Original Article

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Variable association of 24-h peripheral and central hemodynamics and stiffness with hypertension-mediated organ damage: the VASOTENS Registry

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Objective: In this analysis of the telehealth-based Vascular health ASsessment Of The hypertENSive patients Registry, we checked how 24-h central and peripheral hemodynamics compare with hypertension-mediated organ damage (HMOD).

Methods: In 646 hypertensive patients (mean age 52 ± 16 years, 54% males, 65% treated) we obtained ambulatory brachial and central SBP and pulse pressure (PP), SBP, and PP variability, pulse wave velocity and augmentation index with a validated cuff-based technology. HMOD was defined by an increased left ventricular mass index (cardiac damage, evaluated in 482 patients), an increased intima–media thickness (vascular damage, $n = 368$), or a decreased estimated glomerular filtration rate or increased urine albumin excretion (renal damage, $n = 388$).

Results: Ambulatory SBP and PPs were significantly associated with cardiac damage: the largest odds ratio was observed for 24-h central SBP [1.032 (1.012, 1.051), $P = 0.001$] and PP [1.042 (1.015, 1.069), $P = 0.002$], the weakest for brachial estimates. The association was less strong for vascular damage with a trend to the superiority of 24-h central [1.036 (0.997, 1.076), $P = 0.070$] over brachial PP [1.031 (1.000, 1.062), $P = 0.052$]. No statistically significant association was observed for renal damage. SBP and PP variabilities, pulse wave velocity and augmentation index were not associated with any form of HMOD. In the multivariate analysis, age was associated with any type of HMOD, whereas central SBP and PP were predictive of an increased risk of cardiac damage.

Conclusion: In hypertensive patients a variable association exists between peripheral and central hemodynamics and various types of HMOD, with the most predictive power being observed for central SBP and PP for cardiac damage.

Keywords: arterial stiffness, augmentation index, blood pressure, blood pressure telemonitoring, central arterial pressure, hypertension, pulse wave velocity, vascular biomarkers

Abbreviations: ABPM, ambulatory blood pressure monitoring; AIx, augmentation index; ARV, average real variability; BP, blood pressure; CAP, central arterial pressure; e-CRF, electronic case report forms; eGFR, estimated glomerular filtration rate; HMOD, hypertension-mediated organ damage; HR, heart rate; IMT, intima–media thickness; LV, left ventricular; LVH, left ventricular hypertrophy; LVM, left ventricular mass; LVMI, left ventricular mass index; PP, pulse pressure; PWA, pulse wave analysis; PWV, pulse wave velocity; VASOTENS, Vascular health ASsessment Of The hypertENSive patients

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INTRODUCTION

Currently, strong evidence exists that, when measured at rest, central rather than peripheral, hemodynamics are more closely related to hypertension-mediated organ damage (HMOD), though evidence has not always been consistent [1]. In particular, a positive and close relationship has been documented between central arterial pressure (CAP) and left ventricular (LV) mass index (LVMI) and intima–media thickness (IMT), markers of heart and carotid damage, whereas poor or no relation has been shown with impaired renal function [1].

The introduction in recent years of cuff-based technologies able to provide an indirect measurement of central hemodynamics, arterial stiffness and wave reflections over the 24-h through pulse wave analysis (PWA) of oscillometric brachial tracings has the advantage of providing information on the behavior of vascular health in dynamic conditions during the waking hours and notably during the night sleep hours [2]. As it is well known that HMOD is more closely related to ambulatory than to office blood pressure (BP) [3–5] and since some proof exists that this also applies to measurements of CAP [6,7] and to a lesser extent of pulse wave velocity (PWV) [8], routine measurements of ambulatory central hemodynamics may have some potential for a more affordable and detailed assessment of vascular health in daily-life conditions.

The VASOTENS (Vascular health ASsessment Of The hypertENSive patients) Registry [9] is a large web-based repository of ambulatory BP monitoring (ABPM) recordings obtained with an electronic monitor, which is able to determine CAP, PWV, and augmentation index (AIx) over the 24-h, based on a clinically validated technology of PWA of oscillometric BP measurements [10,11]. Consistency and integrity of data collection are ensured in the study through a telehealth platform, which also provides the engine for the PWA of brachial oscillograms and the extraction of study parameters. As detailed in the publication relative to the study protocol, the study has several objectives [9]. In the current article, we present the results relative to the relationship of peripheral and central hemodynamics, arterial stiffness and wave reflections with HMOD evaluated at the heart, carotid artery and kidney.

METHODS

Study design and population

A detailed description of the VASOTENS Registry study protocol may be found elsewhere [9]. The study has an international, multicenter, observational, nonrandomized, prospective design. It is registered with ClinicalTrials.gov at number NCT02577835 and formally endorsed by the Italian and Russian Societies of Hypertension. A total of 24 centers worldwide are involved in the study. For the purpose of the present analysis 14 of these centers provided data: five centers located in Russia, two in Italy, two in Portugal, and one each in Australia, Mexico, Argentina, Romania, and Kazakhstan.

The eligibility criteria for the inclusion of patients into the study were male or female sex; age at least 18 years; a previous diagnosis of arterial hypertension (AH) of any stage or severity or referral to one of the study centers for routine diagnostic evaluation of a suspected hypertension; a need to perform an ABPM for diagnostic purposes. Exclusion criteria were all those conditions preventing from obtaining reliable automated BP measurements with the oscillometric technique (e.g. atrial fibrillation, frequent ectopic beats or second or third-degree atrioventricular blocks, and mid-upper arm circumference <22 cm), and pregnancy. Patients with an arm circumference larger than 32 cm were not excluded from the study, rather an appropriately sized cuff was used to obtain accurate BP measurements.

The study was performed following the Guidelines for Good Clinical Practice and the Declaration of Helsinki. The protocol was reviewed and approved by the ethics committees of each participating center. All eligible patients willing to participate were fully informed about the study design, purposes, and procedures, and asked to give written informed consent prior to enrolment into the study.

The project did not involve any type of diagnostic evaluation or pharmacological intervention specifically designed for the study and the Investigator was free to manage the patients included in the Registry according to the requirements of clinical practice and current guidelines. However, as guidelines recommend, once enrolled each patient had to be followed-up with visits occurring at regular intervals: ideally every 6 months, and not less than once a year, for a minimum follow-up of 2 years. In the present report data on HMOD collected on the occasion of the enrolment visit were considered and presented.

Data collection was ensured through a certified web-based telehealth platform (THOLOMEUS; Biotechmed Ltd., Somma Lombardo, Varese, Italy) [12]. At each study visit an ABPM was performed and patient's clinical data, such as family history, anthropometric data (height, weight, and waist circumference), smoking and drinking habits, past and current diseases, therapies, office BP, and laboratory tests, including evaluation of HMOD, were collected and entered on the electronic case report form (e-CRF) located on the study website. ABPM recordings were uploaded on the telehealth platform and handled as detailed in the next section.

Office and ambulatory blood pressure measurement

Conventional (office) BP was measured in duplicate in the seated position at 2–3-min intervals in all patients, before starting the ABPM and subsequently recorded on the e-CRF. Readings were obtained with the same device used for ABPM or with a validated automatic or manual BP measuring device, after 5 min of rest and under standardized conditions, as recommended by current guidelines. ABPM recordings were performed according to current recommendations [13]. For this purpose, the clinically validated and accurate electronic, automated, upper arm BPLab device (BPLab GmbH, Schwalbach am Taunus, Hessen, Germany) was employed [10,11,14].

The ABPM device was programmed to have intervals between measurements of at least 20 min during the day (providing a minimum of three readings per hour) and at least 30 min during the night (providing a minimum of two

readings per hour). The monitoring cuff was placed around the nondominant arm. Patients were free to attend their usual daily activities during ABPM. However, they were required to refrain from strenuous exercise during the monitoring period and to remain motionless during each automated BP measurement. They had to complete a diary in which daily activities such as time of sleeping, time of meals, etc. had to be reported together with the time of occurrence of unusual events or poor night sleep quality. The patient had to come back to the outpatient clinic 24 h after fitting the device and starting the recording to have the monitor removed and the recording uploaded on the web-based telemedicine platform. To this purpose, the ABPM device was plugged to the personal computer through a universal serial bus cable. Then, ABPM data were uploaded and transmitted to the website, where they were analyzed in real-time with the production of an electronic report sent by e-mail to the Investigator and simultaneously published in the user-restricted area of the website. Once the results were obtained from the web-based analysis software, the Investigator checked each recording for compliance with quality criteria (see below for details).

Pulse wave analysis

The oscillometric BPLab device allows simultaneous measurement of oscillometric brachial BP, arterial stiffness, and central hemodynamics in ambulatory conditions. According to the technique used in this study, vascular biomarkers were obtained by recording pulsatile pressure changes at the brachial artery level during a step-by-step upper arm cuff deflation. When data stored in the device memory were uploaded on the web-based telemedicine platform, the software processed the signal using proprietary mathematical algorithms. These were based on a specifically developed hemodynamic model to get the PWV and transfer function that utilizes a modification in a certain frequency range within the acquired pulse signal to derive the central pressure wave, and thus to assess CAP and AIx. CAP was estimated relative to measured brachial SBP and DBP, as common for other type I devices. A detailed description of the methodology may be found elsewhere [2,10,11]. The accuracy of the BPLab device for the assessment of vascular indices has been tested and validated in studies against noninvasive measurements of the same parameters obtained with the Sphygmocor device [10,11].

Assessment of hypertension-mediated organ damage

HMOD was defined by the presence of LV hypertrophy (LVH), an increased IMT, or renal impairment. All the measurements required for quantification of HMOD were performed at local sites, following current guidelines recommendations. Ultrasound examinations for determination of LVH and IMT were performed by one expert sonographer at each center, whereas blood and urine samples for evaluation of renal function were analyzed at the central laboratories of the single study centers.

Cardiac damage was evaluated through a standard echocardiography examination, following the recommendations of the American Society of Echocardiography [15]. A two-dimensional examination was performed in each participant while lying in a left lateral decubitus position. The interventricular septum thickness, posterior wall thickness, and LV internal diameter were measured at the end of diastole and averaged over three consecutive cardiac cycles. LV mass (LVM) was then calculated according to the formula of Devereux and normalized by the BSA to obtain the LVMI [16]. Cardiac damage was determined by the presence of an LVH, defined by an LVMI greater than 115 g/m^2 in males and greater than 95 g/m^2 in females [17].

Carotid ultrasound examinations were performed to determine the presence of carotid plaque or stenosis. The IMT was measured by carotid ultrasonography at the level of the common carotid artery and averaged over two replicate measurements: an IMT more than 0.9 mm was deemed compatible with the presence of vascular damage [17].

Renal function assessment was based on the calculation of estimated glomerular filtration rate (eGFR) according to the Cockcroft–Gault equation and/or on the estimation of 24-h albumin excretion, as recommended by current guidelines [17,18]. An eGFR less than 60 ml/min per 1.73 m^2 and/or a urinary albumin excretion at least 30 mg/24-h were considered for renal damage [17].

Statistical analysis

For the purpose of the present analysis two study populations were identified: first, a full-analysis set, consisting of individuals with a valid estimate of any HMOD and a valid ABPM; and second, one population consisting of patients with all valid estimates of HMOD and valid ABPM. The latter dataset was used for the confirmatory (or sensitivity) analysis.

The analysis of each 24-h ABPM recording was preceded by removal of artifacts according to previously described editing criteria [19]. Recordings were considered valid when at least 70% of the expected number of readings was obtained, and at least 20 valid awake and seven valid asleep readings were available over the 24-h, as recommended by current guidelines [13]. ABPMs matching the aforementioned quality criteria were analyzed to obtain 24-h average of brachial SBP, DBP, and pulse pressure (PP, the difference between SBP and DBP); 24-h average of central SBP, DBP, and PP; 24-h average of PWV; 24-h average of AIx; 24-h brachial and central SBP, DBP, and PP variability quantified by the average real variability (ARV), calculated by averaging the successive absolute differences between adjacent BP values over the 24 h [20]. Averages were computed also for the daytime and night time subperiods (defined according to the actual night sleep and waking hours). As AIx depends on heart rate (HR), in each individual AIx was normalized to an HR of 75 bpm [21].

Basic demographic and clinical variables were collected for each individual, including a history of AH, dyslipidemia, diabetes mellitus, and cardiovascular disease. Overweight or obesity was defined by a waist circumference at least 94 cm in males and at least 80 cm in females for white patients or at least 90 cm in males and at least 80 cm in females for Asian and Hispanic patients. When waist circumference was missing a BMI of at least 25 kg/m^2 was used to evaluate overweight or obesity.

Descriptive statistics were provided for all demographic, clinical, and hemodynamic variables by calculating absolute and relative frequencies (categorical variables) and

average value ± SD or 95% confidence interval (CI) (continuous variables). The analysis was run for subgroups according to the type of HMOD assessment cardiac (LVH absent vs. present); vascular (carotid thickening absent vs. present); renal (reduced renal function or albuminuria absent vs. present). In each subgroup differences in hemodynamic indices were assessed by analysis of variance with no adjustment (crude estimate) and after accounting for the center effect and for those factors resulting significantly different between groups in the univariate test (usually age, sex, AH, dyslipidemia, diabetes, cardiovascular disease, and obesity). To address the potential influence within each HMOD group of other types of HMOD, adjustment for the type of HMOD was also entered in the model. In the case of comparisons affecting AIx and ARV an additional adjustment for the mean BP level was also applied.

The association of each SBP and PP estimate, AIx and PWV, with the presence of HMOD was assessed by means of stepwise logistic regression analyses, by calculating odds ratio (OR) and 95% CI adjusted for confounding factors, as in the analysis of variance test. Due to the collinearity between the different BP indices, these parameters were introduced in each model one at a time. A logistic regression analysis was also performed by introducing in the model at the same time all the peripheral and central BPs, separately for SBP and PP. Data management and analysis were carried out by SPSS for Windows version 25 (IBM Corp., Armonk, NY, USA). A P less than 0.05 was considered as the minimum level of statistical significance.

RESULTS

Demographic and clinical data

A total of 646 patients with at least one type of HMOD assessment and with valid 24-h ABPMs were included in this analysis. The average number of valid ambulatory BP readings was 49.6 (range 21–76) during the daytime and 16.4 (range 7–33) during the night-time. Mean patients' age was 51.6 ± 15.8 years, 54.0% of them were males, 72.8% reported a previous diagnosis of AH (65.3% were treated with antihypertensive medications), 44.9% had dyslipidemia, 10.7% diabetes, 20.1% a cardiovascular disease, and 76.0% were overweight or obese.

Of these 646 patients, 482 (74.6%) had an evaluation of cardiac damage, 368 (57.0%) of vascular damage and 388 (60.0%) of renal damage (264 only eGFR, 66 only urine albumin excretion and 58 both). Cardiac damage was detected in 232 of 482 patients (48.1%), vascular damage in 206 of 368 patients (56.0%) and renal damage in 61 of 388 patients (15.7%). Details on demographic and clinical data of the study population according to subgroups of HMOD are reported in Table 1. These data were homogenous across HMOD subgroups.

Cardiac damage

In the 482 patients in which echocardiograms were available, LVMI averaged to 132.8 ± 26.2 g/m^2 in case of LVH, a value which was significantly higher than that measured in patients without LVH (86.3 ± 16.3 g/m^2, $P = 0.0001$). Adjusted 24-h, daytime and night-time brachial and central SBP and PP values (Fig. 1) and clinic brachial SBP and PP

TABLE 1. Demographic and main clinical characteristics of the various study populations

	Cardiac−, $n = 250$	Cardiac+, $n = 232$	P value	All, $n = 482$	Vascular−, $n = 162$	Vascular+, $n = 206$	P value	All, $n = 368$	Renal−, $n = 327$	Renal+, $n = 61$	P value	All, $n = 388$	P value homogeneity test
Age (years)	48.4 ± 14.6	57.3 ± 13.8	0.0001	52.7 ± 14.9	45.7 ± 16.8	58.5 ± 12.3	0.0001	52.8 ± 15.7	53.2 ± 14.2	59.3 ± 15.8	0.003	54.2 ± 14.6	0.316
Male sex	157 (62.8)	105 (45.3)	0.0001	262 (54.4)	76 (46.9)	120 (58.3)	0.030	196 (53.3)	186 (56.9)	32 (52.5)	0.523	218 (56.2)	0.715
Female sex	93 (37.2)	127 (54.7)		220 (45.6)	86 (53.1)	86 (41.7)		172 (46.7)	141 (43.1)	29 (47.5)		170 (43.8)	
BMI (kg/m^2)	27.5 ± 4.6	29.0 ± 4.9	0.001	28.2 ± 4.8	27.2 ± 4.7	28.7 ± 4.6	0.003	28.1 ± 4.7	28.9 ± 4.8	28.3 ± 4.9	0.407	28.8 ± 4.8	0.080
Overweight or obesity	182 (72.8)	198 (85.3)	0.001	380 (78.8)	113 (69.8)	175 (85.0)	0.0001	288 (78.3)	271 (82.9)	46 (75.4)	0.166	317 (81.7)	0.443
Known hypertension	179 (71.6)	202 (87.1)	0.0001	381 (79.0)	116 (71.6)	190 (92.2)	0.0001	306 (83.2)	277 (84.7)	53 (86.9)	0.662	330 (85.1)	0.059
Treated hypertension	155 (62.0)	189 (81.5)	0.0001	344 (71.4)	98 (60.5)	173 (84.0)	0.0001	271 (73.6)	254 (77.7)	47 (77.0)	0.914	301 (77.6)	0.114
Known dyslipidemia	100 (40.0)	145 (62.5)	0.0001	245 (50.8)	76 (46.9)	121 (58.7)	0.0001	197 (53.5)	182 (55.7)	38 (62.3)	0.337	220 (56.7)	0.225
Treated dyslipidemia	43 (17.2)	90 (38.8)	0.0001	133 (27.6)	32 (19.8)	65 (31.6)	0.0001	97 (26.4)	108 (33.0)	22 (36.1)	0.644	130 (33.5)	0.063
Known diabetes	23 (9.2)	32 (13.8)	0.113	55 (11.4)	10 (6.2)	32 (15.5)	0.005	42 (11.4)	30 (9.2)	12 (19.7)	0.015	42 (10.8)	0.955
Treated diabetes	18 (7.2)	28 (12.1)	0.069	46 (9.5)	9 (5.6)	27 (13.1)	0.015	36 (9.8)	25 (7.6)	9 (14.8)	0.071	34 (8.8)	0.878
CV diseases	29 (11.6)	76 (32.8)	0.0001	105 (21.8)	24 (14.8)	50 (24.3)	0.025	74 (20.1)	69 (21.1)	29 (47.5)	0.0001	98 (25.3)	0.219
CV risk factors	186 (74.4)	212 (91.4)	0.0001	398 (82.6)	122 (75.3)	196 (95.1)	0.0001	318 (86.4)	286 (87.5)	55 (90.2)	0.553	341 (87.9)	0.070
Clinic SBP (mmHg)	136.5 ± 18.4	139.6 ± 22.0	0.091	138.0 ± 20.2	136.7 ± 21.8	138.8 ± 18.8	0.314	137.9 ± 20.2	138.3 ± 18.4	138.8 ± 20.7	0.840	138.4 ± 18.8	0.942
Clinic DBP (mmHg)	91.6 ± 15.4	87.9 ± 15.0	0.007	89.8 ± 15.3	88.7 ± 15.8	89.8 ± 15.6	0.490	89.3 ± 15.7	89.2 ± 14.4	87.7 ± 17.7	0.450	89.0 ± 14.9	0.733
Clinic PP (mmHg)	44.9 ± 13.5	51.7 ± 17.2	0.0001	48.2 ± 15.8	48.0 ± 16.2	49.0 ± 15.4	0.546	48.6 ± 15.7	49.0 ± 15.6	51.1 ± 19.6	0.356	49.4 ± 16.3	0.535

Groups are identified according to the absence (−) or presence (+) of hypertension-mediated organ damage. Data are shown as absolute (n) or relative (%) frequencies for categorical variables and as means ± SD for continuous variables. The P values refer to the level of statistical significance of the comparison between each subgroup and to the homogeneity test across all groups. CV, cardiovascular; PP, pulse pressure.

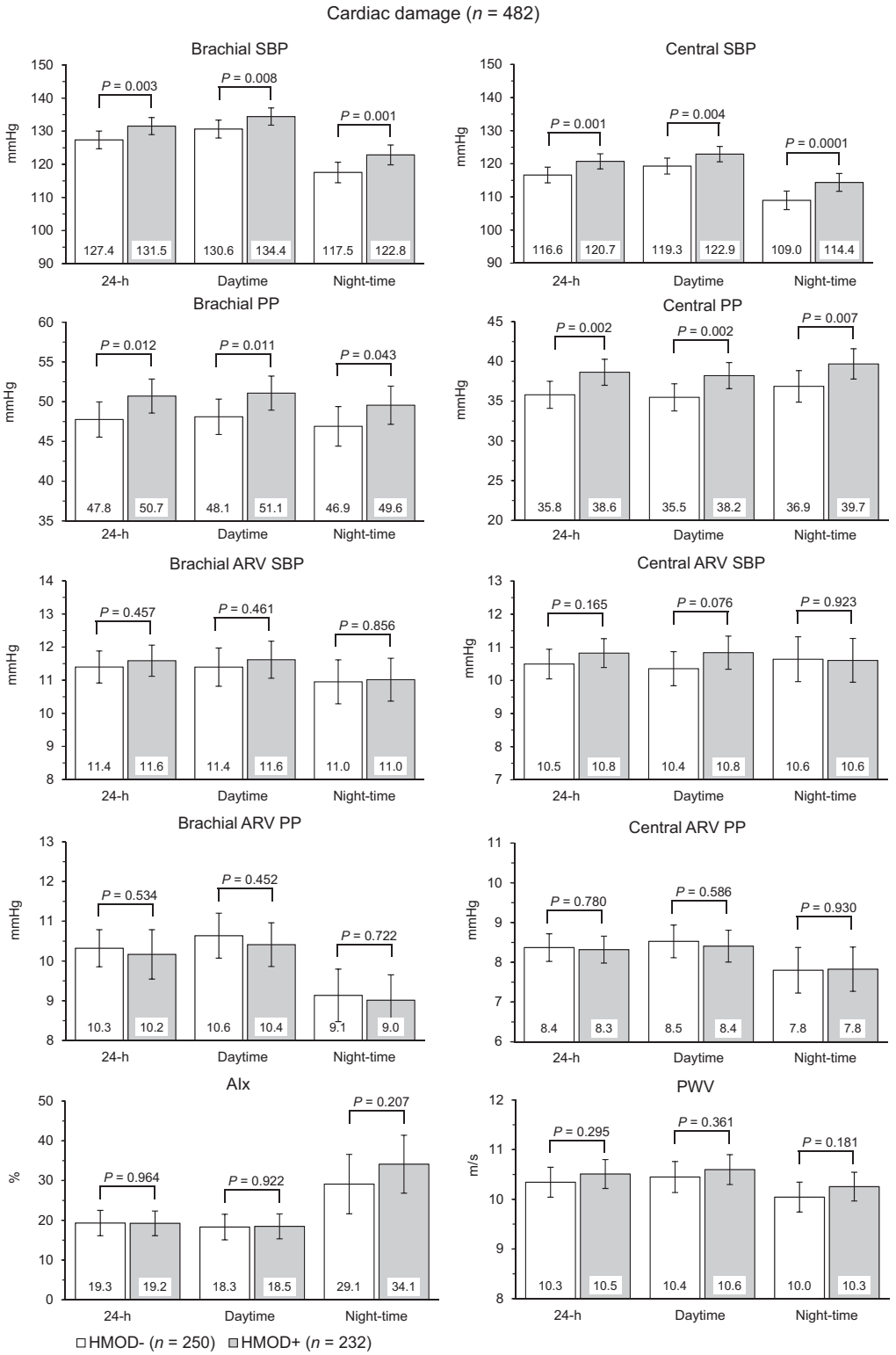

FIGURE 1 24-h, daytime, and night-time averages of brachial and central SBP and pulse pressure, average real variability of brachial and central SBP and pulse pressure, augmentation index and pulse wave velocity in patients without (hypertension-mediated organ damage−, open bars; $n = 250$) and in those with (hypertension-mediated organ damage+, closed bars; $n = 232$) left ventricular hypertrophy. Data are shown as averages adjusted for center, vascular damage, renal damage, age, sex, hypertension, dyslipidemia, cardiovascular disease, and overweight or obesity (and blood pressure for average real variability and augmentation index) and 95% confidence intervals. The *P* values refer to the level of statistical significance of the comparison between each subgroup. HMOD, hypertension-mediated organ damage.

TABLE 2. Clinic blood pressure, 24-h, daytime, and night-time DBP average values and average real variabilities according to the absence (−) or presence (+) of hypertension-mediated organ damage

	Cardiac−, $n=250$	Cardiac+, $n=232$	*P* value	Vascular−, $n=162$	Vascular+, $n=206$	*P* value	Renal−, $n=327$	Renal+, $n=61$	*P* value
Brachial BP (mmHg)									
Clinic SBP	135.9 (132.4, 139.5)	142.4 (138.9, 145.9)	0.002	133.9 (127.8, 140.1)	136.7 (130.8, 142.7)	0.292	141.1 (137.3, 144.9)	139.9 (134.5, 145.3)	0.671
Clinic DBP	90.0 (87.2, 92.7)	89.5 (86.9, 92.2)	0.794	86.7 (81.8, 91.5)	88.7 (84.0, 93.5)	0.329	89.8 (86.9, 92.7)	90.0 (85.9, 94.1)	0.926
Clinic PP	46.0 (43.2, 48.8)	52.8 (50.1, 55.6)	0.0001	47.3 (42.4, 52.1)	48.0 (43.3, 52.7)	0.723	51.3 (48.0, 54.6)	49.9 (45.2, 54.5)	0.564
24-h DBP	79.6 (77.9, 81.3)	80.9 (79.2, 82.5)	0.205	77.8 (75.0, 80.7)	77.9 (75.1, 80.6)	0.973	80.0 (78.2, 81.9)	79.4 (76.8, 82.0)	0.639
Daytime DBP	82.7 (80.9, 84.4)	83.5 (81.8, 85.2)	0.442	80.6 (77.6, 83.6)	80.7 (77.8, 83.6)	0.918	83.1 (81.1, 85.0)	82.3 (79.6, 85.0)	0.596
Night-time DBP	70.6 (68.7, 72.4)	73.2 (71.4, 75.0)	0.013	69.9 (66.9, 72.8)	69.9 (67.0, 72.8)	0.980	71.8 (69.9, 73.7)	72.0 (69.3, 74.6)	0.908
Central DBP (mmHg)									
24-h	80.9 (79.2, 82.6)	82.1 (80.5, 83.8)	0.201	78.9 (76.0, 81.8)	79.2 (76.4, 81.9)	0.857	81.3 (79.4, 83.2)	80.6 (78.0, 83.3)	0.646
Daytime	83.9 (82.1, 85.7)	84.7 (83.0, 86.5)	0.409	81.7 (78.7, 84.8)	82.0 (79.0, 85.0)	0.821	84.3 (82.3, 86.3)	83.5 (80.7, 86.3)	0.611
Night-time	72.0 (70.2, 73.9)	74.6 (72.8, 76.4)	0.015	71.2 (68.2, 74.2)	71.2 (68.3, 74.1)	0.984	73.1 (71.2, 75.0)	73.3 (70.6, 76.0)	0.920
Brachial ARV DBP (mmHg)									
24-h	8.8 (8.3, 9.3)	9.0 (8.5, 9.5)	0.442	8.5 (7.7, 9.3)	8.3 (7.5, 9.1)	0.593	8.5 (7.9, 9.0)	8.5 (7.8, 9.3)	0.851
Daytime	8.9 (8.3, 9.5)	9.2 (8.6, 9.8)	0.344	8.7 (7.7, 9.7)	8.4 (7.4, 9.3)	0.463	8.6 (7.9, 9.2)	8.9 (8.0, 9.8)	0.522
Night-time	8.2 (7.7, 8.8)	8.2 (7.7, 8.7)	0.887	7.6 (6.7, 8.5)	8.1 (7.2, 9.0)	0.190	7.7 (7.1, 8.3)	7.5 (6.7, 8.3)	0.716
Central ARV DBP (mmHg)									
24-h	8.5 (8.0, 9.0)	8.8 (8.3, 9.3)	0.266	8.4 (7.6, 9.1)	8.0 (7.3, 8.8)	0.321	8.3 (7.8, 8.8)	8.3 (7.6, 9.0)	0.845
Daytime	8.5 (7.9, 9.0)	9.0 (8.4, 9.5)	0.131	8.5 (7.6, 9.4)	7.9 (7.0, 8.8)	0.127	8.3 (7.7, 8.9)	8.6 (7.8, 9.5)	0.517
Night-time	8.3 (7.7, 8.8)	8.3 (7.8, 8.8)	0.931	7.6 (6.7, 8.5)	8.2 (7.3, 9.1)	0.120	7.7 (7.1, 8.3)	7.7 (6.8, 8.5)	0.921

Data are shown as mean values and 95% confidence interval. Cardiac organ damage is adjusted for center, vascular damage, renal damage, age, sex, history of hypertension, history of dyslipidemia, history of cardiovascular disease, and overweight or obesity (and average DBP for ARV). Vascular organ damage is adjusted for center, cardiac damage, renal damage, age, sex, history of hypertension, history of dyslipidemia, history of diabetes, history of cardiovascular disease and overweight or obesity (and average DBP for ARV). Renal damage is adjusted for center, cardiac damage, vascular damage, age and history of diabetes and cardiovascular disease (and average DBP for ARV). The *P* values refer to the level of statistical significance of the comparison between each subgroup. ARV, average real variability; BP, blood pressure; PP, pulse pressure.

values (Table 2) were significantly higher in patients with than in those without LVH, whereas no statistically significant between-groups difference was observed for DBP. Brachial and central SBP variability, central PP variability, AIx, and PWV were significantly higher in presence of LVH, before, but not after adjustment (Table 3 and Fig. 1).

Vascular damage

In the subset of 206 patients in which carotid ultrasonography was successfully performed, IMT averaged to 1.6 ± 0.8 mm in the presence vs. 0.7 ± 0.2 mm in the absence of wall thickening or plaque ($P = 0.0001$ between groups). Most of the patients with vascular damage (128, 62.1%) had a simple wall thickening, whereas a carotid plaque was detected in 78 patients (37.9%). Unadjusted 24-h, daytime and night-time average values of brachial and central SBP and PP were significantly larger in case of increased IMT (Table 3), but the difference was no more statistically significant after correction for confounding factors (Fig. 2). No statistically significant between-groups differences were observed for clinic BP, ambulatory DBP mean values and all BP variabilities (Tables 2 and 3 and Fig. 2). PWV was significantly higher in the presence of carotid vascular damage, but the statistical significance of the difference was lost after adjustment (Table 3 and Fig. 2). No between-groups difference was observed for AIx (Table 3 and Fig. 2).

Renal damage

In 322 patients serum creatinine could be assessed and eGFR calculated, whereas 124 patients had urine collected for determination of 24-h urine albumin excretion. In the 61 patients with impaired kidney function, eGFR averaged to 68.6 ± 41.3 ml/min per 1.73 m^2 and albuminuria to 142.1 ± 217.1 mg/24-h: these values were significantly ($P = 0.0001$) different from those reported in case of normal kidney function (106.1 ± 31.9 ml/min per 1.73 m^2 and 9.0 ± 3.8 mg/24-h, for eGFR and albuminuria, respectively). The majority of patients with renal damage had a moderately impaired kidney function (eGFR between 60 and 30 ml/min per 1.73 m^2, 68.3%); only 7.3% had a severe form (eGFR < 30 ml/min per 1.73 m^2). In the adjusted model, an impaired kidney function was not associated with a significantly increased brachial or central SBP and PP (Fig. 3); however, in the unadjusted model, a significantly larger brachial and central PP was observed in case of renal damage (Table 3). Clinic BPs, ambulatory DBP averages, and all BP variabilities were unaffected by renal disease (Table 2 and Fig. 3). Both PWV and AIx were significantly increased in patients with renal damage, but the statistical significance of the difference was lost after adjustment for confounding factors (Table 3 and Fig. 3).

Association of vascular biomarkers with hypertension-mediated organ damage

Figure 4 presents the adjusted ORs for each mmHg increase of office and ambulatory BP for the three different types of HMOD. All brachial and central estimates were significantly associated with cardiac damage, with the largest OR in case of ambulatory central BP and the weakest in case of brachial clinic BP. The association between HMOD and BP was less strong in case of vascular damage: the largest OR was observed for PP, with a trend to the superiority of central over brachial PP. Neither meaningful nor statistically significant association was observed between renal damage and BP estimates. As shown in Table S1, http://links.lww.com/HJH/B175 no statistically significant association between estimates of BP variability, AIx or PWV, and HMOD was observed.

TABLE 3. 24-h, daytime, and night-time averages of brachial and central SBP, DBP, and pulse pressure, average real variability of brachial and central SBP, DBP, and pulse pressure, augmentation index and pulse wave velocity in patients without (−) and in those with (+) a hypertension-mediated organ damage

	Cardiac−, $n=250$	Cardiac+, $n=232$	*P* value	Vascular−, $n=162$	Vascular+, $n=206$	*P* value	Renal−, $n=327$	Renal+, $n=61$	*P* value
Brachial SBP/DBP (mmHg)									
24-h	127.1 ± 13.3/80.9 ± 9.4	128.4 ± 14.2/78.9 ± 10.0	0.308/0.025	124.9 ± 14.0/79.8 ± 10.5	128.6 ± 12.5/80.1 ± 9.5	0.007/0.776	127.2 ± 12.4/80.0 ± 9.4	128.2 ± 14.5/77.5 ± 11.3	0.577/0.063
Daytime	130.7 ± 13.4/83.9 ± 9.6	131.4 ± 14.4/81.5 ± 10.3	0.580/0.009	128.0 ± 14.9/82.4 ± 11.2	131.7 ± 12.8/83.0 ± 10.2	0.009/0.597	131.0 ± 13.0/83.3 ± 10.0	131.0 ± 14.8/80.6 ± 12.3	0.983/0.057
Night-time	116.1 ± 15.3/71.4 ± 10.0	119.4 ± 16.1/70.9 ± 10.6	0.018/0.581	115.7 ± 13.9/71.8 ± 9.9	119.0 ± 15.3/71.4 ± 9.8	0.030/0.716	116.3 ± 13.5/70.7 ± 9.3	120.9 ± 16.9/70.3 ± 11.2	0.021/0.750
Central SBP/DBP (mmHg)									
24-h	115.8 ± 11.6/82.2 ± 9.5	118.2 ± 12.7/80.2 ± 10.1	0.029/0.023	114.3 ± 13.1/81.0 ± 10.6	118.3 ± 11.1/81.5 ± 9.7	0.002/0.701	116.8 ± 11.2/81.4 ± 9.5	117.8 ± 12.4/78.7 ± 11.4	0.525/0.050
Daytime	118.6 ± 11.7/85.2 ± 9.8	120.4 ± 12.8/82.8 ± 10.5	0.107/0.010	116.6 ± 13.9/83.7 ± 11.4	120.9 ± 11.2/84.4 ± 10.3	0.001/0.513	119.9 ± 11.7/84.7 ± 10.2	120.1 ± 12.7/81.8 ± 12.4	0.890/0.049
Night-time	107.0 ± 13.7/73.0 ± 10.1	111.5 ± 15.0/72.4 ± 10.7	0.001/0.525	107.3 ± 13.1/73.2 ± 9.9	110.7 ± 14.4/72.7 ± 10.0	0.018/0.632	108.0 ± 12.7/72.1 ± 9.4	112.1 ± 15.3/71.5 ± 11.4	0.026/0.659
Brachial/Central PP (mmHg)									
24-h	46.2 ± 10.8/33.6 ± 8.0	49.5 ± 11.2/38.0 ± 9.7	0.0001/0.0001	45.1 ± 9.6/33.3 ± 7.6	48.5 ± 11.0/36.9 ± 9.6	0.002/0.0001	47.1 ± 9.9/35.4 ± 8.4	50.6 ± 14.0/39.1 ± 12.2	0.019/0.004
Daytime	46.7 ± 10.8/33.4 ± 7.8	49.8 ± 11.3/37.6 ± 9.7	0.002/0.0001	45.5 ± 9.8/33.0 ± 7.7	48.8 ± 11.0/36.5 ± 9.4	0.004/0.0001	47.7 ± 10.1/35.2 ± 8.5	50.6 ± 14.4/38.3 ± 12.6	0.056/0.016
Night-time	44.7 ± 12.1/34.1 ± 9.4	48.5 ± 12.7/39.2 ± 11.3	0.0001/0.0001	43.9 ± 10.2/34.0 ± 8.5	47.7 ± 12.8/38.0 ± 11.4	0.002/0.0001	45.6 ± 10.8/35.9 ± 9.5	50.6 ± 15.0/40.6 ± 13.3	0.002/0.001
Brachial ARV SBP/DBP (mmHg)									
24-h	11.3 ± 2.5/8.9 ± 2.8	12.2 ± 2.8/9.1 ± 2.7	0.001/0.347	11.4 ± 2.7/9.0 ± 2.6	11.6 ± 2.4/8.6 ± 2.5	0.355/0.123	11.5 ± 2.6/8.7 ± 2.6	11.7 ± 2.3/8.4 ± 2.3	0.430/0.472
Daytime	11.3 ± 2.9/9.0 ± 3.3	12.2 ± 3.3/9.3 ± 3.3	0.002/0.339	11.2 ± 3.0/9.2 ± 3.2	11.6 ± 2.8/8.6 ± 3.1	0.230/0.073	11.5 ± 3.0/8.9 ± 3.2	11.7 ± 2.9/8.7 ± 3.0	0.536/0.606
Night-time	10.8 ± 3.3/8.1 ± 3.1	11.7 ± 3.6/8.2 ± 2.9	0.004/0.727	11.2 ± 3.4/8.1 ± 2.6	11.4 ± 3.5/8.3 ± 3.2	0.630/0.347	11.1 ± 3.3/7.9 ± 2.9	11.5 ± 3.7/7.9 ± 3.5	0.419/0.884
Central ARV SBP/DBP (mmHg)									
24-h	10.4 ± 2.3/8.6 ± 2.7	11.3 ± 2.4/8.9 ± 2.5	0.0001/0.206	10.5 ± 2.5/8.7 ± 2.6	10.9 ± 2.0/8.3 ± 2.3	0.088/0.126	10.6 ± 2.3/8.5 ± 2.5	10.9 ± 2.1/8.3 ± 2.3	0.437/0.661
Daytime	10.2 ± 2.6/8.6 ± 2.9	11.2 ± 2.7/9.0 ± 3.0	0.0001/0.107	10.2 ± 2.7/8.8 ± 2.9	10.7 ± 2.4/8.2 ± 2.8	0.068/0.051	10.5 ± 2.6/8.5 ± 3.0	10.9 ± 2.6/8.5 ± 2.8	0.291/0.853
Night-time	10.6 ± 3.5/8.2 ± 3.1	11.3 ± 3.4/8.3 ± 2.9	0.037/0.728	10.8 ± 3.2/8.1 ± 2.5	11.1 ± 3.4/8.4 ± 3.3	0.357/0.326	10.8 ± 3.3/8.0 ± 2.9	10.9 ± 3.6/8.1 ± 3.4	0.885/0.797
Brachial/Central ARV PP (mmHg)									
24-h	10.7 ± 2.9/8.6 ± 2.2	11.0 ± 2.9/9.2 ± 2.3	0.189/0.003	10.6 ± 2.8/8.6 ± 2.2	10.6 ± 2.7/8.9 ± 2.3	0.794/0.142	10.6 ± 2.7/8.8 ± 2.3	11.0 ± 3.4/9.3 ± 2.6	0.238/0.122
Daytime	11.0 ± 3.5/8.7 ± 2.6	11.4 ± 3.4/9.3 ± 2.6	0.313/0.010	10.7 ± 3.3/8.6 ± 2.5	10.9 ± 3.2/9.0 ± 2.6	0.677/0.127	10.9 ± 3.3/8.9 ± 2.6	11.2 ± 3.9/9.3 ± 3.0	0.504/0.240
Night-time	9.2 ± 3.8/7.9 ± 3.2	9.5 ± 3.4/8.5 ± 3.0	0.308/0.043	9.6 ± 3.7/8.3 ± 3.0	9.5 ± 3.8/8.4 ± 3.4	0.836/0.744	9.3 ± 3.3/8.2 ± 2.9	10.1 ± 4.0/8.8 ± 3.4	0.130/0.167
PWV (m/s)									
24-h	9.6 ± 2.6	11.1 ± 2.6	0.0001	9.8 ± 2.6	11.4 ± 1.8	0.0001	10.7 ± 2.5	11.7 ± 2.6	0.005
Daytime	9.7 ± 2.6	11.2 ± 2.7	0.0001	9.9 ± 2.7	11.5 ± 1.8	0.0001	10.8 ± 2.5	11.7 ± 2.6	0.007
Night-time	9.3 ± 2.6	10.8 ± 2.7	0.0001	9.4 ± 2.6	11.2 ± 1.8	0.0001	10.3 ± 2.5	11.5 ± 2.6	0.002
AIx (%)									
24-h	15.3 ± 18.3	20.7 ± 20.7	0.003	17.8 ± 18.0	17.8 ± 19.4	0.991	16.7 ± 17.3	25.9 ± 26.9	0.001
Daytime	14.8 ± 19.2	20.3 ± 20.1	0.002	17.4 ± 18.4	17.4 ± 20.0	0.980	16.5 ± 17.9	24.8 ± 25.7	0.002
Night-time	26.1 ± 34.4	41.0 ± 43.4	0.0001	31.3 ± 36.4	35.6 ± 43.6	0.293	32.8 ± 43.7	38.8 ± 40.0	0.315

Data are shown as unadjusted average values ± SDs. The *P* values refer to the level of statistical significance of the comparison between each subgroup. AIx, augmentation index; ARV, average real variability; PWV, pulse wave velocity.

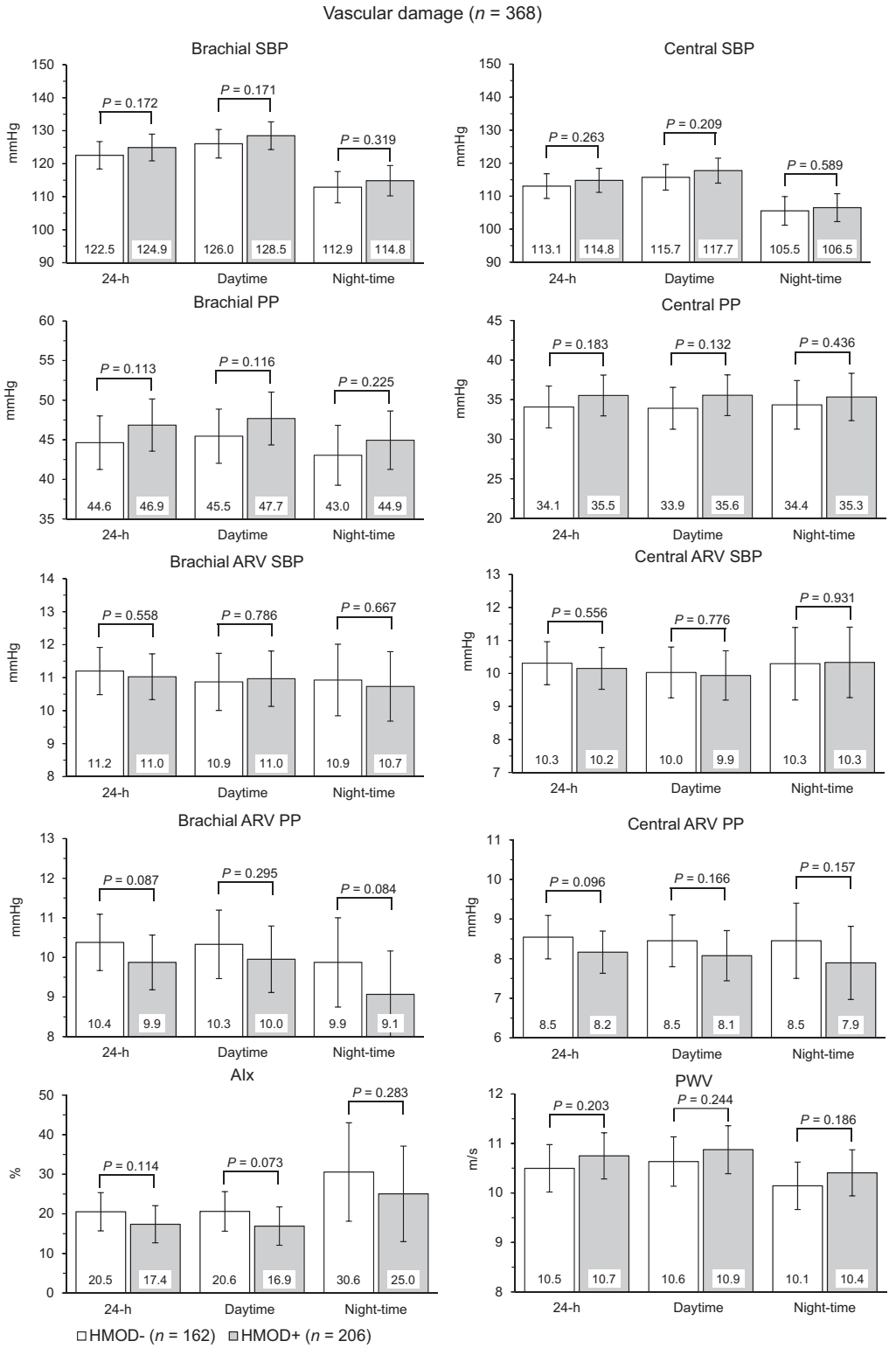

FIGURE 2 24-h, daytime, and night-time averages of brachial and central SBP and pulse pressure, average real variability of brachial and central SBP and pulse pressure, augmentation index and pulse wave velocity in patients without (hypertension-mediated organ damage−, open bars; $n = 162$) and in those with (hypertension-mediated organ damage+, closed bars; $n = 206$) increased carotid intima media thickness. Data are shown as averages adjusted for center, cardiac damage, renal damage, age, sex, hypertension, dyslipidemia, diabetes, cardiovascular disease, and overweight or obesity (and blood pressure for average real variability and augmentation index) and 95% confidence intervals. The *P* values refer to the level of statistical significance of the comparison between each subgroup. HMOD, hypertension-mediated organ damage.

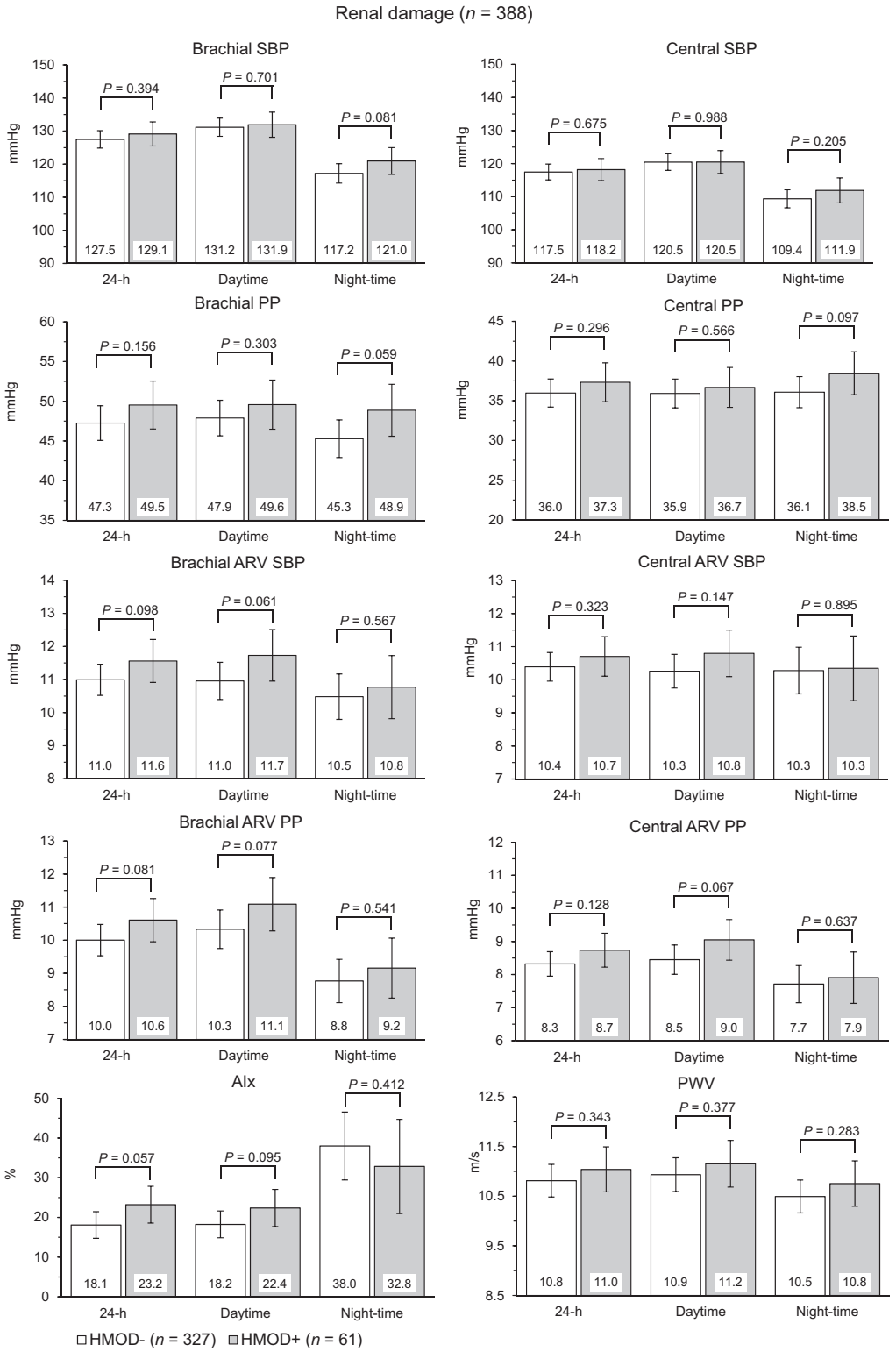

FIGURE 3 24-h, daytime, and night-time averages of brachial and central SBP and pulse pressure, average real variability of brachial and central SBP and pulse pressure, augmentation index and pulse wave velocity in patients with a normal (hypertension-mediated organ damage−, open bars; $n = 327$) and in those with an impaired (hypertension-mediated organ damage+, closed bars; $n = 61$) renal function. Data are shown as averages adjusted for center, cardiac damage, vascular damage, age, diabetes, and cardiovascular disease (and blood pressure for average real variability and augmentation index) and 95% confidence intervals. The *P* values refer to the level of statistical significance of the comparison between each subgroup. HMOD, hypertension-mediated organ damage.

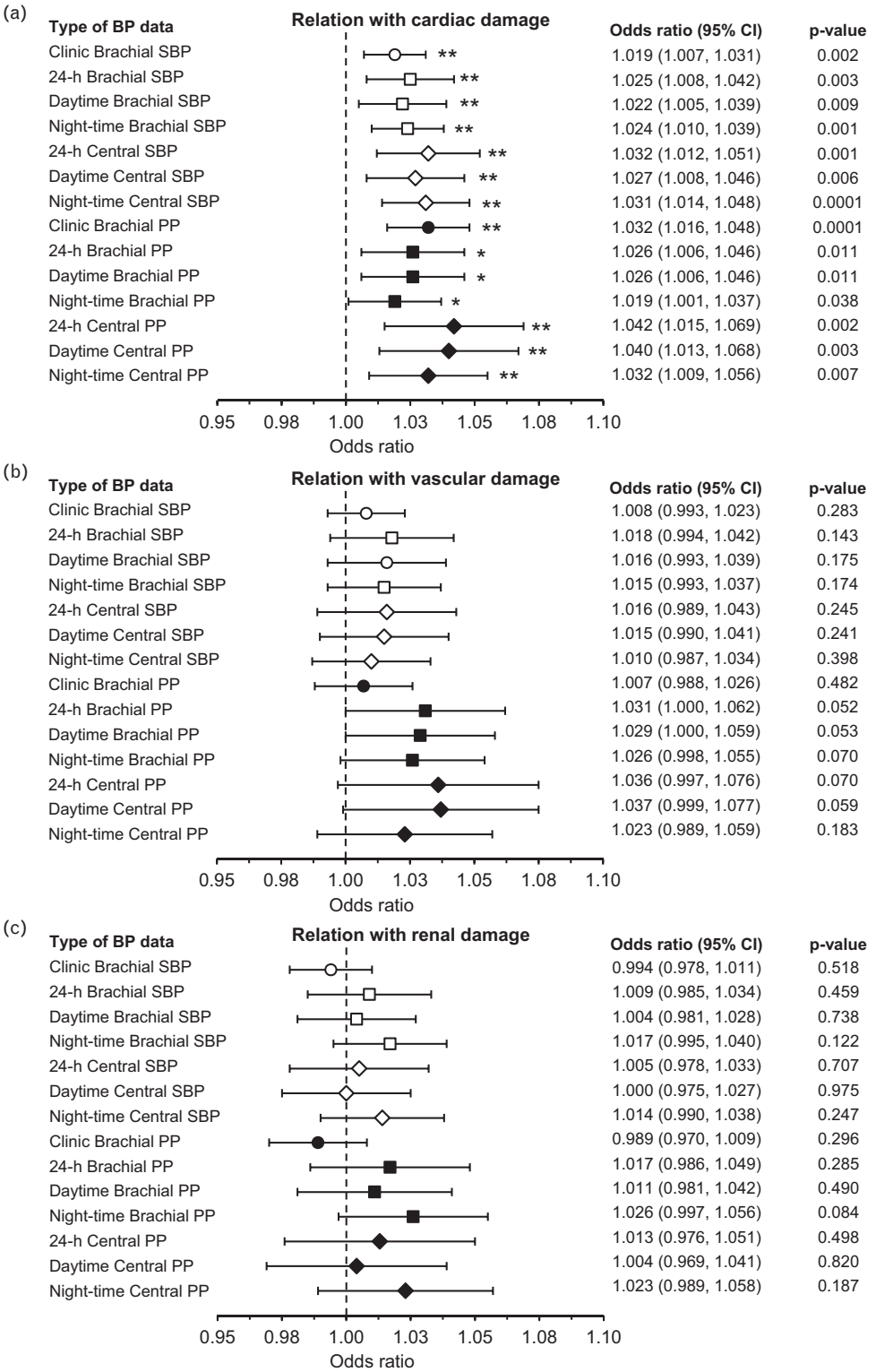

FIGURE 4 Odds ratio and 95% confidence interval and corresponding *P* values for each mmHg increase of the association of clinic brachial SBP and pulse pressure, 24-h, daytime and night-time average brachial and central SBP and pulse pressure, with different types of hypertension-mediated organ damage. The asterisks refer to the level of the statistical significance of the association ($^{*}P < 0.05$ and $^{**}P < 0.01$).

In the multivariate analysis model, age always resulted as a major determinant of any type of HMOD (Table 4). An elevated central SBP or PP was associated with an increased risk of LVH, whereas no association was observed between central hemodynamics and vascular or renal damage.

Sensitivity analysis

A total of 201 of the 646 patients included in the full-analysis set for the different types of HMOD, had simultaneous estimates of all HMOD markers. These patients were included in the sensitivity analysis. In general, as shown in

TABLE 4. Determinants of hypertension-mediated organ damage assessed by logistic regression analysis including the main clinical and demographic variables (age, sex, history of hypertension, dyslipidemia, diabetes or heart disease, obesity) and all the ambulatory SBP and pulse pressure parameters

Model including only SBP			Model including only PP		
Cardiac damage, $n = 482$					
Variables	**Odds ratio (95% confidence interval)**	***P* value**	**Variables**	**Odds ratio (95% confidence interval)**	***P* value**
Age (1-year increase)	1.029 (1.012, 1.047)	0.001	Age (1-year increase)	1.021 (1.001, 1.042)	0.038
Sex (male vs. female)	0.535 (0.339, 0.844)	0.007	24-h Central PP (1-mmHg increase)	1.170 (1.069, 1.280)	0.001
CV disease (yes vs. no)	1.912 (1.068, 3.421)	0.029			
24-h Central SBP (1-mmHg increase)	1.032 (1.015, 1.049)	0.0001			
Vascular damage, $n = 368$					
Variables	**Odds ratio (95% confidence interval)**	***P* value**	**Variables**	**Odds ratio (95% confidence interval)**	***P* value**
Age (1-year increase)	1.079 (1.051, 1.107)	0.0001	Age (1-year increase)	1.077 (1.049, 1.105)	0.0001
Sex (male vs. female)	2.838 (1.531, 5.263)	0.001	Sex (male vs. female)	2.901 (1.558, 5.403)	0.001
Obesity (yes vs. no)	5.113 (2.043, 12.799)	0.0001	Obesity (yes vs. no)	4.711 (1.866, 11.896)	0.001
Renal damage, $n = 388$					
Variables	**Odds ratio (95% confidence interval)**	***P* value**	**Variables**	**Odds ratio (95% confidence interval)**	***P* value**
Age (1-year increase)	1.031 (1.004, 1.058)	0.024	Age (1-year increase)	1.031 (1.004, 1.058)	0.024
CV disease (yes vs. no)	2.732 (1.322, 5.646)	0.007	CV disease (yes vs. no)	2.732 (1.322, 5.646)	0.007

Data are shown as odds ratio and 95% confidence interval with corresponding *P* value. CV, cardiovascular; PP, pulse pressure.

Table S2, http://links.lww.com/HJH/B176, patients in which an HMOD was detected had a worse cardiovascular risk profile, though the between-groups differences were less striking than in the full-analysis set, allegedly because of the smaller size of this group as respect to the full analysis set.

As for the main analysis, 24-h brachial and central SBP and PP averages were significantly larger in patients with than in patients without LVH, whereas no statistically significant difference was observed for these estimates in case of vascular or renal damage (Fig. 5). This figure was replicated also for the daytime and night-time subperiods (Table S3, http://links.lww.com/HJH/B177). No between-groups difference was observed for any HMOD for BP variability, AIx, and PWV (Table S3, http://links.lww.com/HJH/B177). Also in case of the association between HMOD and BP estimates, results of the full-analysis dataset could be replicated: cardiac damage showed strong association with HMOD, particularly in case of central estimates, whereas other vascular biomarkers and other HMOD subtypes did not (Table S4, http://links.lww.com/HJH/B178).

As for the full-analysis set, age was the major determinant of HMOD, whereas a significant association between central SBP or PP and HMOD was observed only for LVH (Table S5, http://links.lww.com/HJH/B179).

DISCUSSION

In our study, we evaluated the association of peripheral and central hemodynamics, arterial stiffness and wave reflections with HMOD in a large sample of hypertensive patients in daily life ambulatory conditions. We were able to document that both peripheral and central SBP and PP are strongly associated with cardiac, but not with carotid or renal damage; ambulatory CAP is more strongly associated with cardiac damage than peripheral BP; ambulatory arterial stiffness and to a less extent wave reflections (estimated by PWV and AIx, respectively) tend to be increased in presence of HMOD, though the strength of the association is lost in adjusted models.

Our results suggest that noninvasive estimation of CAP over the 24-h may improve the individualized LVH risk assessment, beyond the currently available method of 24-h measurement at the brachial artery level. The stronger association of 24-h central than brachial SBP or PP to LVH documented in our study strengthens and confirms the evidence of previous studies performed at rest and based on applanation tonometry at the radial or carotid level [1]. Our results are also in line with those provided by two different studies performed in ambulatory conditions with a different cuff-based technology involving in total 518 patients, of which 101 with LVH [6,7]. Two other studies showed a good association of CAP with LVH, but this was not different from that observed between peripheral SBP and LVH [22,23]. In one of these studies, LVH was assessed through the ECG, using estimates which are not particularly sensitive for LVH detection [22]. It must be acknowledged that in all the aforementioned studies the sample of patients with LVH was limited in size and usually much smaller than that of patients without LVH. Conversely, in our study, we enrolled a larger number of patients with LVH, balanced in a 1 : 1 ratio with those without LVH, and thus our results have greater statistical power than previous studies.

Ambulatory central and peripheral hemodynamics did not have predictive power for either carotid or renal damage, in our patients. In previous studies performed at rest

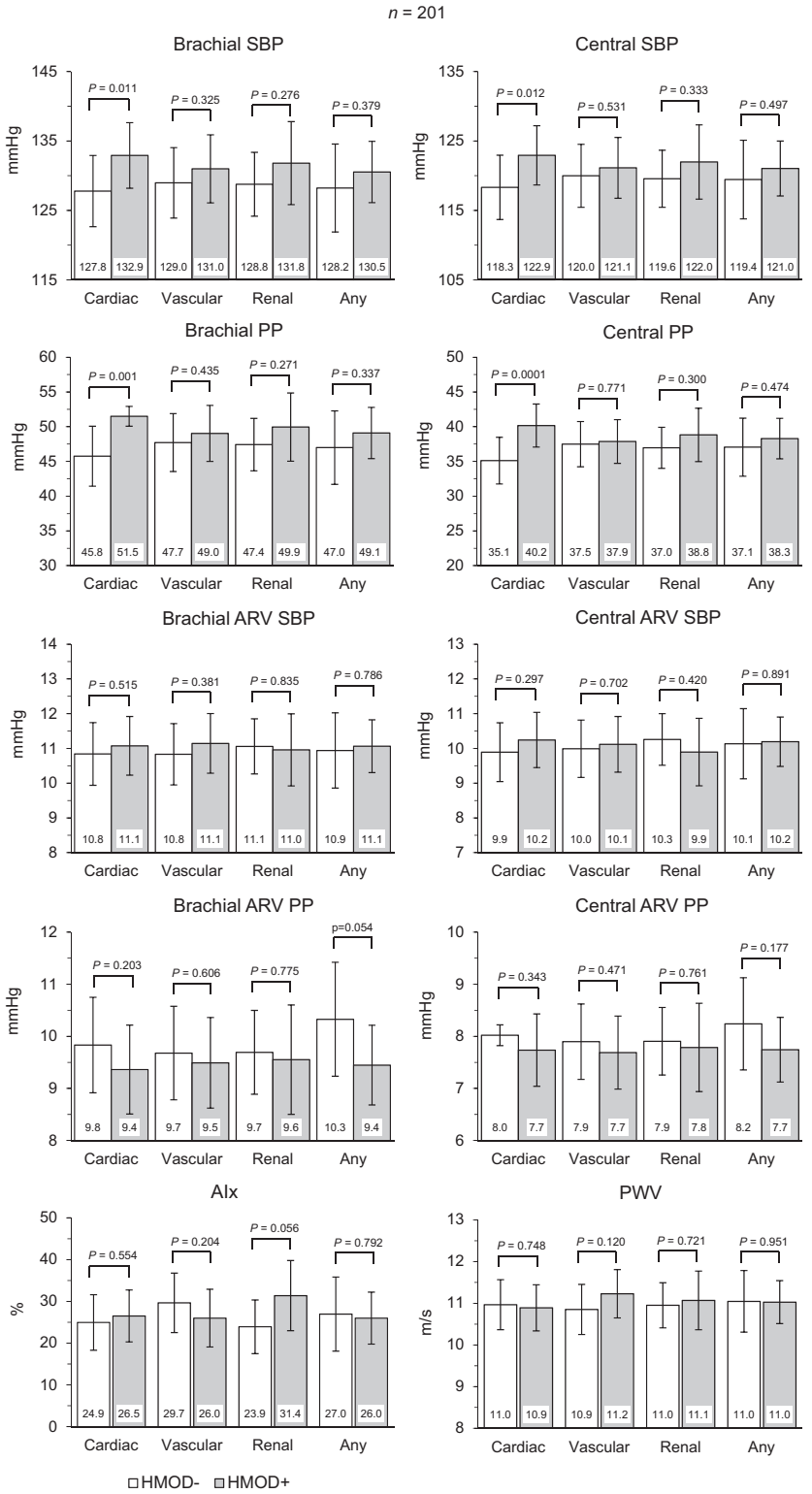

FIGURE 5 24-h averages of brachial and central SBP and pulse pressure, average real variability of brachial and central SBP and pulse pressure, augmentation index, and pulse wave velocity in patients without (hypertension-mediated organ damage−, open bars) and in those with (hypertension-mediated organ damage+, closed bars) hypertension-mediated organ damage (cardiac, vascular, renal, or at least one of the three). Data are shown as averages and 95% confidence intervals, refer to the 201 patients with a valid estimate of cardiac, vascular, and renal damage and are adjusted for confounding factors. The *P* values refer to the level of statistical significance of the comparison between each subgroup.

and using applanation tonometry at the radial or carotid site, central SBP and, to a greater extent, central PP were more strongly associated with an increased IMT than peripheral BPs [1]. In our study, PP was better associated with carotid damage than SBP, but we did not observe any superiority of central over peripheral hemodynamics. Our results are in line with those of the *SAFAR study* in which 24-h brachial and central SBPs were not significantly associated with an increased IMT [24].

In our study, central BP was not better associated with renal impairment than peripheral BP, a finding which is in line with that provided by two previous studies performed in ambulatory conditions [25,26] and by studies performed at rest [1]. This may be justified by the fact that CAP is associated with macrovascular damage, but is not so closely related to microvascular lesion, typical of renal damage [1]. However, at variance from previous studies and meta-analyses [1,25,26], we did not find a positive relation between central or peripheral BP and renal damage, probably because of the relative renal impairment of our patients (the majority of our patients had a mildly or moderately impaired kidney function, and only 7% had a severe form). Indeed, it has been suggested that in the early phases of the kidney disease the relation between BP and renal damage may be weak [27].

Apart from the relation between central and peripheral BP and HMOD, our study provides additional interesting findings about the degree of association of arterial stiffness, wave reflections and BP variability with HMOD. In our patients, ambulatory arterial stiffness, quantified by PWV, was always significantly higher in presence of HMOD as observed in several studies performed at rest [28–32] and in two studies performed in ambulatory conditions [8,25]. AIx (expression of wave reflection) was significantly larger in the presence of cardiac and renal, but not vascular damage, a finding which confirms its predictive value [32]. However, after adjustment for age, sex, and comorbidities, the difference in PWV or AIx between patients with and without HMOD was reduced and did not achieve statistical significance.

An elevated ambulatory BP variability represents a potent independent predictor of hypertension-related cardiovascular complications [33], as well as a marker of HMOD, specifically of carotid artery alteration and LVH, and to a limited extent also of kidney damage [34–38]. An increased ambulatory BP variability is also moderately associated with larger 24-h CAP and stiffness values [39]. In our study 24-h brachial and central SBP variability and central PP variability were higher in patients with than in those without LVH, but the difference was lost after adjustment, and central estimates were not superior to peripheral ones. SBP variabilities did not differ in subgroups according to the carotid or renal damage. Recent studies showed a positive association between ambulatory SBP and HMOD, with contradictory results regarding the superior predictive value of ambulatory central vs. brachial SBP variability [24,40,41]. The discrepancy between our results and those of previous studies may be explained by differences in the sample size of patients included in the various studies and in differences in the quality of the ABPM recording. As far as the first issue is concerned, in our study, we evaluated a larger sample of patients with HMOD than the other two studies. As analyses in a group of patients with a low proportion of HMOD can be easily influenced by the distribution of other variables, our analysis based on larger sample size and adjusted for multiple risk factors appears to be more robust and reliable. Of course, we cannot exclude that our estimation of BP variability may have been inaccurate in some patients due to a possible limited number of measurements available. However, the average and the minimum number of ambulatory BP readings in our patients was sufficiently high (66 and 28, respectively), to exclude that this may have substantially influenced our results. On the contrary, information on quality criteria for selection of valid ABPMs in the other studies are not available and we cannot exclude that the quality of BP variability evaluation in these studies might have been based on poor quality recordings. Thus, given the contrasting evidence coming from a few studies, whether central BP variability carries more prognostic value than brachial BP variability needs to be further addressed and elucidated.

Study limitations

Our results must be interpreted within the context of the potential study limitations. First, the technology used in our study for PWA of brachial oscillograms is based on the brachial SBP and DBP calibration method (type I device). Invasive studies have clearly shown that mean brachial BP and DBP calibration method provides an estimation of central SBP much closer to the invasively determined reference and thus should be preferred [42,43]. As a matter of fact, in two previous studies comparing the association with LVH of the ambulatory central SBP obtained with the two methods, this was larger when the mean BP/DBP calibration method was used [6,7].

Second, the cross-sectional nature of our study allows us to provide only descriptive information on the association between central hemodynamics and HMOD and cannot establish any causality. It will be important in the progression of the data collection to explore the predictive values of central vs. peripheral BP and vascular biomarkers in the development, progression, or regression of HMOD.

Third, most patients (88%) had at least one cardiovascular risk factor among AH, dyslipidemia, diabetes, obesity, or cardiovascular disease and most of them (77%) were taking antihypertensive drug treatment. Though these factors were properly accounted for in the adjusted analysis our data might not be representative of all hypertensive patients.

Fourth, given the observational nature of the study (Registry) standardization of estimation of HMOD across centers was neither possible nor feasible. However, since all centers were expert in hypertension management they followed appropriate international guidelines. Furthermore, to account for potential heterogeneity in the methodology of HMOD assessment and variability across operators we adjusted results by including the center effect. Yet, we acknowledge that the reliability of HMOD estimation in our study may not be ideal.

Fifth, the fact that our results are in some aspects in contrast with previous evidence may not necessarily mean that our results are flawed. Indeed, we included a much larger sample of patients with HMOD than previous studies and thus the power of our results could be greater.

Although the average 24-h brachial and central BP values did not differ between our population and those included in previous studies, the populations show some heterogeneity in terms of the proportion of treated hypertensive patients, as well as for the prevalence of comorbidities. Finally, a sensitivity analysis including only patients with all estimations of HMODs shows results for CAP in line with the full analysis set and with those of a similar study considering altogether the same three types of HMOD of our study [44].

In conclusion, our results documented a variable association of ambulatory peripheral and central BP, arterial stiffness and wave reflections with HMOD. The predictive value was high in case of cardiac damage, whereas it was marginal in case of carotid damage and impaired renal function. These findings corroborate previous evidence collected with a different technology and suggest that 24-h PWA, and in particular 24-h central SBP and PP, may be useful for predicting the risk of HMOD in hypertensive patients, at least when cardiac damage is considered. As our study is currently the largest one evaluating the relation between ambulatory peripheral and central hemodynamics and stiffness and HMOD in hypertensive patients based on a specific technology, the evidence collected will help provide some reference to clinicians making use of the same device employed in this study, for the routine clinical evaluation of their patients. However, we acknowledge that prospective data are warranted to confirm the clinical value of the technology in this context. Such data will be collected in the longitudinal phase of the VASOTENS Registry.

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Conflicts of interest

S.O. is scientific consultant of Biotechmed Ltd, provider of telemedicine services. The other authors declare no conflicts of interest regarding the publication of this article.

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