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ORIGINAL ARTICLE

Blood pressure variability and multiple organ damage in primary hypertension

G Leoncini, F Viazzi, G Storace, G Deferrari and R Pontremoli

Organ damage (OD) is an indicator of increased cardiovascular risk. Blood pressure variability (BPV) is related to greater incidence of events, regardless of the severity of hypertension. We investigated the relationship between ambulatory blood pressure monitoring (ABPM)-derived indices of BPV and the presence of multiple OD in primary hypertension (PH). One hundred and sixty-nine untreated patients with PH were evaluated. Systolic (SBP) and diastolic blood pressure (DBP) variability were assessed as the crude and weighted (w.) standard deviation (s.d.), and average real variability (ARV) of the mean value of 24-h, awake and asleep ABPM recordings. Left ventricular mass index, intima-media thickness, estimated-glomerular filtration rate and urinary albumin excretion were assessed as indices of cardiac, vascular and renal damage, respectively. Risk profile progressively increased starting from patients without OD to patients with only one sign of OD, and then to those with multiple OD. In addition to greater severity of the organ involvement, the only variables that were found to significantly differ between subjects with multiple and single OD were office SBP (160 ± 14 vs 154 ± 11 mm Hg, $P = 0.0423$) and DBP (101 ± 7 vs 97 ± 8 mm Hg, $P = 0.0291$), ambulatory arterial stiffness index (AASI) (0.60 ± 0.10 vs 0.50 ± 0.17, $P = 0.0158$) and indices of BPV (24-h SBP s.d., 23 ± 5 vs 20 ± 6 mm Hg, $P = 0.0300$; awake SBP s.d., 22 ± 6 vs 19 ± 6 mm Hg, $P = 0.0366$; 24-h SBP w.s.d., 20 ± 5 vs 17 ± 5 mm Hg, $P = 0.0385$; and 24-h SBP ARV, 18 ± 4 vs 15 ± 5 mm Hg, $P = 0.0420$). All the above mentioned BPV parameters turned out to be determinants of multiple OD, regardless of several confounding variables, including BP levels. Therefore, in hypertensive patients increased SBP variability is associated with multiple signs of OD, regardless of BP values.

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Keywords: blood pressure load; blood pressure variability; organ damage; ambulatory blood pressure

INTRODUCTION

The presence of subclinical organ damage (OD), that is, left ventricular hypertrophy, carotid atheromatosis and renal abnormalities, has important prognostic and therapeutic implications in the management of patients with arterial hypertension, as acknowledged by international guidelines.[1–3] Interestingly, the relationship between OD and outcome seems to be somewhat graded, with a more adverse prognosis when multiple signs of OD coexist in the same patient.[4–7]

It has recently been suggested that the occurrence of cardiovascular (CV) complications may be related not only to the severity of blood pressure (BP) values, but also to the degree of BP variations. In fact, blood pressure variability (BPV) proved to be an independent predictor of CV mortality in the general population, as well as among hypertensive patients.[8–10] Experimental studies have suggested that steep BP oscillations, by increasing oscillatory shear stress in the vessel wall, may in turn favour vascular remodelling and atherosclerosis through the activation of a number of pathogenetic mechanisms such as pro-oxidative processes[11] and increased expression of adhesion molecules at the endothelial level.[12] Noteworthy, cross-sectional as well as prospective studies have suggested that there is an independent association between the presence of OD and increased BPV in primary hypertension (PH).[13,14]

The possible association between increased BPV and the occurrence of multiple OD has never been systematically investigated. The objective of the present cross-sectional study was to address this issue by evaluating correlates of the severity of OD in a group of previously untreated patients with PH.

MATERIALS AND METHODS

Patients

A total of 169 consecutive, untreated patients with PH attending the outpatient clinic of our institution were included in the present study. Hypertension was defined as an office blood pressure of 140/90 mm Hg or greater on at least two different occasions. Exclusion criteria were the presence of neoplastic or hepatic disease, serum creatinine $\geqslant 1.3$ mg dl^{-1} in males and $\geqslant 1.2$ mg dl^{-1} in females, overt proteinuria, glomerular filtration rate (GFR) < 60 ml min^{-1}, secondary hypertension, chronic heart failure (New York Heart Association classes III and IV), a positive history or clinical signs of ischaemic heart disease, diabetes mellitus, severe obesity (defined as body weight $> 150\%$ of ideal body weight), disabling diseases such as dementia or the inability to cooperate, or any condition that might prevent technically adequate ambulatory blood pressure monitoring (ABPM) (that is, atrial fibrillation and other major dysrhythmias). After obtaining written informed consent, all patients underwent the following procedures: office BP measurement, 24-h ABPM, standard questionnaire to assess history and lifestyle habits, blood and urine sampling, standard 12-lead ECG, echocardiogram and carotid ultrasonography. The study protocol was approved by the ethical committee of our department.

A total of 169 patients with sustained hypertension, defined as an average 24-h ambulatory systolic and diastolic BP $> 130/80$ mm Hg, form the basis of the present report.

BP assessment

Office BP was measured by a trained nurse, with the patient in the sitting position after a 5-min rest, with a mercury sphygmomanometer using an appropriate-sized cuff. The systolic (SBP) and diastolic (DBP) BPs were read to the nearest 2 mm Hg. Disappearance of Korotkoff's sounds (phase V)

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was the criterion for DBP. The mean of three consecutive readings was used for further analysis.

All subjects underwent 24-h ABPM with a validated oscillometric device (Spacelabs 90207; SpaceLabs Inc, Redmond, WA, USA) on a typical working day. They were instructed to carry out their usual activities, but to avoid over-exertion, and to keep their non-dominant arm still and relaxed during measurements. The device was set to obtain BP readings every 15 min during the daytime (0700 to 2300 hours) and every 30 min during the nighttime (2300 to 0700 hours). Subjects were asked to keep a diary of their activities and to record when they went to bed. BP recordings were then analyzed, and were subdivided into 'awake' and 'asleep' periods based on diary entries. Nocturnal dipping was defined as a $>10\%$ reduction in the average SBP and DBP at night as compared with the average awake values. BP load was defined as the proportion of BP readings $\geqslant 130$ mm Hg systolic or $\geqslant 80$ mm Hg diastolic over 24 h. Ambulatory arterial stiffness index (AASI) was calculated as 1 minus the regression slope of DBP plotted against SBP obtained from individual 24-h BP monitoring.[15] The slope was not forced through the origin.

We used the standard deviation (s.d.) and average real variability (ARV) as indices of short-term reading-to-reading BPV. We calculated the s.d. of the mean of all individual readings over the 24-h as well as day and night period. The 24-h SBP and DBP s.d.'s were further analyzed in a weighted fashion (w.s.d.) as the mean of day and night s.d. values corrected for the duration of the corresponding subperiods.[16] The ARV averages the absolute differences in BP between consecutive readings, and thus accounts for the order in which the blood pressure measurements are obtained.[17] The ARV was also calculated weighted for the time interval between consecutive readings.

OD assessment

Albuminuria was evaluated by measuring the urinary albumin to urinary creatinine ratio (ACR). The mean of three nonconsecutive first-morning samples was recorded. Only samples from patients with negative urine cultures were collected. Albuminuria was measured by immunonephelometry on an Immage Immunochemistry System (Beckman Coulter Inc., Milan, Italy). Microalbuminuria was defined as an ACR of $\geqslant 2.5$ mg mmol^{-1} in men and of $\geqslant 3.5$ mg mmol^{-1} in women.

GFR was estimated by using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.[18]

All of the echocardiographic studies were performed using an Acuson Sequoia C-256 (Acuson-Siemens, Mountain View, CA, USA) ultrasound machine. The overall, monodimensional left ventricular measurements and the bidimensional (apical 4- and 2-chamber) views were obtained according to the recommendations of the American Society of Echocardiography. All of the tracings were obtained and read by a single observer blinded to the clinical characteristics of the patients under observation. The presence of LVH was defined as left ventricular mass index (LVMI) $\geqslant 51$ g m$^{-2.7}$.[19]

Carotid arteries were investigated in the longitudinal and the transverse projections by high-resolution, real-time ultrasonography using a 10-MHz in-line duplex Diasonic Spectra System (Diasonic, Milpitas, CA, USA). The intima-media thickness (IMT) of both carotid arteries was always measured on the common carotid artery outside the plaque, if any was present. Carotid plaque was defined as IMT >1.3 mm. Each measurement was calculated by taking the average of three readings. Carotid abnormalities were diagnosed when there was $\geqslant 1$ carotid plaque or when there was diffuse common carotid artery thickening, defined as an average IMT >0.9 mm.

Statistical analysis

All of the data are expressed as mean ± s.d. or median (interquartile range) for skewed variables. Not normally distributed variables were log-transformed (Log) before statistical analysis was carried out. Patients with 24-h SBP or awake SBP below or above the group median (that is, 140 and 144 mm Hg, respectively) were classified as having low or high BP levels. Patients with 24-h SBP s.d., 24-h SBP w.s.d., awake SBP s.d. and 24-h SBP ARV below or above the group median (that is, 19.7 mm Hg, 17.1 mm Hg, 18.6 mm Hg and 15.2 mm Hg, respectively) were classified as having low or high BPV. Analysis of variance (ANOVA) was used to analyze data among patients categorized according to the number of signs of OD. The relationship between ABPM-derived BPV indices and several clinical variables was assessed using Pearson's correlation coefficient analysis and a 95% confidence interval (CI). Relative risk and 95% CIs were calculated by exponentiation of logistic regression coefficients. To assess the independent influence of BPV on the presence of TOD, analyses were performed on the basis of three models: model 1 included variables that were different between patients with only one sign of OD and those with multiple OD (that is, office BP and AASI); the two other models included variables known to influence the presence and extent of OD (model 2: duration of hypertension and SBP load; model 3: SBP load, age, BMI, gender, current smoking, triglycerides, LDL-cholesterol and serum glucose).

All of the statistical analyses were performed with the use of Statview version 5.0.1 for Windows (SAS Institute Inc, Cary, NC, USA). A value of $P<0.05$ was considered statistically significant.

RESULTS

Out of 246 untreated hypertensive patients seen at our clinic between January 2006 and January 2009, 226 (all Caucasian Europeans) fulfilled the inclusion criteria. Among them, 27 were excluded because of unwillingness to participate or for miscellaneous reasons. Among the remaining 199 patients, 188 completed the study having ABPM (at least 70% of valid readings) and ultrasound examinations of good technical quality. Patients who were diagnosed as having sustained hypertension form the basis of the present report. A patient flow chart is showed in Figure 1. Of the participating patients, 149 (88%) had never been treated for hypertension, whereas 20 (12%) had received antihypertensive treatment in the past, albeit intermittently and not during the 6 months prior to the study.

Clinical characteristics and ABPM parameters of the study group stratified according to the presence and number of signs of OD are reported in Tables 1 and 2. Overall, 47% of the study patients ($N=80$) showed signs of organ damage, and among them 70% had single organ involvement, while 30% had multiple organ damage. The most common sign of OD was left ventricular hypertrophy (31%), followed by carotid atherosclerosis (20%) and renal abnormalities (11.8%). Among the 24 patients with multiple OD only 3 patients have all three indices of OD and 21 subjects have two signs of OD, in particular 12 with left ventricular hypertrophy and carotid atherosclerosis, 8 with left ventricular hypertrophy and renal damage, and only one patient with carotid atherosclerosis and renal damage.

Age, duration of hypertension, BMI, triglyceride levels, office SBP and DBP, 24-h SBP, awake SBP, asleep SBP, asleep DBP, AASI, 24-h SBP s.d., asleep SBP s.d., awake SBP s.d., 24-h SBP w.s.d., 24-h SBP ARV, awake SBP ARV, asleep SBP ARV and 24-h wARV progressively increased starting from patients without OD to patients with only one sign of OD, and then to those with multiple OD. Accordingly, the percentage of patients with 24-h SBP w.s.d. or 24-h SBP ARV above the median increased progressively from subjects without OD to those with one sign of OD and even more so in the presence of multiple OD (Figure 2). The relative small sample size and heterogeneity in OD distribution prevents us from further analyses to investigate differences in BPV between patients with specific combinations of OD indices. When we investigated the reciprocal influence of blood pressure load and variability on the occurrence of organ damage, we found that the concomitant presence of higher ABPM-derived BP values and increased BPV, assessed by various methods, was associated with a higher prevalence of OD, while the presence of only one BP abnormality (that is, increased BP values or BPV) did not strongly influence OD (Figure 3). At variance, the presence of multiple OD was mainly related to the presence of increased BPV as compared with higher ABPM-derived BP values (Figure 4). In addition to greater severity of the organ involvement, the only variables that differed significantly between subjects with multiple and single OD were office SBP and DBP, AASI and some indices of BPV (24-h SBP s.d., awake SBP s.d, 24-h SBP w.s.d. and 24-h SBP ARV). Noteworthy, AASI, an index of arterial stiffness, was positively correlated with the BPV parameter (24-h SBP s.d. $r=0.259$, 95% CI 0.106–0.400, $P=0.0011$; awake SBP s.d. $r=0.318$, 95%CI 0.171–0.450,

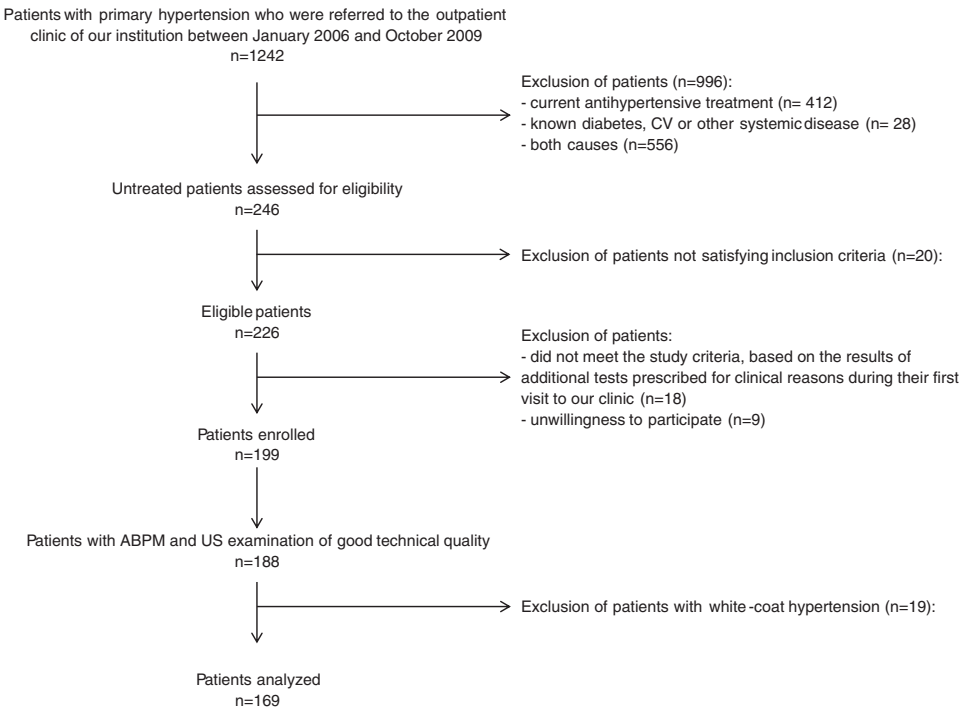

Figure 1. Flow chart of study patients.

Table 1. Clinical characteristics of the study patients

Characteristics	*All* (n = *169*)	*No OD* (n = *89*)	*1 OD* (n = *56*)	⩾*2 OD* (n = *24*)	P-*value*
Age	47.1 ± 9.5	44.3 ± 9.2	49.5 ± 9.5*	52.2 ± 7.0*	<0.0001
Male (%)	66.9	67.4	60.7	79.2	0.2715
Family history of CVD (%)	50.9	49.4	47.3	65.2	0.3244
Current smoking (%)	22.3	20.7	29.1	12.5	0.2316
SBP (mm Hg)	154.4 ± 12.5	153.4 ± 12.6	153.6 ± 11.4	159.8 ± 13.8**	0.0715
DBP (mm Hg)	97.3 ± 8.0	96.6 ± 8.3	96.7 ± 7.6	101.0 ± 7.1**	0.0511
Duration of Ht, months	24.0 (74.0)	20.0 (53.5)	42.0 (73.0)*	60.0 (99.0)*	0.0170
BMI (kg m^{-2})	26.1 ± 3.4	25.4 ± 3.3	26.4 ± 3.2	27.5 ± 4.2*	0.0217
Serum uric acid (mg dl^{-1})	5.1 ± 1.4	5.0 ± 1.4	5.2 ± 1.3	5.5 ± 1.3	0.2769
Serum glucose (mg dl^{-1})	90.8 ± 11.8	90.1 ± 12.0	90.3 ± 11.3	94.8 ± 11.8	0.2130
Total cholesterol (mg dl^{-1})	209.9 ± 44.8	202.9 ± 44.7	216.9 ± 46.4	220.5 ± 38.3	0.0925
Triglycerides (mg dl^{-1})	105.0 (76.5)	97.0 (68.5)	114.0 (64.5)	154.0 (98.8)*	0.0260
LDL-cholesterol (mg dl^{-1})	134.2 ± 42.2	130.4 ± 45.1	136.9 ± 39.5	142.4 ± 36.6	0.4280
GFR (ml min^{-1} per 1.73 m^2)	89 (23)	92 (16)	90 (27)	84 (24)	0.2284
A/C ratio (mg mmol^{-1})	0.5 (0.6)	0.4 (0.3)	0.6 (0.9)*	1.3 (5.3)*	<0.0001
Microalbuminuria (%)	10.7	0.0	12.5*	45.8*,**	<0.0001
CKD(%)	11.8	0.0	14.3*	50.0*,**	<0.0001
Left ventricular mass (g m$^{-2.7}$)	46 ± 11	40 ± 7	50 ± 10*	61 ± 9*,**	<0.0001
Left ventricular hypertrophy (%)	31	0	54*	96*,**	<0.0001
Carotid intima-media thickness (mm)	0.69 ± 0.17	0.62 ± 0.15	0.77 ± 0.17*	0.79 ± 0.15*	<0.0001
Carotid atherosclerosis (%)	20	0	32*	67*,**	<0.0001

Abbreviations are: A/C, urine albumin to creatinine ratio; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; Ht, hypertension; OD, organ damage; SBP, systolic blood pressure. Values are mean ± s.d. or percentage, except for duration of hypertension, triglycerides, GFR and A/C ratio expressed as median (interquartile range). *P < 0.05 vs without OD; **P < 0.05 vs with 1 sign of OD.

P < 0.0001; 24-h SBP w.s.d. r = 0.295, 95%CI 0.145–0.431, P = 0.0002 and 24-h SBP ARV r = 0.324, 95%CI 0.176–0.458, P < 0.0001). Multivariate analysis confirmed 24-h SBP s.d., awake SBP s.d., 24-h SBP w.s.d. and 24-h SBP ARV as determinants of multiple OD, regardless of office BP and AASI (Table 3, model 1), regardless of duration of hypertension and SBP load (Table 3, model 2) and regardless of age, BMI, gender, current smoking, SBP load, triglycerides, LDL-cholesterol and serum glucose (Table 3, model 3).

DISCUSSION

Our findings indicate that increased BPV is associated with the simultaneous presence of atherosclerotic OD at various sites, confirming and extending previous knowledge on the relationship between BP oscillations and OD.

The prevalence of OD reported in our study is fairly high, with approximately half of the patients (47%) showing at least one sign of OD, while the clustering of two or three signs of OD is less frequent, with about one out of three patients with OD showing

Table 2. Ambulatory blood pressure parameters of the study patients

Characteristics	*All* (n = *169*)	*No OD* (n = *89*)	*1 OD* (n = *56*)	*⩾2 OD* (n = *24*)	P
24-h SBP (mm Hg)	142 ± 14	138 ± 12	145 ± 15*	146 ± 16*	0.006
24-h DBP (mm Hg)	88 ± 10	86 ± 9	90 ± 10	88 ± 11	0.0878
SBP load (%)	68	64	72	73	0.0703
DBP load (%)	65	63	69	64	0.3039
Awake SBP (mm Hg)	146 ± 14	142 ± 12	149 ± 15*	150 ± 18*	0.0086
Awake DBP (mm Hg)	91 ± 10	90 ± 10	93 ± 9	91 ± 12	0.1627
Asleep SBP (mm Hg)	127 ± 16	123 ± 13	130 ± 17*	131 ± 18*	0.0109
Asleep DBP (mm Hg)	77 ± 11	75 ± 10	80 ± 11*	79 ± 11	0.0216
Non Dipper (%)	36	34	35	49	0.5516
AASI	0.50 ± 0.17	0.47 ± 0.17	0.50 ± 0.17	0.60 ± 0.10*,**	0.0044
24-h SBP s.d. (mm Hg)	19.7 ± 5.9	18.8 ± 5.8	19.8 ± 6.0	22.9 ± 5.4*,**	0.0107
24-h DBP s.d. (mm Hg)	16.6 ± 4.6	16.1 ± 4.8	16.8 ± 4.6	17.7 ± 4.1	0.3279
Awake SBP s.d. (mm Hg)	18.5 ± 6.3	17.3 ± 6.1	18.9 ± 6.3	22.1 ± 5.8*,**	0.0048
Awake DBP s.d. (mm Hg)	16.3 ± 5.7	15.5 ± 5.9	16.7 ± 5.7	18.2 ± 4.7*	0.1007
Asleep SBP s.d. (mm Hg)	13.6 ± 5.5	12.3 ± 4.5	14.7 ± 6.5*	15.8 ± 5.3*	0.0062
Asleep DBP s.d. (mm Hg)	10.9 ± 4.1	10.2 ± 3.7	12.0 ± 4.8*	11.4 ± 3.7	0.0367
24-h SBP w.s.d. (mm Hg)	16.8 ± 5.3	15.7 ± 5.0	17.3 ± 5.4	19.9 ± 4.7*,**	0.0021
24-h DBP w.s.d. (mm Hg)	14.3 ± 4.5	13.6 ± 4.5	14.8 ± 4.5	15.9 ± 4.0*	0.0689
24-h SBP ARV (mm Hg)	15.1 ± 4.8	14.3 ± 4.6	15.1 ± 5.0	17.6 ± 4.3*,**	0.0163
24-h DBP ARV (mm Hg)	13.5 ± 5.1	13.1 ± 5.3	13.5 ± 5.0	15.2 ± 4.4	0.1929
Awake SBP ARV (mm Hg)	15.9 ± 5.7	14.9 ± 5.3	16.3 ± 6.1	18.6 ± 5.3*	0.0154
Awake DBP ARV (mm Hg)	14.8 ± 6.4	14.1 ± 6.5	15.1 ± 6.4	16.9 ± 5.4	0.1657
Asleep SBP ARV (mm Hg)	13.0 ± 5.3	12.0 ± 4.4	14.0 ± 6.4*	14.8 ± 4.9*	0.0251
Asleep DBP ARV (mm Hg)	9.9 ± 3.6	9.5 ± 3.4	10.5 ± 4.1	10.3 ± 3.2	0.2672
24-h SBP w.ARV (mm Hg)	15.1 ± 5.0	14.1 ± 4.5	15.7 ± 5.6	17.2 ± 4.6*	0.0122
24-h DBP w.ARV (mm Hg)	13.5 ± 4.9	12.9 ± 4.7	14.0 ± 5.5	14.7 ± 4.1	0.1975

Abbreviations: ARV, average real variability; DBP, diastolic blood pressure; OD, organ damage; SBP, systolic blood pressure; s.d., standard deviation; w., weighted. Values are mean ± s.d. or percentage. *$P<0.05$ vs without OD; **$P<0.05$ vs with one sign of OD.

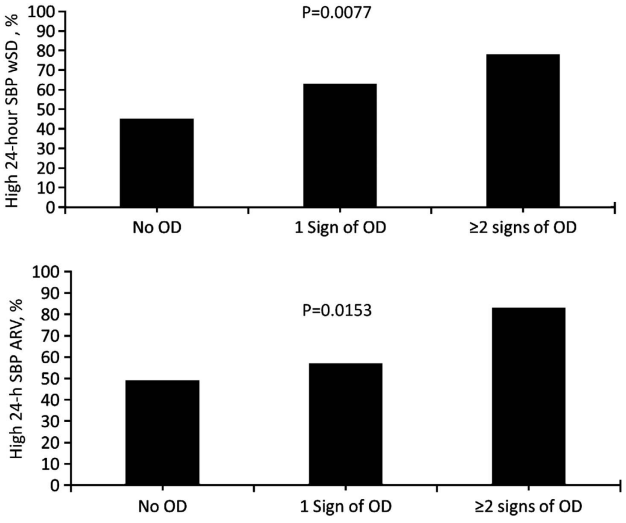

Figure 2. Prevalence of high BPV according to the presence and number of signs of OD. The term 'high' refers to values above the median.

multiple involvement. This is likely due to the relatively young age of our study group and the selection criteria we adopted, by which patients with diabetes, previous CV events and overt renal damage were excluded.

Noteworthy, the relationship between BPV and multiple OD was consistent using different indices to assess BPV, in particular those taking into account the entire recorded period and are not affected by the magnitude of the day–night BP difference. In accordance with some[20] although not all[21,22] previous studies, nighttime BPV was not an independent correlate of OD in our study. This could possibly be due to the increased influence of daytime physical exercise and emotional stress on the association between BPV and OD as compared with nighttime. On the other hand, the sampling interval of 30 min we used during the nighttime period for practical reasons might have limited the ability to detect BP oscillations within this time period.

The relationship between steep blood pressure oscillations and changes in vessel wall tension is not entirely understood, and is likely influenced by a complex interplay of several autonomic and hormonal control mechanisms, as well as environmental stimuli. In the present study the strong association between BPV and multiple OD persisted even after adjusting for potential confounders such as blood pressure severity and duration of hypertension.

Interestingly, the presence of subclinical abnormalities, most often involving only one of the three target organs we evaluated, is influenced both by BP load and BPV (Figure 3), while the coexistence of multiple signs of OD in the same patient seems to be more closely related to increased BPV (Figure 4). These findings may suggest that blood pressure excursions, together with blood pressure levels, are important determinants of the development of organ damage. On the other hand, one could hypothesise that more widespread vascular damage may cause greater BP dynamics. We acknowledge that the cross-sectional design of the present study only allows us to describe correlations and to generate hypotheses, but not to distinguish cause from effect. Therefore, we are not able to determine whether higher BPV promotes the development of OD at various levels or multiple OD represents a risk factor for increased BPV rather than being a consequence of it. Otherwise, both cardiovascular OD and BPV may reflect other underlying pathophysiological factors.

Experimental studies have suggested that increased oscillatory shear stress at the vessel wall level caused by BPV may favour vascular remodelling by activating the pro-oxidant process[11] and

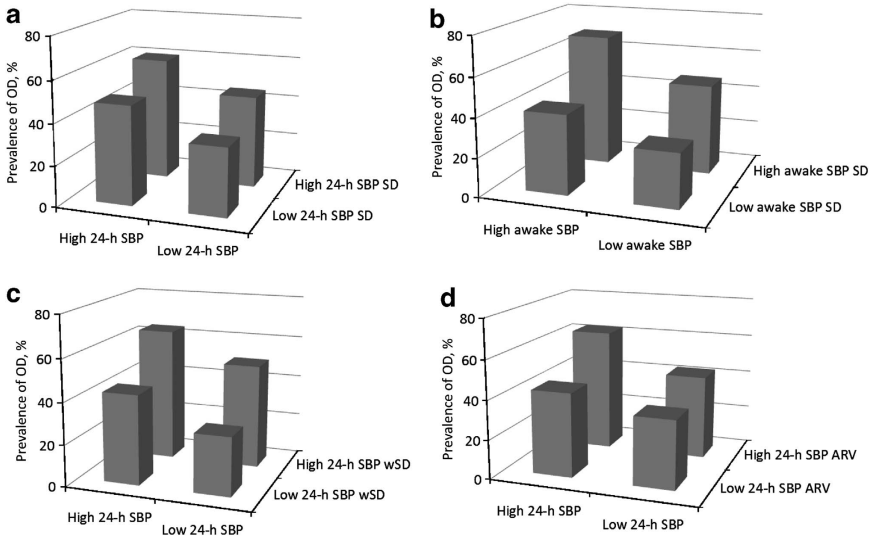

Figure 3. Prevalence of OD according to ABPM-derived blood pressure values and BPV. The term 'low' refers to values below the median and the term 'high' to values above the median. (**a**) Overall $P = 0.0939$, high 24-h SBP/high 24-h SBP s.d. vs low 24-h SBP/low 24-h SBP s.d. $P = 0.0223$; (**b**) overall $P = 0.0019$, high awake SBP/High awake SBP s.d. vs low awake SBP/low awake SBP s.d. $P = 0.0005$; (**c**) overall $P = 0.0090$, high awake SBP/high awake SBP w.s.d. vs low awake SBP/low awake SBP w.s.d. $P = 0.0017$; (**d**) overall $P = 0.0510$, high 24-h SBP/high 24-h SBP ARV vs low 24-h SBP/low 24-h SBP ARV $P = 0.0157$.

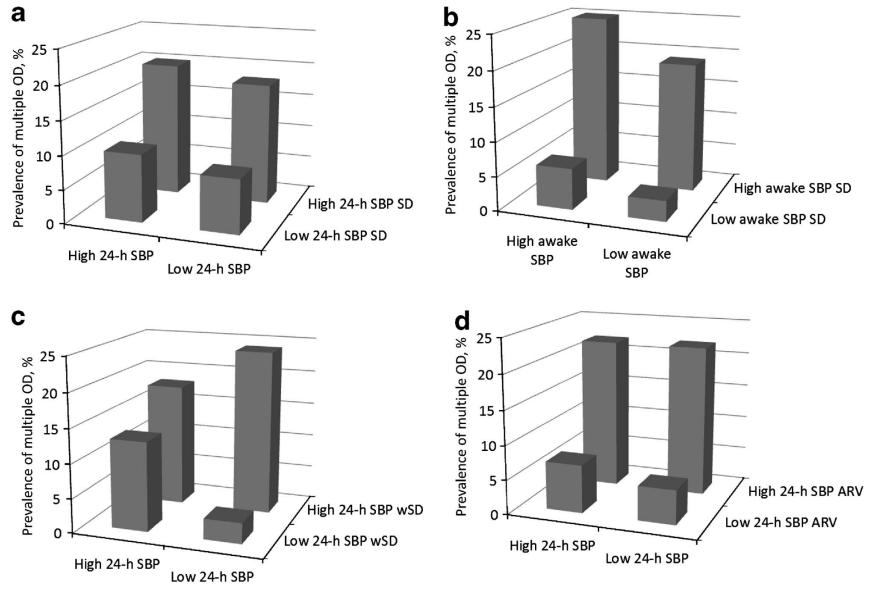

Figure 4. Prevalence of multiple OD according to ABPM-derived blood pressure values and BPV. The term 'low' refers to values below the median and the term 'high' to values above the median. (**a**) Overall $P = 0.3212$; (**b**) overall $P = 0.0117$, high awake SBP/high awake SBP s.d. vs low awake SBP/low awake SBP s.d. $P = 0.0131$, low awake SBP/high awake SBP s.d. vs low awake SBP/low awake SBP s.d. $P = 0.0644$; (**c**) overall $P = 0.0569$, high awake SBP/High awake SBP w.s.d. vs low awake SBP/low awake SBP w.s.d. $P = 0.0513$, low awake SBP/High awake SBP w.s.d. vs low awake SBP/low awake SBP w.s.d. $P = 0.0157$; (**d**) overall $P = 0.0553$, high 24-h SBP/high 24-h SBP ARV vs low 24-h SBP/low 24-h SBP ARV $P = 0.0525$, Low 24-h SBP/High 24-h SBP ARV vs Low 24-h SBP/Low 24-h SBP ARV $P = 0.0676$.

by enhancing the expression of adhesion molecules[12] at the endothelial level, while laminar shear stress may induce a compensatory antioxidant response.[11] Furthermore, it has been shown that increased BPV produced by sinoaortic denervation may account for changes in the aortic wall structure (that is, increased aortic wall cross-sectional area and collagen content) and consequent reduction in aortic distensibility.[23] Therefore, it could be argued that in the presence of multiple hypertensive organ damage, increased BPV might reflect reduced compliance of the arterial wall, that is, arterial stiffness. Accordingly, despite similar BP values as assessed by means of ABPM, our study patients with multiple OD showed an increase in both 24-h BPV and in the AASI, an indirect measure of arterial stiffness, as compared with subjects with single organ involvement. We also found a correlation between AASI and 24-h BPV, and patients with greater AASI showed increased BPV (data not shown). Finally, the results of logistic regression analysis indicate that BPV and arterial stiffness are significantly related to multiple OD, and suggest a

Table 3. Multivariate-adjusted odds relating organ damage to blood pressure variability

	Unadjusted OR (95% CI)	*Model 1 OR (95% CI)*	*Model 2 OR (95% CI)*	*Model 3 OR (95% CI)*
(a) 24-h SBP SD				
Dependent variable: one sign of organ damage				
24-h SBP s.d., per unit increase	1.032 (0.969–1.098)	1.026 (0.962–1.094)	1.026 (0.963–1.094)	1.031 (0.960–1.107)
AASI, per 0.1 unit increase		1.004 (0.851–1.346)		
Office SBP, per 1 mm Hg increase		0.999 (0.971–1.029)		
Duration of Ht, per month increase			1.003 (0.998–1.008)	
SBP load, %, per percent increase			1.015 (0.998–1.031)	1.011 (0.993–1.030)
Age, per year increase				**1.051 (1.001–1.105)**
BMI, per kg m^{-2} increase				1.083 (0.935–1.255)
Female gender				1.419 (0.567–3.553)
Current smoking				1.141 (0.670–1.941)
Triglycerides, per mg dl^{-1} increase				1.003 (0.995–1.010)
LDL-cholesterol, per mg dl^{-1} increase				1.001 (0.991–1.012)
Serum glucose, per mg dl^{-1} increase				0.993 (0.958–1.030)
Dependent variable: two or more signs of organ damage				
24-h SBP s.d., per unit increase	**1.125 (1.038–1.218)**	**1.119 (1.026–1.221)**	**1.117 (1.030–1.212)**	**1.103 (1.003–1.212)**
AASI, per 0.1 unit increase		**1.258 (1.150–2.265)**		
Office SBP, per 1 mm Hg increase		1.026 (0.987–1.067)		
Duration of Ht, per month increase			1.004 (0.997–1.011)	
SBP load, %, per percent increase			1.013 (0.990–1.038)	1.021 (0.993–1.049)
Age, per year increase				**1.101 (1.025–1.182)**
BMI, per kg m^{-2} increase				1.101 (0.909–1.333)
Female gender				0.796 (0.196–3.229)
Current smoking				0.892 (0.423–1.880)
Triglycerides, per mg dl^{-1} increase				1.008 (0.998–1.049)
LDL-cholesterol, per mg dl^{-1} increase				1.003 (0.989–1.017)
Serum glucose, per mg dl^{-1} increase				1.019 (0.970–1.071)
(b) Awake SBP SD				
Dependent variable: one sign of organ damage				
Awake SBP s.d., per unit increase	1.044 (0.985–1.106)	1.036 (0.975–1.101)	1.043 (0.983–1.108)	1.031 (0.963–1.103)
AASI, per 0.1 unit increase		1.006 (0.863–1.349)		
Office SBP, per 1 mm Hg increase		1.001 (0.972–1.030)		
Duration of Ht, per month increase			1.003 (0.998–1.009)	
SBP load, %, per percent increase			1.013 (0.997–1.029)	1.008 (0.991–1.027)
Age, per year increase				**1.057 (1.006–1.110)**
BMI, per kg m^{-2} increase				1.105 (0.956–1.276)
Female gender				1.561 (0.639–3.814)
Current smoking				1.182 (0.701–1.995)
Triglycerides, per mg dl^{-1} increase				1.001 (0.994–1.008)
LDL-cholesterol, per mg dl^{-1} increase				1.000 (0.990–1.010)
Serum glucose, per mg dl^{-1} increase				0.993 (0.958–1.030)
Dependent variable: two or more signs of organ damage				
Awake SBP s.d., per unit increase	**1.126 (1.044–1.215)**	**1.121 (1.031–1.219)**	**1.127 (1.043–1.218)**	**1.114 (1.012–1.227)**
AASI, per 0.1 unit increase		**1.219 (1.113–2.186)**		
Office SBP, per 1 mm Hg increase		1.030 (0.990–1.071)		
Duration of Ht, per month increase			1.005 (0.998–1.012)	
SBP load, %, per percent increase			1.014 (0.990–1.039)	1.021 (0.993–1.049)
Age, per year increase				**1.103 (1.027–1.185)**
BMI, per kg m^{-2} increase				1.083 (0.893–1.313)
Female gender				0.663 (0.166–2.649)
Current smoking				0.986 (0.468–2.081)
Triglycerides, per mg dl^{-1} increase				1.006 (0.997–1.015)
LDL-cholesterol, per mg dl^{-1} increase				1.000 (0.987–1.013)
Serum glucose, per mg dl^{-1} increase				1.025 (0.974–1.078)
(c) 24-h SBP w.s.d.				
Dependent variable: one sign of organ damage				
24-h SBP w.s.d., per unit increase	1.065 (0.992–1.143)	1.062 (0.986–1.143)	1.059 (0.984–1.138)	1.052 (0.969–1.141)
AASI, per 0.1 unit increase		1.001 (0.812–1.295)		
Office SBP, per 1 mm Hg increase		1.000 (0.971–1.030)		
Duration of Ht, per month increase			1.003(0.997–1.008)	
SBP load, %, per percent increase			1.015 (0.998–1.032)	1.011 (0.993–1.030)
Age, per year increase				**1.052 (1.001–1.105)**
BMI, per kg m^{-2} increase				1.073 (0.925–1.244)
Female gender				1.371 (0.546–3.439)

Table 3. (Continued)

	Unadjusted OR (95% CI)	*Model 1 OR (95% CI)*	*Model 2 OR (95% CI)*	*Model 3 OR (95% CI)*
Current smoking				1.159 (0.679–1.978)
Triglycerides, per mg dl^{-1} increase				1.003 (0.995–1.010)
LDL-cholesterol, per mg dl^{-1} increase				1.001 (0.991–1.012)
Serum glucose, per mg dl^{-1} increase				0.994 (0.958–1.031)
Dependent variable: two or more signs of organ damage				
24-h SBP w.s.d., per unit increase	**1.168 (1.064–1.283)**	**1.180 (1.059–1.314)**	**1.160 (1.055–1.275)**	**1.149 (1.023–1.290)**
AASI, per 0.1 unit increase		**1.232 (1.122–2.223)**		
Office SBP, per 1 mm Hg increase		1.033 (0.992–1.077)		
Duration of Ht, per month increase			1.004 (0.997–1.011)	
SBP load, %, per percent increase			1.014 (0.990–.038)	1.021 (0.993–1.050)
Age, per year increase				**1.102 (1.026–1.184)**
BMI, per kg m^{-2} increase				1.070 (0.877–1.305)
Female gender				0.736 (0.179–3.028)
Current smoking				0.931 (0.436–1.988)
Triglycerides, per mg dl^{-1} increase				1.007 (0.998–1.017)
LDL-cholesterol, per mg dl^{-1} increase				1.003 (0.989–1.017)
Serum glucose, per mg dl^{-1} increase				1.021 (0.971–1.073)
(c) 24-h SBP ARV				
Dependent variable: one sign of organ damage				
24-h SBP ARV, per unit increase	1.038 (0.963–1.120)	1.030 (0.951–1.115)	1.026 (0.949–1.109)	1.023 (0.935–1.118)
AASI, per 0.1 unit increase		1.004 (0.840–1.347)		
Office SBP, per 1 mm Hg increase		1.001 (0.972–1.031)		
Duration of Ht, per month increase			1.003 (0.997–1.008)	
SBP load, %, per percent increase			1.014 (0.998–1.031)	1.011 (0.993–1.029)
Age, per year increase				**1.053 (1.003–1.106)**
BMI, per kg m^{-2} increase				1.083 (0.932–1.258)
Female gender				1.338 (0.527–3.396)
Current smoking				0.992 (0.957–1.029)
Triglycerides, per mg dl^{-1} increase				1.003 (0.996–1.010)
LDL-cholesterol, per mg dl^{-1} increase				1.002 (0.991–1.012)
Serum glucose, per mg dl^{-1} increase				0.994 (0.958–1.031)
Dependent variable: two or more signs of organ damage				
24-h SBP ARV, per unit increase	**1.151 (1.042–1.271)**	**1.167 (1.037–1.313)**	**1.134 (1.025–1.256)**	**1.140 (1.004–1.295)**
AASI, per 0.1 unit increase		**1.238 (1.129–2.234)**		
Office SBP, per 1 mm Hg increase		1.036 (0.994–1.079)		
Duration of Ht, per month increase			1.004 (0.997–1.011)	
SBP load, %, per percent increase			1.012 (0.988–1.035)	1.018 (0.991–1.046)
Age, per year increase				**1.096 (1.022–1.176)**
BMI, per kg m^{-2} increase				1.060 (0.865–1.299)
Female gender				0.560 (0.128–2.444)
Current smoking				0.931 (0.436–1.988)
Triglycerides, per mg dl^{-1} increase				1.008 (0.999–1.017)
LDL-cholesterol, per mg dl^{-1} increase				1.002 (0.988–1.016)
Serum glucose, per mg dl^{-1} increase				1.022 (0.972–1.074)

Abbreviations: AASI, ambulatory arterial stiffness index; ARV, average real variability; CI, confidence interval; Ht, hypertension; LV, left ventricle; OR, odds ratio; SBP, systolic blood pressure; s.d., standard deviation; w, weighted. Values are odds ratios (95% confidence interval) expressing the risk per unit increase in the predictor variable. Significant odds ratios are expressed in bold. Model 1 adjusted for AASI and office SBP. Model 2 adjusted for duration of hypertension and SBP load. Model 3 adjusted for SBP load, age, BMI, gender, current smoking, triglycerides, LDL-cholesterol, serum glucose.

synergistic effect of these two parameters on multiple OD involvement.

We acknowledge some limitations of the present study. The relatively small sample size and the fact that our study group is a rather selected one and includes patients at relatively high risk as indicated by the high prevalence of OD, and the exclusion of patients with diabetes or previous CV disease make our findings not entirely applicable to the population of hypertensive population at large or to patients seen by general practitioners.

In conclusion, the present study provides further evidence that increased BPV is associated with unfavourable abnormalities in the cardiovascular system, namely greater extent and severity of OD involvement in patients with PH. Further studies aimed at identifying a causal link between BPV and the development of organ damage, and at defining the role of arterial stiffening in this relationship are certainly needed.

What is known about the topic

- In hypertensive patients cardiovascular risk is related not only to the degree of blood pressure levels, but also to blood pressure variability.
- Subclinical organ damage is a strong and independent predictor of cardiovascular morbidity and mortality among hypertensive patients.
- The relationship between organ damage and prognosis seems to be graded, with a more unfavourable outcome when multiple signs of organ damage are present in the same patients.

What this study adds

- Increased blood pressure variability is associated with multiple organ damage, and this relationship is consistent using different indices to assess BP variability.
- The association persisted even after adjusting for potential confounders, including blood pressure load.
- Arterial stiffness may be involved in the association between blood pressure variability and multiple organ damage.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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