with resistant hypertension). The correlation observed between higher UAE levels and uncontrolled nighttime SBP in these patients suggests that more therapeutic efforts should be addressed to lower nighttime SBP, even when daytime SBP is at goal. It remains to be determined whether targeting nighttime SBP leads to a reduction of UAE rate and, even more, to prevent those patients from cardiovascular diseases. In any case, according to the data shown, the performance of a 24-hour ABPM registry when abnormal amounts of albuminuria are detected in resistant hypertensives, whatever office BP levels they have, and especially if office BP is within the normal range, would appear to be mandatory.

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Disclosures

None.

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ONLINE SUPPLEMENT

URINARY ALBUMIN EXCRETION IS ASSOCIATED WITH NOCTURNAL SYSTOLIC BLOOD PRESSURE IN RESISTANT HYPERTENSIVES

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