Original Article

Awake Blood Pressure Variability, Inflammatory Markers and Target Organ Damage in Newly Diagnosed Hypertension

Alfonso TATASCIORE[1)], Marco ZIMARINO[1)], Giulia RENDA[1)], Maria ZURRO[1)], Manola SOCCIO[1)], Concetta PRONTERA[2)], Michele EMDIN[2)], Mariarosaria FLACCO[3)], Giuseppe SCHILLACI[4)], and Raffaele DE CATERINA[1)]

Increased blood pressure (BP) may stimulate vascular inflammation, which may itself induce pathological arterial changes. BP variability has been associated with target-organ damage and future cardiovascular complications. We hypothesized that BP variability, as derived from ambulatory BP monitoring, is related to inflammatory markers in newly diagnosed hypertension. Systolic (S) and diastolic (D) BP variabilities were assessed as the SD of 24-h pressure recordings in a cohort of 190 recently (<6 months) diagnosed, untreated hypertensive subjects. Target organ damage, assessed by measuring the carotid artery intima-media thickness, left ventricular mass index, and microalbuminuria, was related to plasma high-sensitivity C-reactive protein (hsCRP) and soluble (s) E-selectin, an endothelium-specific molecule. The patients' age (mean±SD) was 53.0±8.5 years, and 59% were male. Multivariable analysis identified awake SBP variability (95% confidence interval [CI]: 0.002–0.042, $p=0.034$) as an independent correlate of hsCRP and awake SBP (95% CI: 0.003–0.014, $p=0.003$), awake SBP variability (95% CI: 0.003–0.035, $p=0.018$), and microalbuminuria (95% CI: 0.075–0.280, $p=0.001$) as independent correlates of sE-selectin. When patients were divided into low and high awake SBP variability groups, age ($p=0.001$), hsCRP ($p=0.0001$), and sE-selectin ($p=0.005$) were significantly different in the two groups. After adjusting for age, these differences remained significant ($p=0.022$ and $p=0.001$ for hsCRP and sE-selectin, respectively). In recently diagnosed hypertensive subjects, hsCRP and sE-selectin levels are related to awake SBP variability. High SBP variability is likely associated with vascular inflammation in newly diagnosed hypertension, independent of SBP. (*Hypertens Res* 2008; 31: 2137–2146)

***Key Words*: hypertension, blood pressure variability, target-organ damage, C-reactive protein, E-selectin**

Introduction

Vascular inflammation plays a key role in the pathogenesis and progression of atherosclerosis (*1*) and hypertension (*2*). Essential hypertension is characterized by increased peripheral vascular resistance to blood flow (*3*), where resistance arteries play an important role (*4*), contributing to hypertension itself and to its complications (*5*). In hypertension, resistance arteries undergo a process of inflammatory remodeling involving extracellular matrix deposition (*5*) and chronic vasoconstriction (*6*). Tissue expression and plasma concen-

From the [1)]Institutes of Cardiology and [3)]Clinical Pathology, Center of Excellence on Aging, "G. d'Annunzio" University, Chieti, Italy; [2)]Consiglio Nazionale delle Ricerche (CNR) Institute of Clinical Physiology, Pisa, Italy; and [4)]Department of Clinical and Experimental Medicine, The University of Perugia, Perugia, Italy.

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Address for Reprints: Raffaele De Caterina, M.D., Ph.D., Institute of Cardiology, "G. d'Annunzio" University, Chieti, c/o Ospedale SS. Annunziata, Via dei Vestini, 66013 Chieti, Italy. E-mail: rdecater@unich.it

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trations of inflammatory markers and mediators are increased in patients with vascular disease (*7*). These include high-sensitivity (hs) C-reactive protein (CRP) (*7*) and soluble (s) adhesion molecules, including vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and E-selectin (*7–9*).

CRP is a 115-kDa pentamer expressed almost exclusively by hepatocytes as part of the non-specific acute-phase response to tissue damage, infection, inflammation, and malignancies (*10*). High-sensitivity CRP is associated with the future development of hypertension (*11*, *12*). Experimental data suggest that elevated blood pressure (BP) may stimulate a pro-inflammatory response and that endothelial inflammation may also herald changes in the arterial wall that characterize the hypertensive state (*13*, *14*). Both hsCRP and BP are independent determinants of cardiovascular risk, and, in combination, these parameters have been reported to have additive predictive value (*15*).

Soluble endothelial leukocyte adhesion molecules have been proposed in the past few years as new markers of vascular function. Among these, sE-selectin is an endothelium-specific molecule (*16*) and has been reported to be elevated in various diseases (*17*). Compared with normotensive controls, increased levels of sE-selectin have been reported in hypertensive subjects (*18*) and are correlated with structural vascular damage (*19*).

Although the degree of hypertension has been clearly established over the past years as a predictor of target-organ damage and a determinant of prognosis, the notion that daily variability in BP levels may also impact prognosis is much newer. BP variability, which is the result of a complex interaction between external environmental stimuli and the response of cardiovascular control mechanisms, is enhanced in hypertension and increases with increased severity of hypertension (*20*). Previous studies have shown a direct association between increased 24-h systolic BP (SBP) variability and a higher incidence of cardiovascular complications in patients with treated hypertension (*21–23*), after accounting for the increased risk due to the elevation of mean BP levels. Awake SBP variability has recently been linked to both intima-media thickness (IMT) and left ventricular mass index (LVMI), independent of mean BP values, in a cohort of recently diagnosed, previously untreated hypertensive subjects (*24*).

Against this background, we sought to analyze the relationship between BP variability, as derived from ambulatory BP monitoring (ABPM), and inflammatory markers, including hsCRP and sE-selectin, in newly diagnosed untreated subjects referred for suspected hypertension.

Methods

Patients

The findings reported here are part of a more general investigation aimed at studying the prognostic impact of BP variability, for which a first report has been recently published (*24*). We calculated a sample size of 61 subjects per subgroup to provide a study power of 80% to detect a difference of 0.1 mg/dL in hsCRP and a sample size of 80 subjects per subgroup to detect a difference of 3.0 pg/dL in sE-selectin between the low and high awake BP variability groups, with a 1-side type I error of 0.05. We screened 230 consecutive outpatients on the basis of a recent (<6 months) diagnosis of suspected hypertension detected by clinic BP measurement according to standard criteria (clinic SBP ≥140 mmHg and/or diastolic BP [DBP] ≥90 mmHg to define hypertension) (*25*, *26*). Of these subjects, we excluded patients with diabetes ($n=11$), renal dysfunction (serum creatinine ≥2 mg/dL, $n=2$, or macroalbuminuria [>300 mg/24 h], $n=3$), secondary hypertension ($n=3$), heart failure ($n=7$), coronary heart disease ($n=4$) and previous stroke ($n=2$), all conditions associated with changes in autonomic nervous system activity that are potentially able to influence BP variability over 24 h. For the same reasons, we also a priori excluded subjects with night-time working habits ($n=8$).

Clinic BP measurements were performed according to standard criteria (*27*). After the original hypertension screening, all subjects underwent ABPM and a standard diagnostic work-up as part of a primary prevention program. A net number of 190 subjects was therefore the final study population. This population was slightly larger compared with our previous study (*24*) because of the inclusion of a few additional subjects with newly diagnosed arterial hypertension in its early phases (Table 1). Data on the presence of other risk factors, such as a family history of hypertension, tobacco smoking, coffee or alcohol consumption (dichotomized as present or absent) and the level of physical activity (defined as aerobic exercise on a regular basis, such as walking, jogging or swimming for at least 30 to 45 min 3 times per week), were also recorded, together with biohumoral variables.

Informed consent was obtained from each participant and the study protocol was approved by the local ethics committee.

ABPM and Assessment of BP Variability

All subjects underwent a 24-h non-invasive ABPM with a validated oscillometric device (SpaceLabs 90207 Monitor Inc., Redmond, USA). BP monitoring was performed on a working day with the subjects performing usual daily activities and refraining from heavy physical exercise. BP and heart rate readings were obtained every 15 min during the day (between 7 AM and 11 PM) and every 30 min during the night (between 11 PM and 7 AM). Subjects were instructed to keep a diary of their activities and note the time they retired to bed, and ABPM recordings were subdivided accordingly into "awake" or "asleep" periods based on these diary entries (rather than on arbitrary time definitions), which practically coincided, in most subjects, with arbitrarily defined day

Table 1. Baseline Demographic, Biohumoral Data, Awake Blood Pressure Parameters and Target-Organ Damage in the Study Population

Variables	Baseline data
Age (years)	53.0±8.5
Sex (male, %)	59
BMI (kg/m^2)	27.1±4.5
Family history of hypertension (%)	58
Smoking (%)	27
Physical activity (%)	46
Coffee drinking (%)	91
S-creatinine (mg/dL)	0.9±0.2
Creatinine clearance (mL/min)	96±24
Total cholesterol (mg/dL)	207±38
Triglycerides (mg/dL)	119±71
LDL-C (mg/dL)	127±35
HDL-C (mg/dL)	56±21
Systolic BP (mmHg)	139.0±12.0
Diastolic BP (mmHg)	85.0±9.2
HR (bpm)	76.0±8.1
Systolic BP variability (mmHg)	12.9±4.1
Diastolic BP variability (mmHg)	10.8±3.8
% nocturnal systolic BP fall*	−8.7±5.9
% nocturnal diastolic BP fall*	−13.2±8.2
Dippers, systolic BP (%)*	49
Dippers, diastolic BP (%)*	73
LVMI (g/m^2)	96.1±17.7
IMT (mm)	0.68±0.18
Microalbuminuria (mg/h)	1.0±0.6
hsCRP (mg/dL) median (interquartile range)	0.07 (0.03–0.14)
sE-selectin (pg/dL) median (interquartile range)	4.01 (1.30–8.63)

Data are expressed as mean±SD unless otherwise indicated. BMI, body mass index; S-creatinine, serum creatinine; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; BP, blood pressure; HR, heart rate; LVMI, left ventricular mass index; IMT, intima-media thickness; hsCRP, high sensivity C-reactive protein; sE-selectin, soluble E-selectin. *Variables calculated over 24 h.

and night subperiods.

BP variability was calculated as the SD of mean awake and asleep SBP and DBP (*28*). BP variability over the 24 h was obtained from the weighted average of day and night BP SD values (*29*), thus correcting for the degree of nocturnal BP fall. Nocturnal dipping was defined as a reduction in the average SBP and DBP at night >10% compared with the average awake values.

We treated data on nocturnal dipping as both a continuous (% nocturnal SBP and DBP fall) and a discrete (dippers, SBP and DBP, %) variable.

Cardiac and Carotid Ultrasonography

The echocardiographic and carotid ultrasonographic investigations were performed with a General Electric VingMed Vivid 3®-Pro apparatus (General Electric, Aliso Viejo, USA), equipped with a 2.5- to 3.5-MHz linear-array transducer and with a 10-MHz linear-array transducer for cardiac and carotid examinations, respectively. These were performed as described in the previous study of this series (*24*) by obtaining LVMI as an index of cardiac damage and IMT as an index of vascular damage.

Laboratory Measurements

Biohumoral data and microalbuminuria (MA), as an index of renal damage, were assessed as previously described (*24*). Creatinine clearance was measured using the Cockcroft-Gault formula.

Plasma hsCRP protein concentrations were measured using the Latex-Enhanced CRP nephelometric assay (High Sensitivity CRP Assay; Dade Behring, Marburg, Germany) (*30*). The inter-assay coefficient of variation for plasma hsCRP was 2% at both low and high concentrations.

Soluble E-selectin was measured by a commercially available enzyme-linked immunosorbent assay (Bender MedSystems GmbH, Vienna, Austria). Assays were performed in duplicate on duplicate samples, each assayed at a minimum of 2 different dilutions. The development of a color reaction from the conversion of the chromogenic substrate (tetramethyl-benzidine), directly proportional to the amount of the analyte assayed, was followed for 5 to 20 min with an ELISA plate reader (ETI-System; Sorin Biomedica, Saluggia, Italy) at 450 nm, up to an optimal reading of positive wells. The enzyme reaction was stopped by the addition of 4 Eq/L-sulfuric acid. Results were calculated by interpolation of a standard curve consisting of at least 5 measurable points. Intra- and inter-assay precision (coefficients of variation) for these assays was 6.9% and 7.5%, respectively.

Statistical Methods

Continuous variables are expressed as means±SD. Discrete variables are expressed as percentages. Subjects were analyzed for baseline demographics, biohumoral data, awake BP monitoring variables, target-organ damage and early inflammatory markers. High-sensitivity CRP and sE-selectin data were skewed to the left and therefore logarithmically transformed.

The relationships of each clinical, demographic, biohumoral, BP variables and indices of target-organ damage with hsCRP and sE-selectin were tested through linear regression analysis. Variables identified by linear regression as significantly related to any of the 2 selected inflammatory markers were further analyzed by multivariable regression analysis, entered one by one with backward selection. All covariates

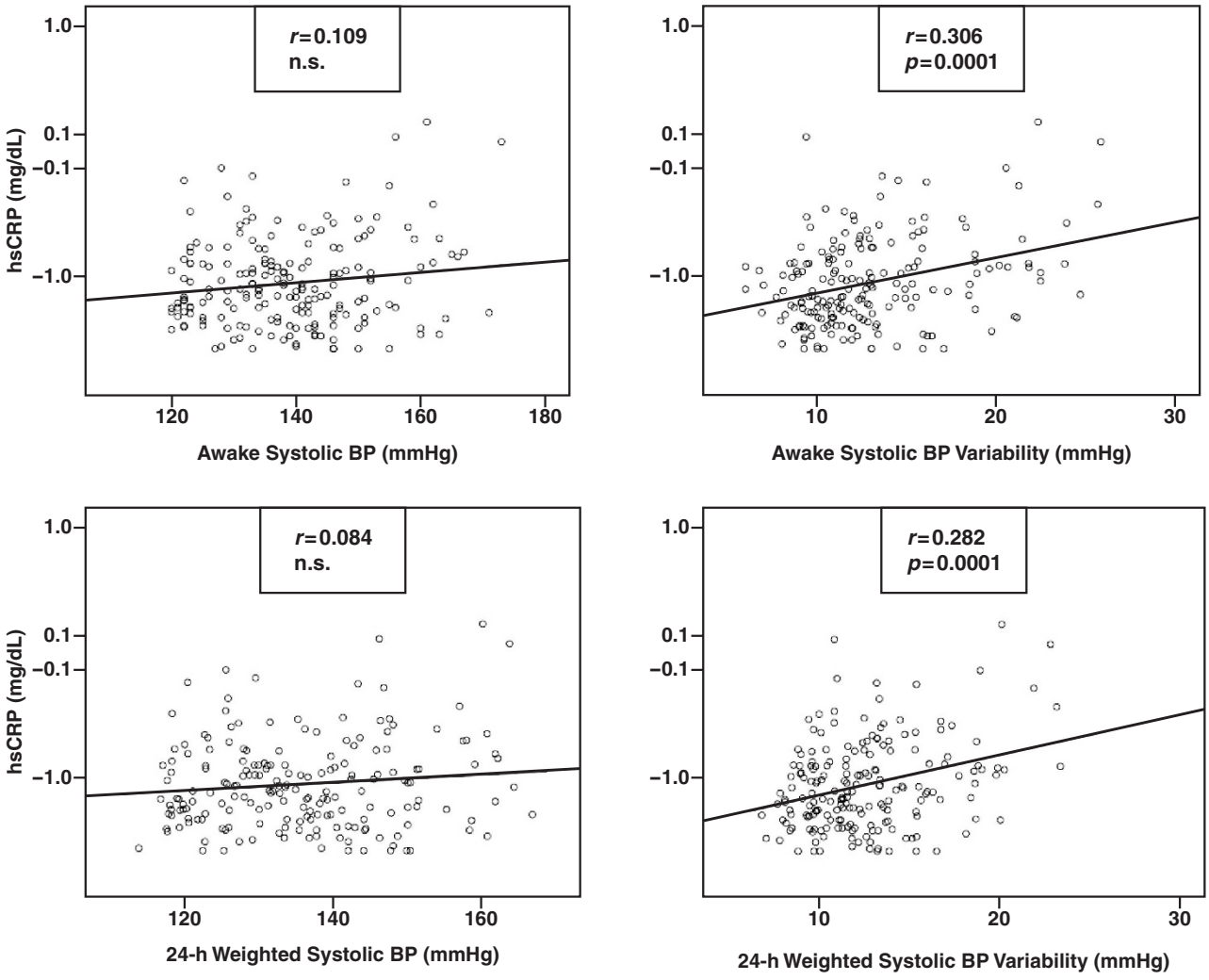

Fig. 1. *The relationship of awake systolic blood pressure (BP) (upper left), 24-h weighted systolic BP (lower left), awake systolic BP variability (upper right) and 24-h weighted systolic BP variability (lower left) with high sensitivity C-Reactive Protein (hsCRP).*

included in the final model were tested for interactions with each other. Age, body mass index (BMI), triglycerides, SBP, DBP, pulse BP, SBP variability, DBP variability, 24-h weighted SBP, 24-h weighted DBP, 24-h weighted SBP variability, 24-h weighted DBP variability, LVMI, IMT, MA, hsCRP, and sE-selectin were tested as independent variables. High-sensitivity CRP and sE-selectin were the dependent variables for each model, all entered as discrete values. Linear regression analyses were also performed for the weighted mean SD of 24-h BP, which excludes the interference of nighttime BP fall on the overall BP variability and allows a more precise assessment of the clinical value of 24-h BP variability (*29*).

The final models were evaluated for linear relationships among variables in the model (collinearity) because of their potential of rendering significance testing unreliable, excluding variables affected by collinearity (tolerance: 0.324–0.975; or variance inflation factor [VIF]: 1.025–3.090). Limits of statistical significance were set at $p<0.05$. Statistical analyses were performed with the aid of the SPSS release 15.0 statistical software (SPSS Inc., Chicago, USA).

Results

Baseline Demographics, Biohumoral Data, and Ambulatory BP Parameters

The patients' age (mean±SD) was 53.0±8.5 years, 59% of patients were male, and the mean BMI was 27.1±4.5 kg/m^2. Other demographic, biohumoral and BP parameters are reported in Table 1.

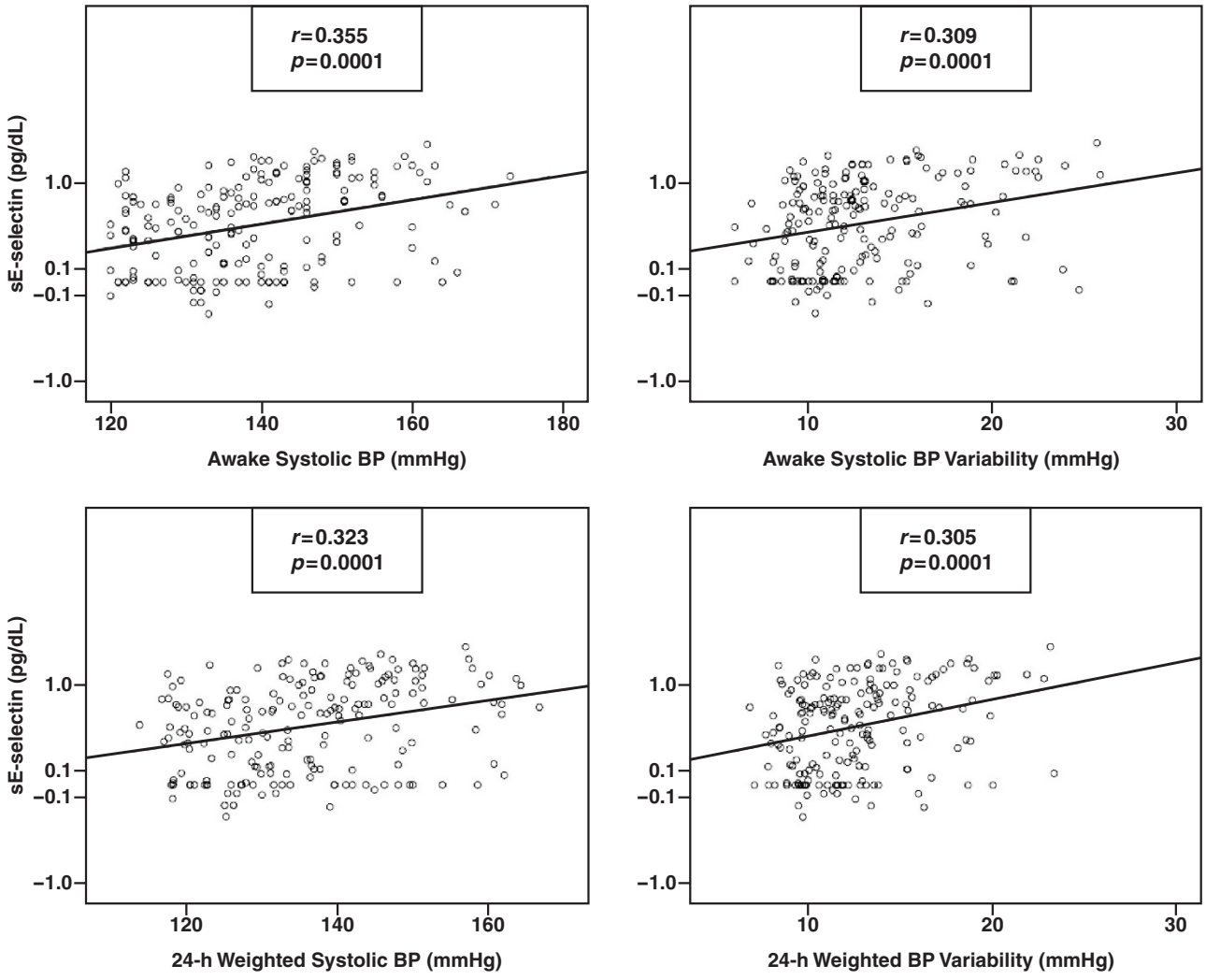

Fig. 2. *The relationship of awake systolic blood pressure (BP) (upper left), 24-h weighted systolic BP (lower left), awake systolic BP variability (upper right) and 24-h weighted systolic BP variability (lower left) with soluble (s) E-selectin (sE-selectin).*

BP Variability, Target-Organ Damage and Markers of Inflammation

Awake SBP and 24-h weighted SBP were not significantly correlated with hsCRP ($r=0.109$, n.s., and $r=0.084$, n.s.; Fig. 1, upper left and lower left, respectively), whereas awake SBP variability and 24-h weighted SBP variability were positively correlated with hsCRP ($r=0.306$, $p=0.0001$, and $r=0.282$, $p=0.0001$; Fig. 1, upper right and lower right, respectively).

Awake SBP and 24-h weighted SBP were significantly correlated with sE-selectin ($r=0.355$, $p=0.0001$, and $r=0.323$, $p=0.0001$; Fig. 2, upper left and lower left, respectively), but awake SBP variability and 24-h weighted SBP variability were also positively correlated with sE-selectin ($r=0.309$, $p=0.0001$, and $r=0.305$, $p=0.0001$; Fig. 2, upper right and lower right, respectively).

The univariable and multivariable linear regression relations of selected clinical, ambulatory BP variables and markers of target-organ damage (IMT, LVMI and MA) as independent variables with markers of inflammation as dependent variables are summarized in Tables 2 and 3 for hsCRP and sE-selectin, respectively. Using multivariable analysis, awake SBP variability ($p=0.034$) was the single independent variable related to hsCRP (Table 2). Using multivariable analysis, awake SBP ($p=0.003$), awake SBP variability ($p=0.018$) and MA ($p=0.001$) were all positively and significantly correlated to sE-selectin (Table 3).

In order to further confirm the existence of an independent relationship of awake SBP variability in the study group as a whole with hsCRP and sE-selectin, an additional analysis was performed with the division of subjects into two subgroups of low and high awake SBP variability, matched for the same MAP. To this aim, as previously described (*24*), subjects were subdivided into four quartiles of awake MAP to adjust for the

Table 2. Biohumoral Data, Ambulatory Awake Blood Pressure Variables and Target-Organ Damage Related to hsCRP

Variables	hsCRP	
	Univariable analysis* p (r)	Multivariable analysis p (β) (CI)
sE-selectin (pg/dL)	0.004 (0.205)	n.s.
Triglycerides (mg/dL)	0.042 (0.148)	n.s.
Pulse BP (mmHg)	0.022 (0.166)	n.s.
Systolic BP variability (mmHg)	0.0001 (0.306)	0.034 (0.022) (0.002–0.042)
Diastolic BP variability (mmHg)	0.0001 (0.276)	n.s.
LVMI (g/m^2)	0.086 (0.125)	n.s.
IMT (mm)	0.042 (0.148)	n.s.

hsCRP, high-sensitivity C-reactive protein; β, coefficient of regression; CI, confidence interval at 95% for β; sE-selectin, soluble E-selectin; BP, blood pressure; LVMI, left ventricular mass index; IMT, carotid intima-media thickness. Only variables significant at univariable analysis are included. *Univariable analysis was performed by means of linear regression.

Table 3. Clinical, Biohumoral Data, Ambulatory Awake Blood Pressure Variables and Target-Organ Damage Related to sE-Selectin

Variables	sE-selectin	
	Univariable analysis* p (r)	Multivariable analysis p (β) (CI)
Age (years)	0.026 (0.162)	n.s.
hsCRP (mg/dL)	0.004 (0.205)	n.s.
BMI (kg/m^2)	0.031 (0.157)	n.s.
Triglycerides (mg/dL)	0.013 (0.179)	n.s.
Systolic BP (mmHg)	0.0001 (0.355)	0.003 (0.008) (0.003–0.014)
Diastolic BP (mmHg)	0.0001 (0.266)	n.s.
Systolic BP variability (mmHg)	0.0001 (0.309)	0.018 (0.019) (0.003–0.035)
Diastolic BP variability (mmHg)	0.011 (0.184)	n.s.
LVMI (g/m^2)	0.002 (0.221)	n.s.
IMT (mm)	0.0001 (0.326)	n.s.
MA (mg/h)	0.0001 (0.342)	0.001 (0.177) (0.075–0.280)

hsCRP, high-sensitivity C-reactive protein; sE-selectin, soluble E-selectin; β, coefficient of regression; CI, confidence interval at 95% for β; BMI, body mass index; IMT, carotid intima-media thickness; BP, blood pressure; LVMI, left ventricular mass index; MA, microalbuminuria. Only variables significant at univariable analysis are included. *Univariable analysis was performed by means of linear regression.

confounding possible effect of average BP levels. Within each quartile, subjects with a SD of awake SBP below or above the median were considered at low or high awake SBP variability. Table 4 shows baseline demographics, biohumoral data, awake BP parameters and markers of inflammation for subjects with low and high awake SBP variability. Age (p=0.001), awake SBP variability (p=0.0001, partition variable) and DBP variability (p=0.0001) were significantly different in the two groups of low and high awake SBP variability, whereas awake SBP, DBP and MAP did not differ. Both hsCRP (p=0.0001) and sE-selectin (p=0.005) were higher in the group with high awake SBP variability (Table 4). These differences remained significant even after adjustment for the effect of age (p=0.022 and p=0.001 for hsCRP and sE-selectin, respectively).

Finally, we analyzed our data by evaluating the weighted mean SD of 24-h BP variability (*29*), which corrects the SD for the nocturnal BP fall. In Table 5 we report data on the relationship of this parameter with inflammatory markers in uni- and multivariable regression analysis, together with the clinical and biohumoral variables, BP parameters and indices of target-organ damage that were significantly related to early inflammatory markers at univariable analysis. The weighted mean SD of 24-h SBP variability (p=0.001) was independently related to hsCRP. Similarly, using multivariable analysis, hsCRP (p=0.036), the 24-h weighted SBP (p=0.014) and the weighted mean SD of 24-h SBP variability (p=0.025) were all positively and significantly related to sE-selectin. Finally, MA (p=0.0001) remained significantly related to sE-selectin with multivariable analysis.

Table 4. Baseline Demographic, Biohumoral Data, Awake Blood Pressure Parameters and Markers of Inflammation of Low and High Variability Groups

Variables	Low variability group (n=95)	High variability group (n=95)	p
Age (years)	51±8	55±9	0.001
Sex (male, %)	58	60	n.s.
BMI (kg/m^2)	26.9±4.6	27.3±4.4	n.s.
Family history of hypertension (%)	60	57	n.s.
Smoking (%)	29	24	n.s.
Physical activity (%)	48	43	n.s.
Coffee drinking (%)	88	93	n.s.
S-creatinine (mg/dL)	0.88±0.2	0.85±0.1	n.s.
Creatinine clearance (mL/min)	97±24	95±24	n.s.
Total cholesterol (mg/dL)	203±41	212±35	n.s.
Triglycerides (mg/dL)	110±54	129±83	n.s.
LDL-C (mg/dL)	124±37	130±32	n.s.
HDL-C (mg/dL)	57±24	56±16	n.s.
Systolic BP (mmHg)	137.8±12.8	140.2±11.1	n.s.
Diastolic BP (mmHg)	85.6±9.4	84.3±9.0	n.s.
Mean BP (mmHg)	102.0±10.0	102.5±8.9	n.s.
Systolic BP variability (mmHg)	10.1±1.6	15.8±3.8	0.0001
Diastolic BP variability (mmHg)	9.1±2.3	12.5±4.4	0.0001
% nocturnal systolic BP fall*	−8.8±5.5	−8.6±6.3	n.s.
% nocturnal diastolic BP fall*	−12.6±9.2	−13.9±6.9	n.s.
hsCRP (mg/dL)	0.09±0.14	0.18±0.24	0.0001
sE-selectin (pg/dL)	4.64±5.21	7.64±7.99	0.005

BMI, body mass index; S-creatinine, serum creatinine; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol; BP, blood pressure; hsCRP, high-sensitivity C-reactive protein; sE-selectin, soluble E-selectin. *Variables calculated over 24 h.

Table 5. Clinical, Biohumoral Data, Ambulatory 24-h Weighted BP Variables and Target-Organ Damage Related to Markers of Inflammation

Variables	hsCRP		sE-selectin	
	Univariable analysis* p (r)	Multivariable analysis p (β) (CI)	Univariable analysis* p (r)	Multivariable analysis p (β) (CI)
Age (years)			0.026 (0.162)	n.s.
BMI (kg/m^2)			0.031 (0.157)	n.s.
hsCRP (mg/dL)			0.004 (0.265)	0.036 (0.137) (0.009–0.266)
sE-selectin (pg/dL)	0.004 (0.205)	n.s.		
Triglycerides (mg/dL)	0.042 (0.148)	n.s.	0.013 (0.179)	n.s.
24-h weighted SBP (mmHg)			0.0001 (0.323)	0.014 (0.007) (0.001–0.012)
24-h weighted DBP (mmHg)			0.0001 (0.283)	n.s.
24-h weighted SBP variability (mmHg)	0.0001 (0.282)	0.001 (0.034) (0.014–0.055)	0.0001 (0.305)	0.025 (0.022) (0.003–0.041)
24-h Weighted DBP variability (mmHg)	0.004 (0.208)	n.s.		
LVMI (g/m^2)	0.086 (0.125)	n.s.		
IMT (mm)	0.042 (0.148)	n.s.	0.0001 (0.257)	n.s.
MA (mg/h)		n.s.	0.0001 (0.316)	0.0001 (0.189) (0.087–0.292)

hsCRP, high-sensitivity C-reactive protein; sE-selectin, soluble E-selectin; β, coefficient of regression; CI, confidence interval at 95% for β; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; LVMI, left ventricular mass index; IMT, carotid intima-media thickness; MA, microalbuminuria. Only variables significant at univariable analysis are included. *Univariable analysis was performed by means of linear regression.

Discussion

We report here that awake SBP variability, as assessed by 24-h ABPM, is a significant correlate of plasma hsCRP and sE-selectin levels, independent of mean awake BP, in newly diagnosed, previously untreated hypertensive subjects. This is the first report on the relationship between awake SBP variability and markers of inflammation and endothelial activation. Because this relationship has been detected in a cohort of subjects recently diagnosed as essentially hypertensive and still untreated, we infer that this relationship occurs early in the natural history of hypertension and likely reveals a role of BP variability, through inflammation, in the pathogenesis of vascular damage.

In a number of previous cross-sectional studies, patients with essential hypertension had increased levels of several inflammatory markers, including soluble leukocyte adhesion molecules (*19*, *31*, *32*). Other studies of this kind reported greater plasma hsCRP concentrations in treated or untreated patients with hypertension than in normotensive subjects (*11*, *12*, *33–37*). The causal role of inflammation in hypertension cannot be assessed in such studies because they were all flawed with possible effects of current or previous antihypertensive treatments and hypertension duration. The independent relation between high BP values and inflammatory markers was later confirmed among so-called pre-hypertensive subjects (*38*), where the effects of treatment and of disease duration is likely to be minimal. Here, the relationship between markers of inflammation and SBP variability is independent of other confounding factors. In such conditions, the finding of a relationship independent of absolute BP levels favors the idea that BP fluctuations induce an "inflammatory" vascular reaction, in turn promoting vascular and myocardial damage recently demonstrated as being associated with BP variability (*24*).

It was previously demonstrated that high BP is associated with inflammatory markers (*19*, *39*), and in recent studies a direct relationship between BP variability and inflammatory markers in normotensive adults (*40*) and hypertensive patients (*41*) was reported. Our data, showing significant relationships of sE-selectin and of hsCRP with BP variability, do not clarify the cause-effect relationships between BP variables and inflammation. On the one hand, high BP and high BP variability might translate into target-organ damage by eliciting vascular inflammatory phenomena. On the other hand, inflammation may be an additive phenomenon contributing to target-organ damage and may contribute to BP variability itself. The clinical implications of these relationships are unclear at the moment in the absence of longitudinal studies. However, an interesting speculation is that an evaluation of inflammatory markers might contribute to risk stratification in hypertensive patients. Because of these possible pathogenetic links and because of the previous demonstration of the relationship of BP variability with target-organ damage (*21*, *24*), it would now appear reasonable to include BP variability measurements as part of the stratification algorithms in hypertensive patients. The pathophysiological importance of hsCRP in this context in particular is still unclear, and whether hsCRP is a risk factor or actually a mediator of vascular disease remains a subject of ongoing debate (*42*). However, both CRP and BP appear to be independent determinants of cardiovascular risk, and, in combination, they have been shown to have additive predictive value (*15*). Therefore, the notion that SBP variability, in addition to mean BP values, relates to a marker in newly diagnosed hypertensive subjects broadly supports the notion of a causal role for BP oscillations in mediating vascular and target-organ damage, as already shown in previous reports (*21*, *24*).

A relatively large set of data also exists on the relationship between sE-selectin and BP parameters. E-selectin is involved in the initial margination and rolling of leukocytes along the vascular endothelium, with a prominent role in acute inflammation (*43*). Previous investigations have reported increased levels of sE-selectin levels in hypertension (*18*), later confirmed by other studies (*19*, *44–47*). Here, we demonstrate for the first time a direct relationship between sE-selectin and both SBP and SBP variability. Notably, in contrast to hsCRP, sE-selectin was also significantly and directly related to MA, which was directly correlated with SBP variability in our previous study (*24*). Because MA has already been correlated with low-grade inflammation in essential hypertension (*48*), these findings suggest that endothelial activation is involved in the pathogenesis of vascular damage associated with short-term SBP oscillations, beyond the association with pressure overload and other conventional risk factors, and that inflammation is involved in transducing the vascular effects of both absolute BP level and BP oscillations. Using multivariate analysis, LVMI and IMT were no longer significantly correlated with hsCRP and sE-selectin, perhaps because of the recent onset of hypertension in our population and the relatively low grade of myocardial and vascular damage at this early stage. On the basis of our data, we certainly cannot exclude a relationship between these variables in a larger population with more advanced target-organ damage.

Usually, SBP is the most important BP variable correlating with outcome. This was also the case for the relationship, among BP variables, with sE-selectin, where with multivariable regression analysis both weighted SBP and weighted SBP variability were significantly related variables, but weighted SBP had a higher correlation coefficient. However, this was apparently not the case for the relationship of BP variables with hsCRP, where only weighted SBP variability (but not weighted SBP) was significantly related to hsCRP with multivariable analysis. Reasons for this are admittedly unclear. Although it is possible that some inflammatory markers are better related to BP variability than to absolute BP levels, as reported in another recent study (*41*), such speculations would need further confirmation.

Our study has limitations in its cross-sectional nature, allowing us to find correlations between BP variables and markers of inflammation, but not to assess cause-effect relationships. However, a causal relationship between BP variability and inflammatory markers is probable on the basis of pathophysiological considerations, as well as the short disease duration in our cases. Finally, as in most current literature, we have based our analyses on data from ABPM rather than on traditionally used clinic BP measurements. However, this is not a true limitation because of recent reports showing a greater impact of ABPM than clinic BP measurements both on target-organ damage (*24*) and on prognosis (*49*).

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