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Ambulatory blood pressure and arterial stiffness web-based telemonitoring in patients at cardiovascular risk. First results of the VASOTENS (Vascular health ASsessment Of The hypertENSive patients) Registry

Stefano Omboni MD[1,2] | Igor Posokhov MD, PhD, ScD[3] | Gianfranco Parati MD[4,5] | Anatoly Rogoza ScD, PhD[6] | Yulia Kotovskaya MD, PhD, DS[7] | Ayana Arystan MD, PhD[8] | Alberto Avolio BE, PhD[9] | Vitaliy Barkan MD, PhD[10] | Natalia Bulanova MD, PhD[2] | Ernesto Cardona Muñoz MD[11] | Elena Grigoricheva MD, PhD[12] | Alexandra Konradi MD, PhD[13] | Irina Minyukhina MD, PhD[14] | Maria Lorenza Muiesan MD[15] | Giuseppe Mulè MD[16] | Iana Orlova MD, PhD[17] | Telmo Pereira PhD[18] | João Manuel Peixoto Maldonado MD[19] | Mikhail E. Statsenko MD, PhD[20] | Ioan Tilea MD, PhD[21] | Gabriel Waisman MD[22] | on behalf of the VASOTENS Registry Study Group*

[1]Clinical Research Unit, Italian Institute of Telemedicine, Varese, Italy

[2]Scientific Research Department of Cardiology, Science and Technology Park for Biomedicine, Sechenov First Moscow State Medical University, Moscow, Russian Federation

[3]Hemodynamic Laboratory Ltd, Nizhniy Novgorod, Russian Federation

[4]Department of Cardiology, Istituto Auxologico Italiano, Milan, Italy

[5]Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

[6]Department of New Diagnostic Methods, Russian Cardiology Research and Production Complex, Moscow, Russian Federation

[7]Russian Clinical and Research Center of Gerontology, Pirogov Russian National Research Medical, Moscow, Russian Federation

[8]Department of Functional Diagnostics, Medical Center Hospital of President's Affairs Administration of The Republic of Kazakhstan, Astana, Kazakhstan

[9]Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Macquarie University, Sydney, New South Wales, Australia

[10]Diagnostics Department, The Hospital within the Russian Railroad Network, Chita, Russian Federation

[11]Department of Physiology, University of Guadalajara, Guadalajara, Mexico

[12]South Ural State Medical University, Chelyabinsk, Russian Federation

[13]Department of Epidemiology, North-West Federal Medical Research Center, St. Petersburg, Russian Federation

[14]Lomonosov Moscow State University Clinic, Moscow, Russian Federation

[15]Dipartimento di Scienze Mediche e Chirurgiche, Università di Brescia, Medicina 2, Brescia, Italy

[16]Unità Operativa di Nefrologia ed Ipertensione, Centro di Riferimento Regionale per l'Ipertensione Arteriosa, Policlinico Paolo Giaccone, Palermo, Italy

[17]Volga District Medical Center, Nizhniy Novgorod, Russian Federation

[18]Escola Superior de Tecnologia da Saúde de Coimbra, Instituto Politécnico de Coimbra, Coimbra, Portugal

[19]Clínica da Aveleira, Instituto de Investigação e Formação Cardiovascular, Coimbra, Portugal

[20]Volgograd State Medical University, Volgograd, Russian Federation

[21]Cardiac Rehabilitation Clinic, Tirgu Mures Emergency Clinical County Hospital, Tirgu Mures, Romania

[22]Servicio de Clínica Médica y Sección Hipertensión Arterial, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

*See Appendix 1 for the VASOTENS Registry Study Group.

Correspondence
Stefano Omboni, MD, Clinical Research Unit, Italian Institute of Telemedicine, Via Colombera 29, 21048 Solbiate Arno (Varese), Italy.
Email: stefano.omboni@iitelemed.org

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Abstract

The VASOTENS Registry is an international telehealth-based repository of 24-hour ambulatory blood pressure monitorings (ABPM) obtained through an oscillometric upper-arm BP monitor allowing combined estimation of some vascular biomarkers. The present paper reports the results obtained in 1200 participants according to different categories of CV risk. Individual readings were averaged for each recording and 24-hour mean of brachial and aortic systolic (SBP) and diastolic blood pressure (DBP), pulse wave velocity (PWV), and augmentation index (AIx) obtained. Peripheral and central BP, PWV and AIx values were increased in older participants (SBP only) and in case of hypertension (SBP and DBP). BP was lower and PWV and AIx higher in females. PWV was increased and BP unchanged in case of metabolic syndrome. Our results suggest that ambulatory pulse wave analysis in a daily life setting may help evaluate vascular health of individuals at risk for CV disease.

1 | INTRODUCTION

Technology advances have recently made available few cuff-based devices allowing combined non-invasive estimation of relevant vascular biomarkers, such as central arterial pressure (CAP) and arterial stiffness, over the 24 hours by ambulatory blood pressure monitoring (ABPM).[1] Such techniques, making use of the oscillometric method, are affordable and may allow a comfortable, accurate, repeated, and prolonged estimation of arterial stiffness and central hemodynamics in daily life conditions; this may help provide more insight into the vascular health of hypertensive participants or high-risk cardiovascular (CV) patients.[1,2] Some studies seem to indicate accuracy, reliability, and feasibility of ambulatory arterial stiffness and hemodynamics evaluation based on analysis of brachial oscillograms, though, at present, there is limited proof on the actual clinical benefit of such an approach in the daily clinical management of hypertensive patients.[1,3] Unfortunately, the few data collected so far in ambulatory conditions are in most cases based on small sample-sized cross-sectional studies.[1] Only one large prospective study performed in a relatively large sample of hemodialysis patients has recently documented that pulse wave velocity (PWV), augmentation index (AIx), and central pulse pressure measured non-invasively over the 24-hours are associated with increased risk of CV events and mortality.[4]

To provide further insight on the matter, we devised and implemented a few years ago a large Registry of ABPM recordings obtained with an ABP monitor, which is able to determine CAP, PWV and AIx over the 24-hours, based on a clinically validated technology of pulse wave analysis of oscillometric BP measurements.[5-7] As detailed in the publication relative to the study protocol, the VASOTENS (Vascular health ASsessment Of The hypertENSive patients) Registry has several objectives, including the evaluation of clinical usefulness of 24-hour measures of vascular biomarkers, their changes following treatment, and their impact on hypertension-mediated organ damage and CV prognosis.[5] The novelty of the project is that data collection is made through a telehealth solution which ensures standardized and centralized data collection, prompt data validation and analysis, effective study monitoring and auditing, easy and real-time distribution of software updates and bug corrections. Ultimately, the international nature of the study coupled with the telemonitoring tool may help foster the implementation of an advanced screening option for patients with hypertension or at risk for CV disease through a worldwide network of expert centers linked together through telehealth.

In the current paper, we present the results relative to the baseline data collected in the patients enrolled in the study. Clinical data and vascular biomarkers are shown and compared according to different categories at risk of CV disease in order to provide some insight into the potential for this non-invasive technique in the assessment of vascular health.

2 | METHODS

2.1 | Study population

Details on the study protocol of the VASOTENS Registry may be found in a previous specific publication.[5] The Registry is an international, multicenter, observational, non-randomized, prospective study endorsed by the Italian and Russian Societies of Hypertension. The trial is registered with ClinicalTrials.gov at number NCT02577835. A total of 24 hypertension centers worldwide were involved in the study (12 in Russia, 2 in Italy, 2 in Argentina, 2 in Portugal, 1 in Australia, 1 in Mexico, 1 in Romania, 1 in Ukraine, 1 in Kazakhstan, and 1 in Armenia), of which 16 actively recruited male or female adult participants (age ≥ 18 years) referred to the study centers for routine diagnostic evaluation of a suspected

hypertension or with established hypertension of any severity or stage, and requiring an ABPM for evaluating their condition, according to current recommendations.[5] Participants could not be enrolled in case of atrial fibrillation, frequent ectopic beats, second- or third-degree atrioventricular blocks, or other conditions which might have made difficult or unreliable the automatic BP measurement with the oscillometric technique. Pregnant women and participants with an arm circumference < 22 cm were excluded as well.

The study was conducted according to Good Clinical Practice guidelines and the Declaration of Helsinki. The data collection was started in each center only after approval of the study protocol by the local Independent Ethics Committee. All eligible participants willing to participate were fully informed about the study design and purposes and asked to give written informed consent prior to enrollment into the study.

2.2 | Study procedures

The project did not involve any type of diagnostic evaluation or pharmacologic intervention specifically designed for the study purpose and the investigator was free to manage the patients included in the Registry according to the requirements of clinical practice and current guidelines.[8] 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.

Data collection was ensured by a certified web-based telemedicine platform (THOLOMEUS®, Biotechmed Ltd.) available at the following Web site: www.tholomeus.net.[9] At each study visit, an ABPM was performed and patient's clinical data, such as family history, anthropometric data, smoking and drinking habits, past and current diseases, therapies, office BP, and laboratory tests, including evaluation of hypertension-mediated organ damage, were collected, and entered on the electronic Case Report Form (e-CRF) located on the study Web site.

2.3 | Office and ambulatory BP measurement

Two sequential conventional (office) BP and heart rate (HR) readings were taken in the sitting position at the time of ABPM placement (with the same device used for ABPM or with a validated automatic or manual BP measuring device) and recorded on the e-CRF. Twenty-four-hour ABPM was performed with a BPLab device (BPLab GmbH), which has been found to be accurate for the estimation of both BP and vascular indices in properly conducted validation studies.[6,7,10] Current guidelines were followed for proper recording performance.[11] In order to reduce patient's discomfort and to ensure a reliable minimum number of BP measurements for the subsequent data analysis, the device was programmed to measure BP at least every 20 minutes during the day (providing a minimum of 3 readings per hour) and at least 30 minutes during the night (providing a minimum of 2 readings per hour). Whenever possible, recordings were started between 8 AM and 11 AM, in order to standardize data collection and comparisons. The monitoring cuff was placed around the non-dominant arm. Patients were instructed to keep their arm still and to avoid any movement during each automatic BP measurement. They were free to attend their usual daily activities during ABPM (avoiding strenuous exercise). They had to complete a diary in which daily activities such as time of sleeping, time of meals 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 on the second day of the recording (after at least 24 hours) to remove the monitor. Shortly after the device removal, the recording was uploaded on the web-based telemedicine platform by plugging the ABPM device to the personal computer (PC) through a universal serial bus (USB) cable. ABPM data were transmitted to the Web site and 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 Web site. Once the investigator obtained the results from the web-based analysis software, he/she checked each recording for compliance with quality criteria (see below for details). In case of a bad quality recording, the investigator had to repeat the recording, whenever feasible, as soon as possible, preferably in the next two days.

2.4 | Pulse wave analysis

The oscillometric BPLab device also allowed measurements of ambulatory arterial stiffness and central hemodynamics, by recording pulsatile pressure changes at the brachial artery level. Briefly, during BP measurement, the pressure waveforms in the cuff were recorded during a step-by-step deflation, and then digitalized and stored in the device memory. When data 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 aortic 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.[5-7] The accuracy of the BPLab device for the assessment of vascular indices has been validated in studies against non-invasive measurements of the same parameters obtained with the Sphygmocor device.[6,7]

2.5 | Statistical analysis

For the purpose of this study, only patients with valid ABPM recordings performed at study entry were considered. Valid recordings were those with at least 70% of the expected number of readings and at least 20 valid readings during the daytime and 7 during the nighttime, as recommended by current guidelines.[11] Analysis of 24-hour recordings was preceded by removal of artifacts according to previously described editing criteria.[12] Individual readings obtained over the 24-hours were averaged in order to obtain: (a) 24-hour mean of brachial systolic blood pressure (SBP) and diastolic blood pressure (DBP); (b) 24-hour mean of aortic SBP and DBP; (c) 24-hour mean of PWV; (d) 24-hour mean of AIx. Averages were computed also for the daytime

and nighttime subperiods (defined according to the actual night sleep and waking hours) and for each hour of the recording. Since AIx depends on HR, in each individual 24-hour AIx was normalized to an HR of 75 bpm.[13] Day-night changes in BP, PWV, and AIx were calculated and presented as a percentage of daytime mean values.

Basic descriptive statistics were provided for all demographic and clinical variables by calculating absolute and relative frequencies (categorical variables) and average value ± standard deviation (SD) or 95% confidence interval (continuous variables). Analysis was run for the whole population and for subgroups defined according to (a) age (young participants, <65 years vs old participants, ≥65 years); (b) sex (male vs female participants); (c) arterial hypertension (no vs yes); (d) dyslipidemia (no vs yes); (e) diabetes mellitus (no vs yes); (f) any CV disease (no vs yes, including transient ischemic attack, stroke, myocardial infarction, angina, heart failure, peripheral vascular disease, kidney disease); (g) metabolic syndrome (no vs yes).

The classification of patients according to the presence or absence of arterial hypertension, dyslipidemia, diabetes mellitus, and CV disease was based on patient's self-reported knowledge and use of specific medications. The presence of metabolic syndrome was evaluated according to the harmonized definition[14] by the presence of 3 out of 5 of the following risk factors: (a) elevated waist circumference (≥94 cm in males and ≥80 cm in females for Caucasian participants; ≥90 cm in males and ≥80 cm in females for Asian and Hispanic participants); (b) elevated triglycerides (≥150 mg/dL) or specific lipid-lowering treatment; (c) reduced HDL cholesterol (<40 mg/dL for males and <50 mg/dL for females) or specific lipid-lowering treatment; (d) elevated BP (≥130 mm Hg for SBP and/or ≥80 mm Hg for DBP) or antihypertensive treatment; (e) elevated fasting glucose (≥100 mg/dL) or treatment for diabetes. When waist circumference was missing, a BMI ≥ 25 kg/m^2 was used to evaluate obesity as a component of the metabolic syndrome.

The differences in hemodynamic indices within each subgroup were assessed by analysis of variance with no adjustment (crude estimate) and after accounting for age, sex, CV risk factors (including obesity, known arterial hypertension, dyslipidemia, diabetes, CV disease). In the case of comparison affecting AIx, an adjustment for mean BP level was also applied, whereas comparisons including relative day-night changes in PWV and AIx were adjusted also for day-night changes in BP.

Data management and analysis were carried out by SPSS for Windows version 25. A $P < .05$ was considered as the minimum level of statistical significance.

3 | RESULTS

3.1 | Demographic and clinical data

A total of 1342 patients was recruited and submitted to a full 24-hour ABPM. However, recordings were successful in 1200 participants (89.4%): 142 recordings (11%) could not be included because the oscillograms did not allow to obtain proper parameters for a sufficient number of readings.

Mean participants' age was 52.6 ± 15.5 years, with 75.4% of participants younger than 65 years. Male participants were more prevalent than females (55.3% vs 44.7%). High BP, dyslipidemia, diabetes, metabolic syndrome, and CV disease were reported by 47.5%, 27.0%, 6.8%, 35.3%, and 9.9% of participants, respectively.

Details on demographic and clinical data of the whole-study population are reported in Table 1, whereas Table S1 summarizes the same data by each subgroup of the study.

3.2 | Hemodynamic variables in the whole-study population

As expected, 24-hour average brachial SBP and DBP values (128.1 ± 14.3/79.4 ± 9.6 mm Hg) were significantly ($P = .0001$ for both SBP and DBP) lower than office ones (141.3 ± 20.3/90.2 ± 14.2 mm Hg). Twenty-four-hour average brachial SBP was significantly ($P = .0001$) higher and 24-hour brachial DBP significantly ($P = .0001$)

TABLE 1 Demographic and main clinical characteristics of the study population

	All (n = 1200)
Age (y)	52.6 ± 15.5
Young (<65 y)	905 (75.4)
Old (≥65 y)	295 (24.6)
Sex	
Male	664 (55.3)
Female	536 (44.7)
Ethnicity	
Caucasian	1057 (88.1)
Hispanic	81 (6.8)
Asian	59 (4.9)
Black	3 (0.3)
BMI (kg/m^2)	28.1 ± 4.8
Waist circumference (cm)	96.5 ± 14.0
Overweight or obesity	626 (52.2)
Known hypertension (untreated or treated)	570 (47.5)
Treated hypertension	513 (42.8)
Known dyslipidemia (untreated or treated)	326 (27.0)
Treated dyslipidemia	177 (14.8)
Known diabetes (untreated or treated)	81 (6.8)
Treated diabetes	69 (5.8)
Metabolic syndrome	423 (35.3)
CV diseases	119 (9.9)
CV risk factors (hypertension, dyslipidemia, diabetes, or cardiovascular disease)	608 (50.7)
Concomitant diseases	577 (48.1)
Concomitant medications	535 (44.6)

Note: Data are reported as absolute and relative frequency (percentage in brackets) or as mean value and standard deviation.
Abbreviations: BMI, Body Mass Index; CV, Cardiovascular.

lower than 24-hour average aortic BP (117.2 ± 12.8/80.7 ± 9.7 mm Hg) (Figure 1A,B). The proportion of participants showing sustained hypertension (simultaneously elevated office and ambulatory BP) was slightly larger than that with a known history of hypertension (56.7% vs 47.5%). Brachial and aortic BP displayed a typical parallel circadian pattern with values increasing during the waking hours and diminishing during the night sleep; both brachial daytime and nighttime BP values remained significantly ($P = .0001$) higher than the corresponding CAPs (Figure 1A,B). The pulse amplification (the difference between brachial and aortic SBP) was significantly ($P < .0001$) larger during the daytime (11.6 ± 4.2 mm Hg) than during the nighttime (8.8 ± 3.9 mm Hg).

Mean 24-hour values of PWV and AIx were 10.6 ± 2.6 m/s and 18.0 ± 18.6%, respectively. As shown in Figure 1A, PWV values were lower ($P = .0001$) during the night (10.3 ± 2.7 m/s) than during the day (10.7 ± 2.6 m/s), whereas AIx values were higher ($P = .0001$) during the night (32.5 ± 37.7%) and lower during the day (17.5 ± 19.0%) (Figure 1A,B).

3.3 | Results according to age

Twenty-four-hour average values of brachial and aortic SBP and PWV were significantly larger in older individuals, with differences accentuated during the night sleep (Table 2, Table S2, and Figure 2A). Conversely, 24-hour, daytime and nighttime average brachial and aortic DBP values were significantly lower in the case of older individuals (Table 2, Table S2, and Figure 2A). Also, AIx showed larger values in old participants (Figure 2A and Table 2). Finally, nocturnal BP and PWV drops were significantly larger in younger participants, whereas no between-groups difference was observed for the nighttime increase in AIx (Table S2).

3.4 | Results according to sex

Twenty-four-hour average brachial and aortic BP values were significantly higher in male than in female participants (Table 2), with more striking between-sexes differences during the daytime, particularly for central BP (Table S2 and Figure 2B). 24-hour average PWV and AIx values were higher in female than in male participants (Table 2). PWV and AIx values showed a circadian pattern in both sexes (Figure 2B and Table S2). During the night sleep, SBP, but not DBP dropped significantly more in males than females (Table S2). PWV was reduced significantly more in females than in males during the night, whereas the AIx increase did not differ between sexes after adjustment for confounding factors (Table S2).

3.5 | Results according to the history of hypertension, dyslipidemia or diabetes

In participants reporting a previous history of hypertension, 24-hour average brachial and aortic BPs, PWV and AIx were significantly larger than in participants free from the condition (Table 2 and Figure 2C). Between-groups differences were more evident during the nighttime (Table S2 and Figure 2C).

No relevant differences were observed for BP in the subgroups with dyslipidemia or diabetes, except for lower brachial and aortic SBP values in dyslipidemic participants and higher brachial SBP values in diabetics (Table 2 and Figure 2D,E). Although PWV values showed significantly higher values in patients reporting dyslipidemia and diabetes, the difference was lost after adjustment for confounding factors (Table 2 and Figure 2D,E). AIx values did not differ between patients with or without dyslipidemia and between those with or without diabetes (Table 2, Table S2 and Figure 2D,E). No significant difference in BP drops during the night sleep was observed, whereas day-to-night PWV reduction was significantly less pronounced in patients with hypertension, dyslipidemia, or diabetes, before adjustment for confounding factors (Table S2). AIx increased during night sleep, with no statistically significant difference across subgroups (Table S2).

3.6 | Results according to the metabolic syndrome

Average ambulatory values of brachial and aortic SBP and DBP values did not significantly differ in participants with and without the metabolic syndrome, regardless of the period of the 24 hours considered (Table 2, Table S2, and Figure 2F). However, a significant increase in 24-hour, daytime and nighttime PWV was observed in presence of the metabolic syndrome, also after adjustment for confounding factors (Table 2, Table S2, and Figure 2F). No differences were observed in AIx between participants with and without the metabolic syndrome. The nighttime reduction in PWV was significantly blunted in participants with the metabolic syndrome, while no statistically significant difference in the BP reduction and AIx increase during night sleep was observed between participants with vs those without the metabolic syndrome (Table S2).

3.7 | Results according to concomitant CV disease

Twenty-four-hour, daytime and nighttime average brachial and aortic SBP values were similar in participants with and without concomitant CV disease, whereas 24-hour and daytime average brachial and aortic DBP values were significantly lower in participants with a history of CV disease (Table 2, Table S2, and Figure 2G). PWV averages were significantly larger in case of concomitant CV disease, but no more differences were observed after adjustment (Table 2, Table S2, and Figure 2G). AIx did not significantly differ between groups. In participants with a known CV disease, the BP reduction during the night sleep was significantly less pronounced than in CV disease-free participants (Table S2). No statistically significant between-groups differences in PWV and AIX changes during sleep were noted.

4 | DISCUSSION

In our study, we evaluated non-invasively various central and peripheral hemodynamic indices in ambulatory conditions over the 24 hours in specific subgroups at high CV risk. We observed a

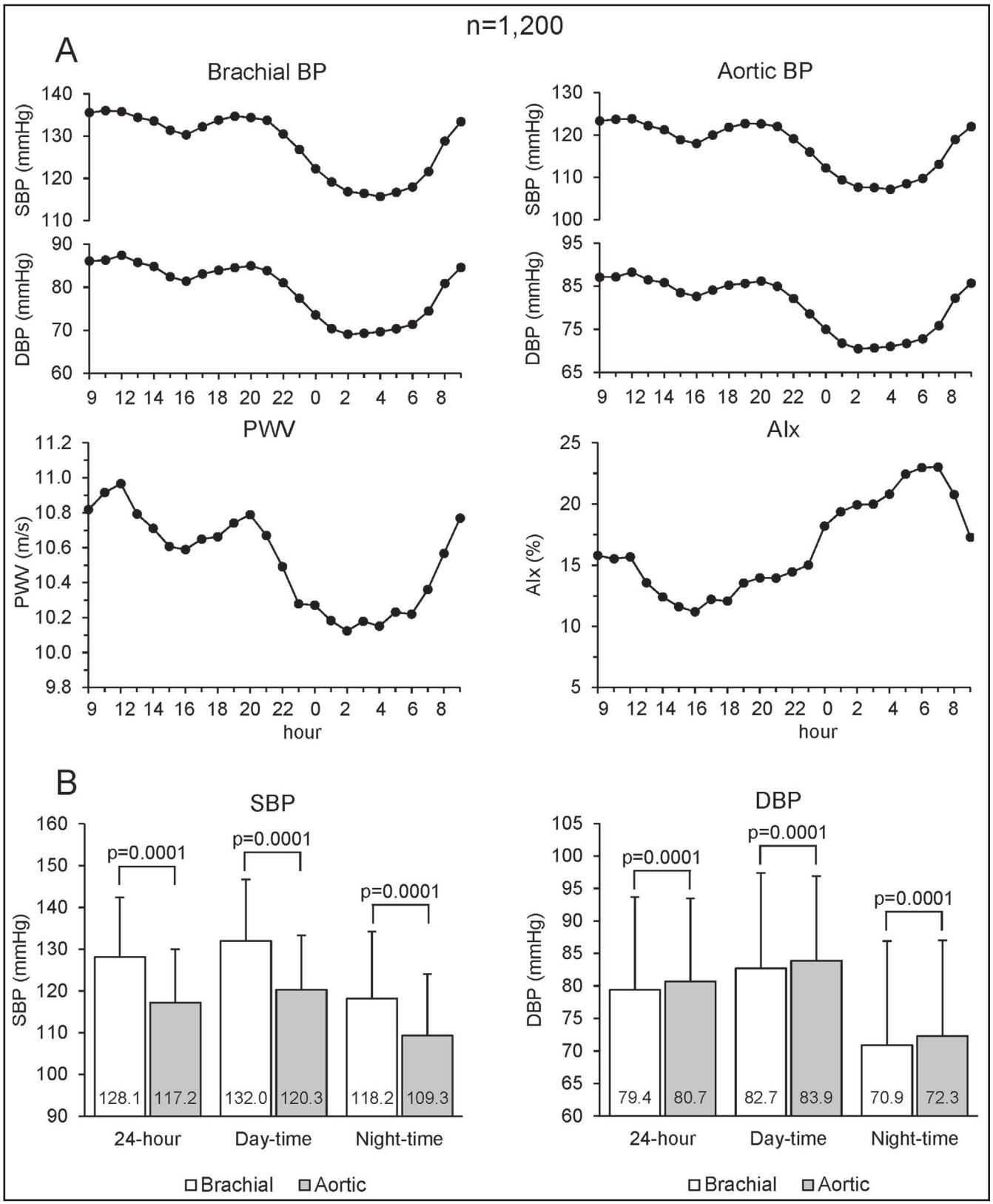

FIGURE 1 A, Hourly averages of brachial and aortic systolic blood pressure (SBP) and diastolic blood pressure (DBP), pulse wave velocity (PWV), augmentation index (AIx), and B, 24-h, daytime and nighttime averages (±standard deviation) of brachial (open bars) and aortic (full bars) SBP and DBP for the whole-study population. *P*-values refer to the comparison between brachial and aortic BP

TABLE 2 24-h hemodynamics in the various study subgroups

Young vs old	Unadjusted	Adjusted	Male vs female	Unadjusted	Adjusted	Hypertension − vs +	Unadjusted	Adjusted	Dyslipidemia − vs +	Unadjusted	Adjusted
bSBP (mm Hg)			*bSBP (mm Hg)*			*bSBP (mm Hg)*			*bSBP (mm Hg)*		
Young	127.4 ± 14.0	127.4 (126.4, 128.3)	Male	130.0 ± 14.1	130.1 (129.1, 131.2)	Hypertension −	127.5 ± 14.6	127.0 (125.8, 128.3)	Dyslipidemia −	128.3 ± 14.4	128.9 (127.9, 129.9)
Old	130.3 ± 14.9	130.5 (128.9, 132.1)	Female	125.9 ± 14.2	125.6 (124.4, 126.8)	Hypertension +	128.9 ± 13.9	129.3 (127.9, 130.7)	Dyslipidemia +	127.6 ± 14.0	125.8 (124.0, 127.7)
P-value	.003	.001	*P*-value	.0001	.0001	*P*-value	.088	.032	*P*-value	.471	.006
bDBP (mm Hg)			*bDBP (mm Hg)*			*bDBP (mm Hg)*			*bDBP (mm Hg)*		
Young	81.0 ± 9.3	80.9 (80.4, 81.6)	Male	81.3 ± 9.5	81.1 (80.4, 81.8)	Hypertension −	78.7 ± 9.3	78.0 (77.1, 78.9)	Dyslipidemia −	79.5 ± 9.6	79.6 (78.9, 80.3)
Old	74.3 ± 8.6	74.5 (73.5, 75.5)	Female	77.0 ± 9.1	77.3 (76.5, 78.1)	Hypertension +	80.2 ± 9.8	80.9 (80.0, 81.8)	Dyslipidemia +	79.0 ± 9.7	78.8 (77.6, 79.9)
P-value	.0001	.0001	*P*-value	.0001	.0001	*P*-value	.007	.0001	*P*-value	.362	.264
aSBP (mm Hg)			*aSBP (mm Hg)*			*aSBP (mm Hg)*			*aSBP (mm Hg)*		
Young	116.3 ± 12.4	116.3 (115.5, 117.2)	Male	117.8 ± 12.7	118.2 (117.2, 119.1)	Hypertension −	116.3 ± 13.2	115.9 (114.8, 117.1)	Dyslipidemia −	117.2 ± 12.9	117.9 (117.0, 118.8)
Old	119.9 ± 13.4	119.8 (118.4, 121.3)	Female	116.4 ± 12.8	115.9 (114.9, 117.1)	Hypertension +	118.2 ± 12.2	118.6 (117.3, 119.8)	Dyslipidemia +	117.3 ± 12.5	115.3 (113.6, 116.9)
P-value	.0001	.0001	*P*-value	.057	.003	*P*-value	.012	.007	*P*-value	.834	.009
aDBP (mm Hg)			*aDBP (mm Hg)*			*aDBP (mm Hg)*			*aDBP (mm Hg)*		
Young	82.4 ± 9.4	82.3 (81.7, 82.9)	Male	85.2 ± 9.6	82.3 (81.6, 83.0)	Hypertension −	79.9 ± 9.4	79.2 (78.4, 80.1)	Dyslipidemia −	80.8 ± 9.7	80.9 (80.2, 81.5)
Old	75.5 ± 8.7	75.6 (74.6, 76.7)	Female	78.3 ± 9.2	78.6 (77.8, 79.4)	Hypertension +	81.6 ± 9.9	82.3 (81.3, 83.2)	Dyslipidemia +	80.3 ± 9.7	80.1 (78.9, 81.3)
P-value	.0001	.0001	*P*-value	.0001	.0001	*P*-value	.003	.0001	*P*-value	.459	.303
PWV (m/s)			*PWV (m/s)*			*PWV (m/s)*			*PWV (m/s)*		
Young	9.9 ± 2.4	9.9 (9.8, 10.0)	Male	10.2 ± 2.7	10.4 (10.3, 10.6)	Hypertension −	10.0 ± 2.7	10.2 (10.0, 10.4)	Dyslipidemia −	10.3 ± 2.7	10.6 (10.5, 10.8)
Old	12.7 ± 1.8	12.6 (12.3, 12.8)	Female	11.0 ± 2.3	10.7 (10.6, 10.9)	Hypertension +	11.2 ± 2.3	10.9 (10.7, 11.2)	Dyslipidemia +	11.4 ± 2.0	10.4 (10.1, 10.6)
P-value	.0001	.0001	*P*-value	.0001	.007	*P*-value	.0001	.0001	*P*-value	.0001	.084
AIx75 (%)			*AIx75 (%)*			*AIx75 (%)*			*AIx75 (%)*		
Young	15.9 ± 18.1	16.4 (15.4, 17.4)	Male	8.9 ± 15.3	9.4 (8.3, 10.5)	Hypertension −	16.6 ± 18.3	16.3 (15.0, 17.6)	Dyslipidemia −	17.3 ± 18.7	18.5 (17.5, 19.5)
Old	24.6 ± 18.6	22.9 (21.1, 24.6)	Female	29.4 ± 15.8	28.8 (27.5, 30.0)	Hypertension +	19.6 ± 18.8	19.9 (18.5, 21.3)	Dyslipidemia +	19.8 ± 18.2	16.7 (14.8, 18.6)
P-value	0.0001	0.0001	*P*-value	0.0001	0.0001	*P*-value	0.004	0.001	*P*-value	0.041	0.120

Diabetes − vs +	Unadjusted	Adjusted	Metabolic syndrome − vs +	Unadjusted	Adjusted	CV disease − vs +	Unadjusted	Adjusted
bSBP (mm Hg)			*bSBP (mm Hg)*			*bSBP (mm Hg)*		
Diabetes −	127.8 ± 14.2	127.8 (127.0, 128.7)	Metabolic syndrome −	128.1 ± 14.5	128.3 (127.3, 129.3)	CV disease −	128.0 ± 14.1	128.1 (127.3, 128.9)

(Continued)

TABLE 2 (Continued)

Diabetes − vs +	Unadjusted	Adjusted	Metabolic syndrome − vs +	Unadjusted	Adjusted	CV disease − vs +	Unadjusted	Adjusted
Diabetes +	132.5 ± 15.1	132.1 (128.9, 135.4)	Metabolic syndrome +	128.3 ± 13.9	127.9 (126.5, 129.3)	CV disease +	129.4 ± 16.0	128.1 (125.4, 130.8)
P-value	.005	.012	*P*-value	.794	.693	*P*-value	.290	.989
bDBP (mm Hg)			*bDBP (mm Hg)*			*bDBP (mm Hg)*		
Diabetes −	79.5 ± 9.6	79.5 (78.9, 80.0)	Metabolic syndrome −	79.4 ± 9.5	79.1 (78.5, 79.8)	CV disease −	79.6 ± 9.5	79.6 (79.0, 80.1)
Diabetes +	77.5 ± 9.3	77.9 (75.8, 80.0)	Metabolic syndrome +	79.3 ± 9.7	79.8 (78.9, 80.7)	CV disease +	77.1 ± 10.5	77.6 (75.8, 79.4)
P-value	.073	.160	*P*-value	.798	.220	*P*-value	.005	.042
aSBP (mm Hg)			*aSBP (mm Hg)*			*aSBP (mm Hg)*		
Diabetes −	117.0 ± 12.7	117.0 (116.3, 117.8)	Metabolic syndrome −	116.9 ± 13.0	117.3 (116.4, 118.2)	CV disease −	117.0 ± 12.6	117.3 (116.5, 118.0)
Diabetes +	120.6 ± 12.8	119.7 (116.7, 122.6)	Metabolic syndrome +	117.7 ± 12.3	116.9 (115.7, 118.2)	CV disease +	118.7 ± 14.0	116.6 (114.1, 119.1)
P-value	.015	.091	*P*-value	.300	.637	*P*-value	.193	.614
aDBP (mm Hg)			*aDBP (mm Hg)*			*aDBP (mm Hg)*		
Diabetes −	80.8 ± 9.7	80.8 (80.2, 81.3)	Metabolic syndrome −	80.7 ± 9.6	80.4 (79.8, 81.0)	CV disease −	81.0 ± 9.5	80.9 (80.4, 81.5)
Diabetes +	79.0 ± 9.3	79.4 (77.2, 81.6)	Metabolic syndrome +	80.6 ± 9.8	81.1 (80.1, 82.0)	CV disease +	78.0 ± 10.6	78.4 (76.6, 80.3)
P-value	.107	.230	*P*-value	.793	.243	*P*-value	.002	.013
PWV (m/s)			*PWV (m/s)*			*PWV (m/s)*		
Diabetes −	10.5 ± 2.6	10.6 (10.5, 10.7)	Metabolic syndrome −	10.1 ± 2.8	10.4 (10.3, 10.6)	CV disease −	10.4 ± 2.6	10.6 (10.4, 10.7)
Diabetes +	11.7 ± 1.9	10.6 (10.1, 11.0)	Metabolic syndrome +	11.4 ± 2.1	10.8 (10.6, 11.0)	CV disease +	12.1 ± 2.1	10.7 (10.3, 11.0)
P-value	.0001	.939	*P*-value	.0001	.0001	*P*-value	.0001	.939
AIx75 (%)			*AIx75 (%)*			*AIx75 (%)*		
Diabetes −	18.0 ± 18.7	18.2 (17.4, 19.1)	Metabolic syndrome −	17.2 ± 18.9	18.2 (17.2, 19.3)	CV disease −	17.4 ± 18.5	17.7 (16.9, 18.6)
Diabetes +	18.2 ± 17.0	15.1 (11.7, 18.4)	Metabolic syndrome +	19.5 ± 18.0	17.6 (16.2, 19.0)	CV disease +	23.8 ± 18.6	20.6 (17.7, 23.4)
P-value	0.940	0.078	*P*-value	0.039	0.481	*P*-value	0.0001	0.066

Note: Data are reported as mean value ± standard deviation or as mean value and 95% confidence interval. *P*-values for the comparisons between groups are also displayed.
Abbreviations: a, aortic; AIx, augmentation index normalized by HR 75 bpm; b, brachial; CV, cardiovascular; DBP, diastolic blood pressure; HR, heart rate; PWV, pulse wave velocity; SBP, systolic blood pressure. Adjusted estimates are corrected by age, sex, cardiovascular risk factors (including hypertension, diabetes, dyslipidemia, CV disease), and obesity. AIx is also adjusted by BP.

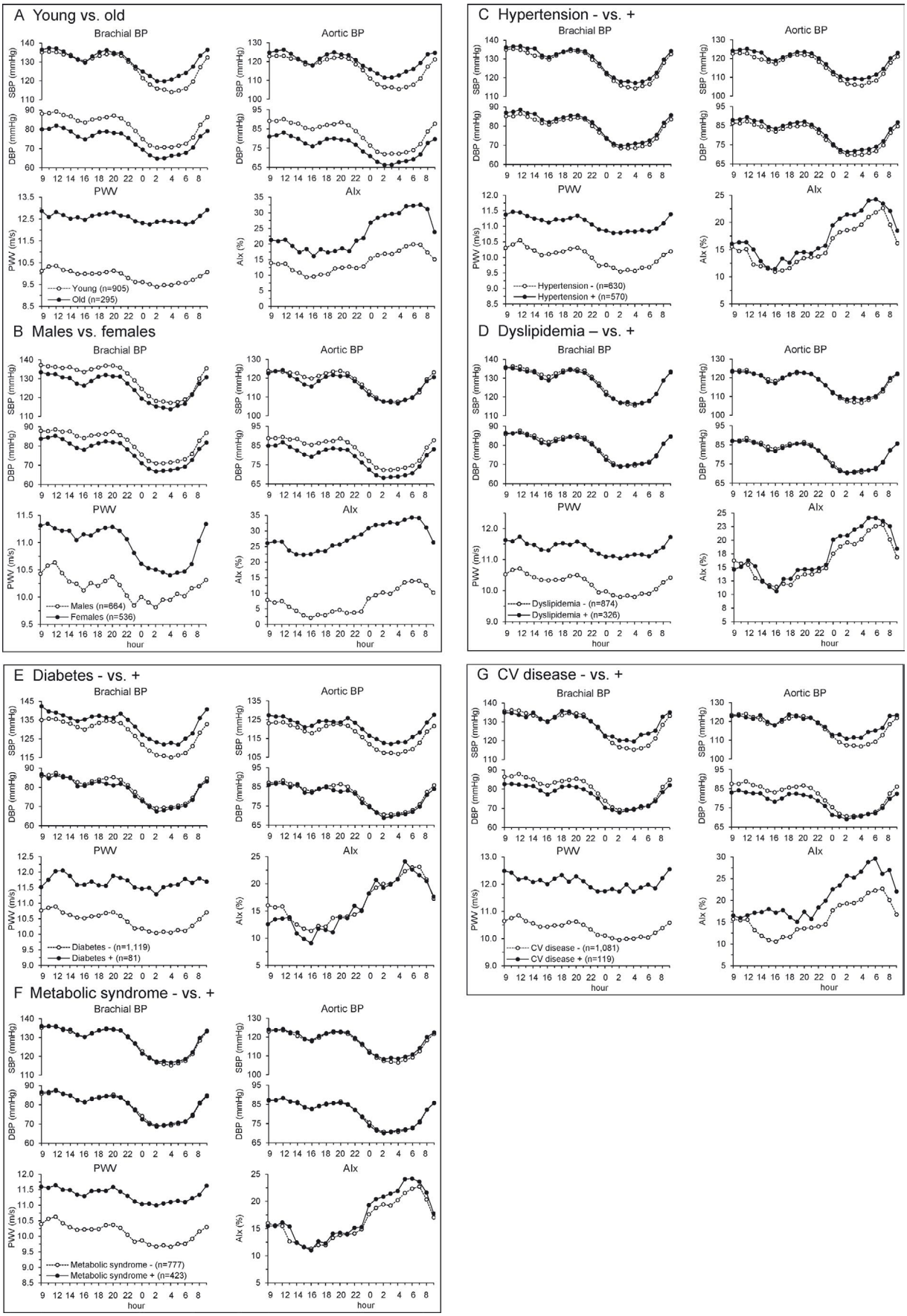

FIGURE 2 Hourly averages of brachial and aortic systolic blood pressure (SBP) and diastolic blood pressure (DBP), pulse wave velocity (PWV), and augmentation index (AIx) in the various study subgroups. CV, Cardiovascular

variable association between these parameters and CV risk, hence confirming and extending to the dynamic conditions of daily life the findings provided by previous studies performed at rest in standardized laboratory conditions. Such studies highlighted the predictive value of arterial stiffness and, to a relatively less extent, of measures of wave reflection and central hemodynamics, in the general population, in elderly participants, in patients with essential hypertension, diabetes mellitus, renal diseases, and CV disease, and helped acknowledge the utility of these estimates as intermediate end points for CV events.[13,15,16]

To our knowledge, ours is the largest cross-sectional observational study of its kind performed in ambulatory conditions and in different high CV risk subgroups of participants. At the moment, the large number of patients enrolled (1200) allowed us to describe the behavior of ambulatory pulse wave indices in specific CV risk categories, providing some clue about the vascular health status of our population and the diagnostic power of cuff-based pulse wave analysis. Whether measures of vascular biomarkers obtained with pulse wave analysis of oscillometric brachial BP in ambulatory conditions may have on the long term the same prognostic value of non-invasive estimates collected in resting laboratory conditions needs, of course, to be demonstrated in the future prospective phase of the VASOTENS Registry.

In the whole participants of the study, ambulatory aortic BP circadian trend mimicked that of ambulatory brachial BP, though SBP was lower and DBP higher at the central than at the peripheral site. Both BPs showed a typical circadian rhythm, with a nocturnal fall smaller centrally than peripherally. PWV and AIx also had a diurnal rhythm, with PWV decreasing and AIx increasing at night. These results are in line with those reported with 24-hour cuff-based pulse wave analysis performed with the same device used in this study[17,18] or with other technologies.[1,19-23]

The main strength of this study is the comprehensive information about major CV risk factors, which enabled us to assess the behavior of arterial stiffness and central hemodynamics over the 24 hours in daily life conditions in different categories of CV risk. A major strength of our study is the description of the different behavior of brachial and central BP, and of PWV and AIx during the waking vs the night sleep hours in different subgroups with a variable degree of CV risk. This feature may represent the main advantage of ambulatory measures in relation to the conventional awake resting measures.

With aging, arteries become stiffer and the incident and reflected waves accelerate.[24] Previously published data referring to studies performed in resting conditions showed that in older participants an increase in arterial stiffness and wave reflections and an elevation in central and peripheral SBP are observed.[24-29] Our results agreed with data collected at rest and with those of smaller studies performed in ambulatory conditions.[17,18] In our population of older individuals, larger 24-hour SBP values but lower 24-hour DBP values than younger participants were observed. As expected, due to the reduction of the diurnal BP rhythm commonly observed in the elderly, the difference in BP between older and younger participants was more marked during the night sleep. Participants in advanced age had also an increase in PWV and AIx and a blunted PWV reduction during night sleep, as compared to younger individuals, which persisted even after adjusting for CV risk factors.

Also, hypertension played an important role in the determination of arterial stiffness and central BP in our population. After proper adjustment for confounding factors, both peripheral and central BPs, PWV and AIx were increased in patients with a known history of hypertension, confirming previous findings obtained in hypertensive patients studied either at rest[13,15] or in ambulatory conditions.[18,30-32]

Other important factors related to the risk of coronary artery diseases such as dyslipidemia and diabetes mellitus were associated with increased arterial stiffness and BP. However, the association was weak and most of the differences, and particularly the increase in PWV, were lost after proper adjustment. As a matter of fact, although some studies conducted at rest previously showed PWV and AIx increases in diabetics[33-37] as well as in patients with dyslipidemia,[13,15,38] these risk factors are generally regarded as less closely and independently related to arterial stiffness than an elevated BP. We cannot exclude that the lack of difference found for PWV and AIx in our subgroups with dyslipidemia or diabetes may be related to other factors, such as (a) the small sample of participants in these groups, (b) the fact that participants serving as controls had indeed other CV risk factors which may have had some unexpected effect on the estimation of vascular biomarkers, (c) the fact that, as suggested by some authors, in patients with diabetes PWV may be increased in the lower limb but not in the upper-limb arteries, namely the site where we derived the pulse waveform for the evaluation of arterial stiffness,[35,39] (d) the potential for a reduced accuracy of the oscillometric device in the estimation of PWV and AIx in dynamic conditions compared to devices assessing the same parameters at rest in a controlled laboratory setting with applanation tonometry.

Interestingly when the major CV risk factors previously discussed (hypertension, dyslipidemia, diabetes, and obesity) clustered in the metabolic syndrome some negative effects on the arterial stiffness could be observed. In fact, in the patients with the metabolic syndrome, no difference in central and peripheral BP levels was observed as respect to patients with no metabolic syndrome, but they displayed higher values of PWV, also when results were adjusted for confounding factors. This suggests that when taken individually some components of the metabolic syndrome (in particular dyslipidemia and diabetes) may have a non-systematic effect on arterial stiffness, while the aggregation of such risk factors may worsen arterial stiffness. This finding, which is documented in studies performed at rest,[40-43] is now in absolute reported for the first time in ambulatory conditions in the participants of our study.

It is well known that arterial stiffness and central hemodynamics are strong predictors of CV events and all-cause mortality,[15] but there is also evidence that they are associated with the presence of CV disease.[13] Among the remaining modern vascular biomarkers, these indexes are closest to being "surrogate endpoints" of CV events.[15] This is in part confirmed in the patients of our study with

known CV disease, in whom we observed a trend to larger PWV and AIx values compared to patients free from CV disease, a trend which was consistently reappraised when we adjusted the results for confounding factors. The limited sample of participants with CV disease in our study could have prevented to show differences in arterial stiffness and wave reflections found in previous studies performed in resting conditions in patients with CV disease.[44-46] The longitudinal phase of the VASOTENS Registry may help us better clarify this aspect.

In our study, we also attempted to assess differences in arterial stiffness and wave reflections according to sex. Male participants had higher central and peripheral BP values than females. However, female participants showed higher PWV and AIx values also after adjustment for confounding factors (including age). Several studies have shown that central hemodynamics and arterial stiffness differ considerably between men and women in terms of etiology, pathogenesis, and clinical outcomes because of numerous endogenous factors, such a body size, sex hormones, and biochemical properties of the arteries and various exogenous factors.[13,15] A significant sex difference in the rate of change in aortic stiffness with age exists. In general, arterial elasticity is better in younger women than in age-matched men. However, this benefit tends to rapidly decline in females between the age of 45 and 50 years, since females, after the menopause and with aging, show a steeper decline in aortic distensibility, a larger increase in stiffness and an earlier return of the reflected wave than males.[27,47] In previous studies performed at rest and based on applanation tonometry, AIx values were found invariably larger in women than in men[26,47-50]: This was true also in our study. In previous studies performed non-invasively, sex differences in PWV values were not always univocal. In general, arterial stiffness values (PWV) were found to be higher in women than in men at an advanced age,[50] whereas they were larger in men than in women when individuals were matched by age.[26,29,47,48,51] The fact that in our study women were older than men (55.3 vs 50.5 years, $P = .0001$) and that measures were collected in ambulatory conditions could explain the finding of larger PWV values in females; as a matter of fact, such differences were consistently reduced, but still persisted after adjusting for subject-related factors (including age). Thus, differences in PWV according to sex are controversial and should always be seen in the context of age and of other factors which could not be fully explored in our study.[51]

4.1 | Study limitations

We wish to stress some limitations of our work. First, although the non-invasive character of the methodology employed in our study is essential for collecting data on a large scale, it also implies some limitations inherent to the accuracy of the indirect and non-invasive technique. The oscillometric device used in this study was previously validated vs non-invasive measurements done with applanation tonometry (Sphygmocor) and not vs the gold standard (intra-arterial measurement). However, the accuracy of the non-invasive reference used in these validation studies has been extensively checked against intra-arterial measurements and it may be considered a reliable reference for non-invasive validation studies. Though clinically validated, we cannot entirely exclude that given the dynamic nature of the measurements, the occurrence of some errors might have occurred in our study. However, we must acknowledge that the system is able to automatically discard readings with oscillograms which are inappropriate for the pulse wave analysis, and thus, it may substantially limit the inaccuracy of the measurement. Visual check of possible artifacts is also possible by the investigator. As a matter of fact, 142 of the 1342 recruited participants (11%) could not be included because the oscillograms did not allow to obtain proper parameters for a sufficient number of readings. Second, given the observational nature of the study, we could not collect detailed clinical information such as duration of underlying disease or specific number and type of antihypertensive or any other CV drug used by the patients. Since the intensity of specific treatments (eg, antihypertensive or CV drugs) may have affected the estimation of 24-hour hemodynamics, the knowledge of this information may have made our analysis more reliable. However, we were able to categorize the participants on the basis of the main CV risk factors. Third, the proportion of participants with hypertension was low, but this categorization was based on self-reported hypertension. Since a substantial proportion of participants was submitted to ABPM to check the occurrence of hypertension, it is reasonable to assume that at the end of the diagnostic evaluation the proportion of patients with prevalent hypertension would have been larger. Fourth, except for the large sample of participants enrolled, the study may have limited elements of novelty. However, this is the first large study based on a specific technology and thus our evidence will provide some reference to clinicians making using of the same device used in this study, for routine clinical evaluation of their patients. Finally, this study currently lacks prospective data, but we are planning a cross-sectional analysis based on hypertension-mediated organ damage, a surrogate hard end point of CV risk. Additionally, the study is proceeding on the way of its longitudinal phase with repeated ABPMs and collection of CV outcomes. These data will be presented in future publications.

5 | CONCLUSIONS

Epidemiological studies demonstrated that increased aortic stiffness, indexed as an increased PWV, is an independent risk factor for CV events, even when the impact of age, BP, and other known risk factors are taken into account. In our study, we found that ambulatory central BP and PWV are increased in advanced age and in presence of arterial hypertension, two conditions which are thus confirmed as important determinants of vascular health and future CV outcomes. We also documented that an often common condition such as the metabolic syndrome is characterized by an increased arterial stiffness, thus confirming its burden as an important risk factor for future CV disease. All these findings taken together suggest that prevention or reduction not only of ambulatory brachial BP but

also of ambulatory CAP and PWV may carry substantial health benefits, though this needs to be proved in the longitudinal phase of the VASOTENS Registry. They also support the value of ambulatory pulse wave analysis in a daily life setting for evaluation of individuals at risk for CV disease.

CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. Stefano Omboni ran the analysis and drafted the manuscript. Igor Posokhov contributed to its refinement. Ayana Arystan, Alberto Avolio, Vitaliy Barkan, Natalia Bulanova, Ernesto Cardona Muñoz, Elena Grigoricheva, Alexandra Konradi, Irina Minyukhina, Maria Lorenza Muiesan, Giuseppe Mulè, Iana Orlova, Telmo Pereira, João Manuel Peixoto Maldonado, Mikhail E. Statsenko, Ioan Tilea, and Gabriel Waisman recruited the patients and provided the data for the analysis. Gianfranco Parati, Anatoly Rogoza, Yulia Kotovskaya, Ayana Arystan, Alberto Avolio, Vitaliy Barkan, Natalia Bulanova, Ernesto Cardona Muñoz, Elena Grigoricheva, Alexandra Konradi, Irina Minyukhina, Maria Lorenza Muiesan, Giuseppe Mulè, Iana Orlova, Telmo Pereira, João Manuel Peixoto Maldonado, Mikhail E. Statsenko, Ioan Tilea, and Gabriel Waisman critically revised and approved the final manuscript.

ORCID

Stefano Omboni https://orcid.org/0000-0002-7124-2096
Igor Posokhov https://orcid.org/0000-0002-2381-0351
Gianfranco Parati https://orcid.org/0000-0001-9402-7439
Yulia Kotovskaya https://orcid.org/0000-0002-1628-5093
Giuseppe Mulè https://orcid.org/0000-0002-8500-8671
Iana Orlova https://orcid.org/0000-0002-8160-5612
Telmo Pereira https://orcid.org/0000-0001-9119-7774

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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APPENDIX 1

THE VASOTENS REGISTRY STUDY GROUP

Stefano Omboni (Italy) and Igor Posokhov (Russia) are the study coordinators. Stefano Omboni (Italy), Gianfranco Parati (Italy), Igor Posokhov (Russia), and Anatoli Rogoza (Russia) are the members of Steering Committee. Stefano Omboni (Italy), Gianfranco Parati (Italy), Igor Posokhov (Russia), Anatoli Rogoza (Russia), and Yulia Kotovskaya (Russia) are the members of Scientific Committee. Gabriel Waisman and Pedro Forcada (Argentina); Parounak Zelveian (Armenia); Alberto Avolio, Mark Butlin, Edward Barin, and Isabella Tan (Australia); Stefano Omboni, Gianfranco Parati, Giuseppe Mulè, Lorenzo Ghiadoni, Rosa Maria Bruno, Riccardo Sarzani, Emma Espinosa, Massimo Volpe, Carmine Savoia, Giuliano Tocci, Claudio Borghi, Giuseppe Schillaci, Giacomo Pucci, Maria Lorenza Muiesan, Anna Paini, Damiano Rizzoni (Italy); Ayana Arystan (Kazakhstan); Ernesto Cardona Muñoz, Carlos Ramos, and Adrian Alanis (Mexico); Telmo Pereira and João Manuel Peixoto Maldonado (Portugal); Ioan Tilea and Andreea Varga (Romania); Igor Posokhov, Anatoli Rogoza, Dmitriy Volkov, Yulia Kotovskaya, Iana Orlova, Natalya Kurlykina, Alexandra Konradi, Oxana Rotar, Alexander Orlov, Vladimir Gorbunov, Sergey Boytsov, Elena Fedorova, Viktoria Korneva, Tatyana Kuznetsova, Natalya Kulikova, Elena Grigoricheva, Vitaly V. Evdokimov, Anastasiya Kuznetsova, Elena Zheleznyak, Zhanna Kobalava, Irina Minyukhina, Irina Borisova, Tatiana Svetozarsky, Vitaliy Barkan, Marina Gubanova, Viktoria Lazareva, Mikhail Statsenko, Maria V. Derevyanchenko, Philippe Kopylov, Natalia Bulanova (Russia); Yuriy Sirenko and Oksana Recovets (Ukraine) are the investigators of this study; Stefano Omboni (Italy) and Igor Posokhov (Russia) involved in data management.

Table S1. Demographic and main clinical characteristics of the study population according to the specific study subgroups. Data are reported as absolute and relative frequency (percentage in brackets) or as mean value and standard deviation. P-values for the comparisons between groups are also displayed. BMI: Body Mass Index; CV: Cardiovascular.

	Young (n=905)	**Old (n=295)**	**p-value**	**Males (n=664)**	**Females (n=536)**	**p-value**	**Hypertension - (n=630)**	**Hypertension + (n=570)**	**p-value**
Age (years)	46.5 ± 12.5	71.3 ± 5.3	0.0001	50.5 ± 15.9	55.3 ± 14.5	0.0001	50.4 ± 16.6	55.0 ± 13.7	0.0001
Young (<65 years)	905 (100.0)	-	-	517 (77.9)	388 (72.4)	0.029	485 (77.0)	420 (73.7)	0.185
Old (≥65 years)	-	295 (100.0)		147 (22.1)	148 (27.6)		145 (23.0)	150 (26.3)	
Sex									
Male	*517 (57.1)*	*147 (49.8)*	*0.029*	*664 (100.0)*	-	-	*355 (56.3)*	*309 (54.2)*	*0.457*
Female	*388 (42.9)*	*148 (50.2)*		-	*536 (100.0)*		*275 (43.7)*	*261 (45.8)*	
Ethnicity									
Caucasian	*804 (88.8)*	*253 (85.8)*	*0.234*	*588 (88.6)*	*469 (87.5)*	*0.233*	*568 (90.2)*	*489 (85.8)*	*0.124*
Hispanic	*59 (6.5)*	*22 (7.5)*		*39 (5.9)*	*42 (7.8)*		*34 (5.4)*	*47 (8.2)*	
Asian	*39 (4.3)*	*20 (6.8)*		*34 (5.1)*	*25 (4.7)*		*27 (4.3)*	*32 (5.6)*	
Black	*3 (0.3)*	-		*3 (0.5)*	-		*1 (0.2)*	*2 (0.4)*	
BMI (kg/m^2)	28.2 ± 4.9	27.9 ± 4.6	0.520	28.0 ± 4.3	28.3 ± 5.4	0.399	26.8 ± 4.2	28.7 ± 5.0	0.0001
Waist circumference (cm)	96.6 ± 14.2	96.3 ± 13.6	0.864	98.9 ± 13.4	93.9 ± 14.4	0.001	95.3 ± 12.9	96.7 ± 14.2	0.557
Overweight or obesity	480 (53.0)	146 (49.5)	0.290	342 (51.5)	284 (53.0)	0.610	170 (27.0)	456 (80.0)	0.0001
Known hypertension (untreated or treated)	420 (46.4)	150 (50.8)	0.185	309 (46.5)	261 (48.7)	0.457	-	570 (100.0)	-
Treated hypertension	367 (40.6)	146 (49.5)	0.007	280 (42.2)	233 (43.5)	0.651	-	513 (90.0)	-
Known dyslipidemia (untreated or treated)	225 (24.9)	101 (34.2)	0.002	173 (26.1)	153 (28.5)	0.335	26 (4.1)	300 (52.6)	0.0001
Treated dyslipidemia	108 (11.9)	69 (23.4)	0.0001	114 (17.2)	63 (11.8)	0.009	12 (1.9)	165 (28.9)	0.0001
Known diabetes (untreated or treated)	46 (5.1)	35 (11.9)	0.0001	47 (7.1)	34 (6.3)	0.614	8 (1.3)	73 (12.8)	0.0001
Treated diabetes	39 (4.3)	30 (10.2)	0.0001	39 (5.9)	30 (5.6)	0.838	8 (1.3)	61 (10.7)	0.0001
Metabolic syndrome	298 (32.9)	125 (42.4)	0.003	231 (34.8)	192 (35.8)	0.710	55 (8.7)	368 (64.6)	0.0001
CV diseases	56 (6.2)	63 (21.4)	0.0001	65 (9.8)	54 (10.1)	0.869	14 (2.2)	105 (18.4)	0.0001
CV risk factors	450 (49.7)	158 (53.6)	0.252	330 (49.7)	278 (51.9)	0.455	38 (6.0)	570 (100.0)	0.0001
Concomitant diseases	421 (46.5)	156 (52.9)	0.058	313 (47.1)	264 (49.3)	0.466	38 (6.0)	539 (94.6)	0.0001
Concomitant medications	388 (42.9)	147 (49.8)	0.037	293 (44.1)	242 (45.1)	0.723	18 (2.9)	517 (90.7)	0.0001

Table S1. Continues.

	Dyslipidemia - (n=874)	Dyslipidemia + (n=326)	p-value	Diabetes - (n=1,119)	Diabetes + (n=81)	p-value	Metabolic syndrome - (n=777)	Metabolic syndrome + (n=423)	p-value	CV disease - (n=1,081)	CV disease + (n=119)	p-value
Age (years)	50.4 ± 16.3	58.5 ± 11.1	0.0001	52.0 ± 15.6	60.8 ± 10.5	0.0001	50.0 ± 16.5	57.4 ± 12.1	0.0001	51.4 ± 15.3	63.6 ± 11.9	0.0001
Young (<65 years)	680 (77.8)	225 (69.0)	0.002	859 (76.8)	46 (56.8)	0.0001	607 (78.1)	298 (70.4)	0.003	849 (78.5)	56 (47.1)	0.0001
Old (≥65 years)	194 (22.2)	101 (31.0)		260 (23.2)	35 (43.2)		170 (21.9)	125 (29.6)		232 (21.5)	63 (52.9)	
Sex												
Male	*491 (56.2)*	*173 (53.1)*	*0.335*	*617 (55.1)*	*47 (58.0)*	*0.614*	*433 (55.7)*	*231 (54,6)*	*0.710*	*599 (55.4)*	*65 (54.6)*	*0.869*
Female	*383 (43.8)*	*153 (46.9)*		*502 (44.9)*	*34 (42.0)*		*344 (44.3)*	*192 (45.4)*		*482 (44.6)*	*54 (45.4)*	
Ethnicity												
Caucasian	*778 (89.0)*	*279 (85.6)*	*0.010*	*987 (88.2)*	*70 (86.4)*	*0.901*	*689 (88.7)*	*368 (87.0)*	*0.231*	*951 (88.0)*	*106 (89.1)*	*0.065*
Hispanic	*62 (7.1)*	*19 (5.8)*		*75 (6.7)*	*6 (7.4)*		*55 (7.1)*	*26 (6.1)*		*78 (7.2)*	*3 (2.5)*	
Asian	*32 (3.7)*	*27 (8.3)*		*54 (4.8)*	*5 (6.2)*		*31 (4.0)*	*28 (6.6)*		*50 (4.6)*	*9 (7.6)*	
Black	*2 (0.2)*	*1 (0.3)*		*3 (0.3)*	-		*2 (0.3)*	*1 (0.2)*		*2 (0.2)*	*1 (0.8)*	
BMI (kg/m^2)	27.3 ± 4.6	29.5 ± 4.8	0.0001	27.8 ± 4.7	31.0 ± 5.3	0.0001	26.8 ± 4.5	29.5 ± 4.7	0.0001	28.0 ± 4.8	29.2 ± 5.1	0.011
Waist circumference (cm)	94.2 ± 13.9	98.3 ± 13.9	0.005	96.0 ± 14.2	101.5 ± 11.0	0.029	92.6 ± 14.1	98.2 ± 13.7	0.0001	95.5 ± 14.4	101.2 ± 11.3	0.003
Overweight or obesity	353 (40.4)	273 (83.7)	0.0001	553 (49.4)	73 (90.1)	0.0001	264 (34.0)	362 (85.6)	0.0001	527 (48.8)	99 (83.2)	0.0001
Known hypertension (untreated or treated)	270 (30.9)	300 (92.0)	0.0001	497 (44.4)	73 (90.1)	0.0001	202 (26.0)	368 (87.0)	0.0001	465 (43.0)	105 (88.2)	0.0001
Treated hypertension	236 (27.0)	277 (85.0)	0.0001	441 (39.4)	72 (88.9)	0.0001	170 (21.9)	343 (81.1)	0.0001	416 (38.5)	97 (81.5)	0.0001
Known dyslipidemia (untreated or treated)	-	326 (100.0)	-	269 (24.0)	57 (70.4)	0.0001	-	326 (77.1)	-	246 (22.8)	80 (67.2)	0.0001
Treated dyslipidemia	-	177 (54.3)	-	137 (12.2)	40 (49.4)	0.0001	-	177 (41.8)	-	121 (11.2)	56 (47.1)	0.0001
Known diabetes (untreated or treated)	24 (2.7)	57 (17.5)	0.0001	-	81 (100.0)	-	1 (0.1)	80 (18.9)	0.0001	49 (4.5)	32 (26.9)	0.0001
Treated diabetes	20 (2.3)	49 (15.0)	0.0001	-	69 (85.2)	-	1 (0.1)	68 (16.1)	0.0001	42 (3.9)	27 (22.7)	0.0001
Metabolic syndrome	97 (11.1)	326 (100.0)	0.0001	343 (30.7)	80 (98.8)	0.0001	-	423 (100.0)	-	330 (30.5)	93 (78.2)	0.0001
CV diseases	39 (4.5)	80 (24.5)	0.0001	87 (7.8)	32 (39.5)	0.0001	26 (3.3)	93 (22.0)	0.0001	-	119 (100.0)	-
CV risk factors	282 (32.3)	326 (100.0)	0.0001	527 (47.1)	81 (100.0)	0.0001	209 (26.9)	399 (94.3)	0.0001	489 (45.2)	119 (100.0)	0.0001
Concomitant diseases	251 (28.7)	326 (100.0)	0.0001	496 (44.3)	81 (100.0)	0.0001	179 (23.0)	398 (94.1)	0.0001	458 (42.4)	119 (100.0)	0.0001
Concomitant medications	241 (27.6)	294 (90.2)	0.0001	455 (40.7)	80 (98.8)	0.0001	171 (22.0)	364 (86.1)	0.0001	432 (40.0)	103 (86.6)	0.0001

Table S2. Day and night hemodynamics and corresponding percentage (%) day-night changes (Δ) in the various study subgroups. Data are reported as mean value ± standard deviation. P-values for the comparisons between groups are also displayed, before and after adjustment for confounding factors (age, sex, hypertension, diabetes, dyslipidemia, CV disease and obesity, plus BP for AIx; in case of day-night changes in PWV and AIx p-values were also adjusted for day-night changes in BP). b: Brachial; a: Aortic; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; PWV: Pulse Wave Velocity; AIx: Augmentation Index; CV: Cardiovascular.

Young vs. old	**Day**	**Night**	**Δ day-night (%)**	**Male vs. female**	**Day**	**Night**	**Δ day-night (%)**	**Hypertension – vs. +**	**Day**	**Night**	**Δ day-night (%)**
bSBP (mmHg)				bSBP (mmHg)				bSBP (mmHg)			
Young	131.6 ± 14.5	116.7 ± 15.0	-11.2 ± 7.2	Male	134.1 ± 14.5	119.4 ± 15.7	-10.9 ± 7.5	Hypertension -	131.4 ± 15.1	117.3 ± 15.7	-10.6 ± 7.2
Old	133.2 ± 15.1	122.8 ± 17.8	-7.8 ± 8.6	Female	129.2 ± 14.5	116.7 ± 16.2	-9.6 ± 7.9	Hypertension +	132.6 ± 14.1	119.3 ± 16.2	-10.0 ± 8.1
p-value unadj.	0.092	0.0001	0.0001	p-value unadj.	0.0001	0.004	0.004	p-value unadj.	0.158	0.030	0.131
p-value adj.	0.044	0.0001	0.0001	p-value adj.	0.0001	0.0001	0.054	p-value adj.	0.025	0.057	0.932
bDBP (mmHg)				bDBP (mmHg)				bDBP (mmHg)			
Young	84.5 ± 9.9	72.1 ± 9.7	-14.4 ± 7.9	Male	84.8 ± 10.1	72.6 ± 10.0	-14.2 ± 8.0	Hypertension -	81.9 ± 9.9	70.3 ± 9.7	-14.1 ± 7.9
Old	77.1 ± 8.8	67.2 ± 9.6	-12.7 ± 8.2	Female	80.0 ± 9.6	68.8 ± 9.4	-13.8 ± 7.9	Hypertension +	83.5 ± 10.4	71.7 ± 10.2	-13.9 ± 8.1
p-value unadj.	0.0001	0.0001	0.002	p-value unadj.	0.0001	0.0001	0.419	p-value unadj.	0.010	0.017	0.806
p-value adj.	0.0001	0.0001	0.001	p-value adj.	0.0001	0.0001	0.850	p-value adj.	0.0001	0.003	0.239
aSBP (mmHg)				aSBP (mmHg)				aSBP (mmHg)			
Young	119.7 ± 12.9	107.7 ± 13.7	-10.0 ± 7.4	Male	121.2 ± 12.9	109.2 ± 14.8	-9.7 ± 7.7	Hypertension -	119.5 ± 13.5	108.2 ± 14.6	-9.4 ± 7.4
Old	122.0 ± 13.4	114.4 ± 16.4	-6.3 ± 8.7	Female	119.1 ± 13.1	109.2 ± 14.8	-8.3 ± 8.1	Hypertension +	121.2 ± 12.4	110.6 ± 14.7	-8.7 ± 8.4
p-value unadj.	0.008	0.0001	0.0001	p-value unadj.	0.006	0.815	0.002	p-value unadj.	0.025	0.005	0.139
p-value adj.	0.006	0.0001	0.0001	p-value adj.	0.0001	0.102	0.036	p-value adj.	0.004	0.0001	0.639
aDBP (mmHg)				aDBP (mmHg)				aDBP (mmHg)			
Young	85.8 ± 10.0	73.5 ± 9.9	-14.1 ± 7.8	Male	86.0 ± 10.2	74.0 ± 10.2	-13.8 ± 8.0	Hypertension -	83.1 ± 9.9	71.6 ± 9.8	-13.8 ± 7.8
Old	78.3 ± 8.9	68.5 ± 9.7	-12.4 ± 8.1	Female	81.3 ± 9.7	70.2 ± 9.5	-13.5 ± 7.9	Hypertension +	84.8 ± 10.6	73.1 ± 10.3	-13.6 ± 8.1
p-value unadj.	0.0001	0.0001	0.001	p-value unadj.	0.0001	0.0001	0.457	p-value unadj.	0.004	0.007	0.698
p-value adj.	0.0001	0.0001	0.001	p-value adj.	0.0001	0.0001	0.793	p-value adj.	0.033	0.002	0.271
PWV (m/s)				PWV (m/s)				PWV (m/s)			
Young	10.0 ± 2.5	9.6 ± 2.5	-4.6 ± 7.8	Male	10.3 ± 2.7	10.0 ± 2.8	-2.6 ± 8.3	Hypertension -	10.2 ± 2.7	9.7 ± 2.8	-4.7 ± 7.7
Old	12.7 ± 1.9	12.5 ± 1.9	-1.9 ± 7.2	Female	11.2 ± 2.4	10.6 ± 2.4	-5.5 ± 6.6	Hypertension +	11.3 ± 2.4	10.9 ± 2.4	-3.0 ± 7.6
p-value unadj.	0.0001	0.0001	0.0001	p-value unadj.	0.0001	0.0001	0.0001	p-value unadj.	0.0001	0.0001	0.0001
p-value adj.	0.0001	0.0001	0.0001	p-value adj.	0.0001	0.970	0.0001	p-value adj.	0.0001	0.0001	0.157
AIx (%)				AIx (%)				AIx (%)			
Young	15.4 ± 18.4	28.1 ± 34.0	+82.5 ± 99.2	Male	8.1 ± 15.5	23.3 ± 38.6	+187.7 ± 335.0	Hypertension -	16.1 ± 18.5	30.7 ± 33.8	+90.7 ± 102.0
Old	24.0 ± 19.3	46.2 ± 44.8	+92.5 ± 82.0	Female	29.3 ± 16.3	44.1 ± 33.3	+50.5 ± 33.1	Hypertension +	19.1 ± 19.4	34.6 ± 41.7	+81.2 ± 90.1
p-value unadj.	0.0001	0.0001	0.885	p-value unadj.	0.0001	0.0001	0.714	p-value unadj.	0.008	0.072	0.784
p-value adj.	0.0001	0.0001	0.959	p-value adj.	0.0001	0.0001	0.797	p-value adj.	0.003	0.290	0.750

Table S2. Continues.

Dyslipidemia – vs. +	**Day**	**Night**	**Δ day-night (%)**	**Diabetes – vs. +**	**Day**	**Night**	**Δ day-night (%)**	**Metabolic syndrome - vs. +**	**Day**	**Night**	**Δ day-night (%)**
bSBP (mmHg)				bSBP (mmHg)				bSBP (mmHg)			
Dyslipidemia -	132.2 ± 14.8	118.2 ± 15.9	-10.5 ± 7.5	Diabetes -	131.7 ± 14.6	117.8 ± 15.7	-10.4 ± 7.7	Metabolic syndrome -	131.9 ± 15.0	118.0 ± 15.8	-10.5 ± 7.4
Dyslipidemia +	131.2 ± 14.2	118.3 ± 16.1	-9.8 ± 8.1	Diabetes +	135.8 ± 15.0	124.1 ± 18.6	-8.7 ± 8.1	Metabolic syndrome +	132.0 ± 14.0	118.6 ± 16.2	-10.1 ± 8.2
p-value unadj.	0.271	0.920	0.113	p-value unadj.	0.016	0.001	0.052	p-value unadj.	0.961	0.535	0.394
p-value adj.	0.008	0.006	0.337	p-value adj.	0.018	0.013	0.534	p-value adj.	0.722	0.503	0.380
bDBP (mmHg)				bDBP (mmHg)				bDBP (mmHg)			
Dyslipidemia -	82.9 ± 10.1	71.0 ± 9.9	-14.2 ± 8.0	Diabetes -	82.8 ± 10.2	71.0 ± 9.9	-14.1 ± 8.0	Metabolic syndrome -	82.8 ± 10.1	71.0 ± 10.0	-14.0 ± 8.0
Dyslipidemia +	82.0 ± 10.1	70.8 ± 10.0	-13.5 ± 8.0	Diabetes +	80.5 ± 9.7	69.8 ± 9.8	-13.1 ± 7.6	Metabolic syndrome +	82.5 ± 10.3	70.8 ± 9.8	-13.9 ± 8.0
p-value unadj.	0.186	0.797	0.167	p-value unadj.	0.043	0.286	0.307	p-value unadj.	0.704	0.754	0.863
p-value adj.	0.172	0.339	0.913	p-value adj.	0.155	0.221	0.911	p-value adj.	0.240	0.670	0.344
aSBP (mmHg)				aSBP (mmHg)				aSBP (mmHg)			
Dyslipidemia -	120.3 ± 13.2	109.0 ± 14.7	-9.3 ± 7.7	Diabetes -	120.1 ± 13.1	109.0 ± 14.5	-9.2 ± 7.9	Metabolic syndrome -	120.0 ± 13.4	108.9 ± 14.7	-9.2 ± 7.6
Dyslipidemia +	120.2 ± 12.6	110.1 ± 14.8	-8.4 ± 8.4	Diabetes +	123.1 ± 12.4	114.2 ± 16.7	-7.4 ± 8.5	Metabolic syndrome +	120.7 ± 12.4	110.1 ± 14.8	-8.7 ± 8.5
p-value unadj.	0.867	0.277	0.053	p-value unadj.	0.049	0.003	0.051	p-value unadj.	0.389	0.178	0.286
p-value adj.	0.014	0.012	0.555	p-value adj.	0.126	0.087	0.600	p-value adj.	0.730	0.478	0.586
aDBP (mmHg)				aDBP (mmHg)				aDBP (mmHg)			
Dyslipidemia -	84.1 ± 10.2	72.3 ± 10.0	-13.8 ± 7.9	Diabetes -	84.1 ± 10.3	72.4 ± 10.1	-13.7 ± 7.9	Metabolic syndrome -	84.0 ± 10.2	72.4 ± 10.1	-13.7 ± 7.8
Dyslipidemia +	83.4 ± 10.2	72.2 ± 10.1	-13.3 ± 8.0	Diabetes +	81.9 ± 9.7	71.3 ± 9.9	-12.9 ± 7.9	Metabolic syndrome +	83.8 ± 10.4	72.2 ± 10.0	-13.7 ± 8.1
p-value unadj.	0.300	0.889	0.222	p-value unadj.	0.070	0.338	0.348	p-value unadj.	0.811	0.686	0.938
p-value adj.	0.264	0.331	0.943	p-value adj.	0.228	0.270	0.925	p-value adj.	0.205	0.737	0.344
PWV (m/s)				PWV (m/s)				PWV (m/s)			
Dyslipidemia -	10.4 ± 2.7	9.9 ± 2.8	-4.4 ± 7.9	Diabetes -	10.6 ± 2.6	10.2 ± 2.7	-4.1 ± 7.8	Metabolic syndrome -	10.3 ± 2.8	9.8 ± 2.8	-4.6 ± 7.9
Dyslipidemia +	11.5 ± 2.1	11.2 ± 2.1	-2.6 ± 7.2	Diabetes +	11.8 ± 2.0	11.6 ± 1.9	-1.7 ± 6.0	Metabolic syndrome +	11.5 ± 2.1	11.2 ± 2.1	-2.7 ± 7.1
p-value unadj.	0.0001	0.0001	0.000	p-value unadj.	0.0001	0.0001	0.010	p-value unadj.	0.0001	0.0001	0.0001
p-value adj.	0.087	0.821	0.758	p-value adj.	0.990	0.714	0.500	p-value adj.	0.002	0.0001	0.014
AIx (%)				AIx (%)				AIx (%)			
Dyslipidemia -	16.8 ± 18.9	31.1 ± 34.8	+85.1 ± 95.5	Diabetes -	17.5 ± 19.1	32.0 ± 37.0	+82.9 ± 93.1	Metabolic syndrome -	16.7 ± 19.1	31.4 ± 36.0	+88.0 ± 100.8
Dyslipidemia +	19.5 ± 19.3	36.3 ± 44.5	+85.6 ± 95.0	Diabetes +	17.8 ± 17.7	40.1 ± 46.5	+125.3 ± 134.9	Metabolic syndrome +	18.9 ± 18.9	34.5 ± 40.8	+82.5 ± 90.1
p-value unadj.	0.030	0.036	0.906	p-value unadj.	0.889	0.067	0.951	p-value unadj.	0.057	0.168	0.849
p-value adj.	0.332	0.309	0.812	p-value adj.	0.141	0.575	0.948	p-value adj.	0.487	0.141	0.947

Table S2. Continues.

CV disease - vs. +	Day	Night	Δ day-night (%)
bSBP (mmHg)			
CV disease -	131.9 ± 14.5	117.8 ± 15.5	-10-6 ± 7.6
CV disease +	132.3 ± 15.8	122.2 ± 18.9	-7.7 ± 8.1
p-value unadj.	0.792	0.005	0.0001
p-value adj.	0.606	0.238	0.025
bDBP (mmHg)			
CV disease -	83.0 ± 10.0	71.0 ± 9.8	-14.3 ± 7.9
CV disease +	79.6 ± 10.7	70.3 ± 11.2	-11.7 ± 8.0
p-value unadj.	0.001	0.461	0.001
p-value adj.	0.009	0.673	0.010
aSBP (mmHg)			
CV disease -	120.2 ± 13.0	108.9 ± 14.4	-9.3 ± 7.8
CV disease +	120.8 ± 13.8	113.2 ± 17.1	-6.3 ± 8.4
p-value unadj.	0.662	0.003	0.0001
p-value adj.	0.305	0.518	0.027
aDBP (mmHg)			
CV disease -	84.3 ± 10.1	72.4 ± 9.9	-13.9 ± 7.9
CV disease +	80.5 ± 10.8	71.3 ± 11.3	-11.3 ± 7.9
p-value unadj.	0.0001	0.280	0.001
p-value adj.	0.002	0.403	0.008
PWV (m/s)			
CV disease -	10.5 ± 2.6	10.1 ± 2.6	-4.1 ± 7.7
CV disease +	12.2 ± 2.2	11.9 ± 2.2	-2.2 ± 7.8
p-value unadj.	0.0001	0.0001	0.011
p-value adj.	0.513	0.699	0.781
AIx (%)			
CV disease -	17.0 ± 18.9	31.5 ± 37.8	+85.3 ± 98.6
CV disease +	22.8 ± 19.5	42.7 ± 35.3	+86.8 ± 73.2
p-value unadj.	0.002	0.002	0.962
p-value adj.	0.139	0.592	0.871