Morning surge, pulse wave velocity, and autonomic function tests in elderly adults

Diego F. Sanchez Gelós, Matilde E. Otero-Losada, Francisco Azzato and José Milei

Objective **To assess the complex interplay between morning surge (MS), the autonomic reflex response at the cardiovascular level, and target organ damage (arterial stiffening, left ventricle hypertrophy).**

Methods **Fifty-nine consecutive elder patients (>65 years old) underwent a 24-h ambulatory blood pressure monitoring. Pulse wave velocity (PWV) was measured as an indicator of arterial stiffness. Autonomic status was assessed by scoring five conventional tests [handgrip, orthostatic pressor response, Valsalva maneuver, heart rate variation during deep breathing ('I:E'), and immediate heart rate response to standing ('30 : 15')].**

Results **(a) MS was correlated to left ventricle mass ($P<0.005$), the orthostatic pressor response ($P<0.02$), and blood pressure variability (BPVar) ($P<0.0001$) ($n=59$). (b) PWV explained 61.4% of MS variation for MS values 40 mmHg or less (84% of patients) ($P<0.03$, $n=49$) and 38% of MS variation in nondippers ($P<0.04$, $n=25$). (c) There were sex-related differences. PWV was associated with the orthostatic pressor response ($P<0.02$), 'I:E' values ($P<0.04$) and the '30 : 15' test ($P<0.04$) in men ($n=14$). In women ($n=41$), the 'I:E' values were associated with MS and BPVar ($P<0.003$).**

Conclusion **MS was closely related to PWV (arterial stiffening) and BPVar in a small urban sample of cardiovascular patients. MS was also associated with dysautonomia (orthostatic blood pressure/heart rate response to challenges), mostly with impaired parasympathetic modulation. MS and high BPVar cause left ventricular hypertrophy, whereas arterial stiffness alters baroreceptor sensitivity, which in turn affects BPVar, perpetuating a vicious cycle. These findings, although obtained in a small number of participants, provide relevant information not yet available in the local databases.** ***Blood Press Monit*** **17:103–109** © **2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Keywords: arterial stiffness, autonomic tests, blood pressure variability, left ventricular hypertrophy, morning surge, pulse wave velocity

Institute of Cardiological Research (ININCA), University of Buenos Aires, National Research Council (UBA-CONICET), Buenos Aires, Argentina

Correspondence to Jose Milei, MD, PhD, Institute of Cardiological Research (ININCA), University of Buenos Aires, National Research Council (UBA-CONICET), Marcelo T de Alvear 2270 (C1122AAJ), Buenos Aires, Argentina
Tel/fax: +54 114 508 3888; e-mail: ininca@fmed.uba.ar

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Introduction

Circadian rhythm in blood pressure (BP) is characterized by a sharp decline in BP during sleep (dipping) and a variable increase upon awakening [morning surge (MS)]. This pattern results from the 24-h cyclic modulation by both neurohumoral factors and the activity of the sympathetic nervous system [1]. The clinical importance of MS is related to its association with an increased cardiovascular risk mainly in hypertensive patients and in the general population as well [2,3]. However, elevated systolic blood pressure (SBP) during sleep is an independent, powerful predictor of cardiovascular risk [4].

In the past, the relevance of MS in BP was not fully understood partly because prospective studies have yielded inconclusive information due to the lack of uniformity in conceptual definitions, experimental context, and designs [3,4].

However, recent studies carried out by the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) have shed light on blood pressure variability (BPVar) over 24 h [5], the prognostic accuracy of day versus night ambulatory BP [4], and MS as a destabilizing factor of atherosclerotic plaque [6]. Recently, the same international group reported that MS values above the 90th percentile predicted cardiovascular outcome and might contribute to risk stratification by ambulatory blood pressure monitoring (ABPM) [3].

Nevertheless, despite these advances, the relationships between MS and BPVar, pulse wave velocity (PWV), and baroreceptor dysfunction have been rarely if even evaluated. In this sense, the increase in BPVar may be attributable to increased stiffness and decreased

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compliance of large elastic arteries caused by high BP [7]. Both increased stiffness of large arteries [8] and high BPVar are associated with cardiovascular morbidity and mortality in hypertensive patients and the general population as well [7].

However, aged hypertensive patients with either orthostatic hypertension or orthostatic hypotension are at a high risk of developing hypertensive cerebrovascular disease [9]. Therefore, the carotid baroreflex is very important in BP modulation particularly during orthostatic stress in the elderly. Baroreceptor dysfunction can cause fatal complications [10], and from 25 to 50% of patients with symptomatic autonomic dysfunction have died within 5–10 years after diagnosis [11].

On the basis of these concepts, we hypothesize that increased stiffness of large arteries reduces baroreceptor sensitivity, leading to increased pressure variability in due time. High pressure variability may be especially important during the morning hours.

This study aims to evaluate the association between MS and arterial stiffness in a small sample of individuals above 65 years old (elders) undergoing clinical, echocardiographical and autonomic nervous system evaluations. Thus, the outcomes of this study may yield useful information and contribute toward a better understanding of the complex interplay between MS, arterial stiffness, and cardiovascular reflex responses mediated by the autonomic system.

Methods

Fifty-nine consecutive ambulatory patients above 65 years of age were enrolled in this study. There were 15 men and 44 women between 65 and 91 years of age (76 ± 2 and 74 ± 1 years, respectively), who were assessed clinically and neurologically. Routine laboratory analyses were performed, which included the following: blood cell count and determination of glucose, urea, creatinine, uric acid, total cholesterol and high-density lipoprotein cholesterol and low-density lipoprotein cholesterol fractions, triglycerides, and potassium levels in plasma, together with microalbuminuria and urinary sediment examination. The patients underwent an electrocardiographic evaluation and they were subjected to 24-h Holter monitoring, eco-Doppler from heart and supra aortic vessels, and 24-h ABPM. The conventional five-test battery of Ewing's protocol was administered to the patients [12] to assess both parasympathetic function (the immediate heart rate response to standing '30 : 15', heart rate variation during deep breathing 'E:I', and the Valsalva maneuver) and sympathetic function (orthostatic pressor response and handgrip tests). The results were classified into four categories: normal, early parasympathetic damage (one out of three parasympathetic function tests abnormal), parasympathetic damage (at least two of the tests of parasympathetic function abnormal), and combined parasympathetic and sympathetic damage (abnormal parasympathetic tests plus at least one sympathetic test altered) [12].

BP was measured after a 5-min rest period in the sitting position at the clinical office using an automatic BP monitor (Omron Hem-742INT; Omron Healthcare Inc., Vernon Hills, Illinois, USA). Noninvasive ABPM was performed for 24 h using one of three automatic devices (ABPM-Spacelab 90207-30, SpaceLab Inc. Redmond, Washington, USA), which recorded BP and heart rate every 15 min during daytime and every 20 min in the night. The sleep-through MS in BP was defined as the mean SBP during the 2 h after awakening minus the mean SBP of the hour that included the lowest sleep SBP [13].

Ambulatory BPVar was estimated as the SD of the 24-h mean (systolic and diastolic) BP recording [14]. BMI was calculated as the ratio between body weight (kg) and the squared height (m^2). PWV, a classic index of arterial stiffness, was measured along the descending thoracoabdominal aorta using the validated foot-to-foot velocity method [15]. Briefly, waveforms were obtained transcutaneously over the common carotid artery and the right femoral artery, and the time delay (t) was measured between the feet of the two waveforms. The distance (D) covered by the waves was assimilated to the distance measured between the two recording sites. PWV was calculated as $PWV = D/t$ (m/s) [15].

Thirty-nine (66.1%) patients had normal office BP values at the time of the study.

After inclusion in the protocol, all hypertensive patients being treated with angiotensin-converting enzyme inhibitors (enalapril), diuretics (furosemide, hydrochlorothiazide), and/or calcium antagonists (amlodipine) continued their respective treatments.

The following were considered as the exclusion criteria: evident illness at the time of study, patients with bradycardia and chronically treated with β blockers, arrhythmia (including atrial fibrillation), severe anemia, diabetic autonomic neuropathy, Guillain–Barré syndrome, and heart failure [10,16].

All participants were ambulatory and provided written consent for the study. This protocol was approved by the Bioethics Committee of the Instituto de Investigaciones Cardiológicas 'Profesor Dr Alberto C. Taquini', University of Buenos Aires – National Research Council (CONICET).

Statistical procedures

After a multiple analysis of variance, data were subjected to multidimensional scaling and bivariate correlation analyses (Pearson's product–moment correlation coefficient) to evaluate the degree of association between pairs of variables. A standard statistical package was used (SPSS version 15.0; SPSS Inc., Chicago, Illinois, USA).

Regression analyses were performed and regression plots (regression lines and 95% prediction intervals) were constructed using GraphPad PRISM 5.0. (San Diego, California, USA).

Results

Demographic and clinical data are summarized in Table 1.

A correlation was found for MS in BP with left ventricle mass (LVM) ($r = 0.420$, $P < 0.005$), left ventricular index (i.e. LVM adjusted for BMI) ($r = 0.400$, $P < 0.008$), the orthostatic pressor response ($r = -0.575$, $P < 0.02$), and BPVar ($r = 0.648$, $P < 0.0001$). Actually, MS accounted for 41% of BPVar (Fig. 1). These relationships are summarized and contextualized in Fig. 2.

PWV explained 61.4% of MS variation for MS values of 40 mmHg or less (40 mmHg = mean MS + 1 SD, 84% of patients) ($r = 0.784$, $P < 0.03$, $n = 49$) (Fig. 3) and 38% of MS variation in nondippers ($r = 0.614$, $P < 0.04$, $n = 25$).

Sex-related differences were observed for some relationships. PWV was directly proportional to the orthostatic pressor response ($r = 0.574$, $P < 0.02$) and the heart rate variation during deep breathing ('I:E') ($r = 0.610$, $P < 0.04$) and it was inversely proportional to the immediate heart response to standing ('30 : 15' = RR30/RR15) ($r = -0.571$, $P < 0.04$) (Fig. 4a–c, $n = 14$) in men. In women, heart rate variation during deep breathing ('I:E') ($r = -0.560$, $P < 0.003$) was inversely associated with MS and BPVar (Fig. 4d and e) ($n = 41$).

PWV explained 13% variation in microalbuminuria ($r = 0.356$, $P < 0.02$, $n = 41$), whereas MS did not ($r = 0.089$, NS). Nondipping behavior strengthened the correlation between PWV and microalbuminuria (31% variation explained, $r = 0.559$, $P < 0.05$, $n = 13$) whereas dipping behavior showed microalbuminuria relationship with LVM (22% reciprocal variation explained, $r = 0.474$, $P < 0.04$, $n = 19$).

Higher LVM values were associated with the presence of carotid plaques ($F_{1,15} = 12.88$, $P < 0.003$).

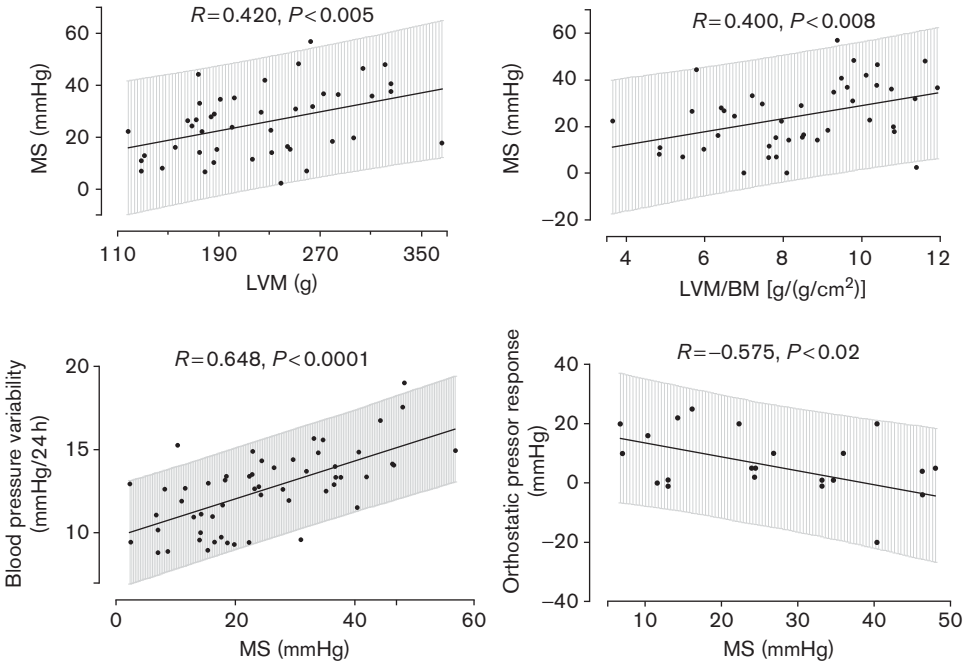
Considering that parasympathetic and sympathetic tones differ between night and day, some associations between variables might likely change if only daytime or nighttime values were used. This hypothesis with interesting clinical implications may be evaluated in future studies.

Table 1 Demographic, clinical and laboratory parameters of patients (data are expressed as mean ± SD or as percentage)

Measure	Men	Women	Total
Age (years)	76.47 ± 5.85	73.2 ± 6.46	74.03 ± 6.43
Anthropometrics			
Weight (kg)	83.57 ± 11.34	64.06 ± 9.21	69.02 ± 12.94
Height (m)	1.7 ± 0.06	1.56 ± 0.07	1.6 ± 0.09
BMI (kg/m^2)	28.79 ± 3.76	26.32 ± 3.84	26.95 ± 3.94
Body surface area (m^2)	2.91 ± 0.22	2.44 ± 0.21	2.56 ± 0.29
Waist (cm)	105 ± 10.03	91.43 ± 10.61	94.88 ± 11.97
Hip (cm)	101.43 ± 8.35	99.97 ± 9.78	100.34 ± 9.39
Waist-to-hip ratio	1.04 ± 0.08	0.92 ± 0.1	0.95 ± 0.11
Pulse wave velocity (m/s)	15.71 ± 2.38	13.57 ± 2.57	14.07 ± 2.66
At clinical office			
SBP (mmHg)	127.33 ± 11.7	135.89 ± 17.76	133.71 ± 16.76
DBP (mmHg)	75.07 ± 9.18	76.57 ± 11.34	76.19 ± 10.77
Heart rate (beats/min)	63.53 ± 7.41	66.77 ± 9.16	65.95 ± 8.82
Ambulatory blood pressure monitoring			
SBP (mmHg)	130.33 ± 9.68	127.52 ± 12.63	127.40 ± 13.21
DBP (mmHg)	75.13 ± 7.51	70.7 ± 8.50	72.02 ± 8.08
Heart rate (beats/min)	68.36 ± 8.89	70.43 ± 8.38	70.95 ± 9.79
Left ventricle mass			
Absolute value (g)	253.48 ± 62.98	212.67 ± 58.9	221.94 ± 61.58
Relative to body surface area (g/m^2)	86.16 ± 21.84	87.75 ± 24.67	87.39 ± 23.82
Smokers (%)	37.5	38.6	25.4
Chronic obstructive pulmonary disease (%)	6.3	9.1	5.8
Arterial hypertension (%)	68.8	84.1	78.4
Diabetes (%)	12.5	13.6	13.7
Sedentarism (%)	12.5	25.0	25.4
Chronic kidney disease (%)	6.3	6.8	5.8
Heart failure history (%)	0	6.8	7.8
Coronary disease (%)	0	4.5	3.8
Stroke (%)	0	18.2	7.8
Dyslipidemia (%)	31.3	54.5	25.4
Cholesterol (mmol/dl)			
Total	211.33 ± 28.67	201.76 ± 40.02	204.1 ± 37.51
LDL fraction	138.67 ± 33.4	121.47 ± 32.19	124.91 ± 32.79
HDL fraction	51.18 ± 15.33	57.06 ± 12.09	55.68 ± 12.98
Triglycerides (mmol/dl)	142 ± 129.13	128.68 ± 59.89	131.47 ± 77.61
Microalbuminuria (mg/24 h)	20.06 ± 28.02	21.56 ± 69.1	21.18 ± 61.09
Amount of antihypertensive drugs (daily intake)	1.20 ± 1.08	1.73 ± 1.25	1.59 ± 1.22

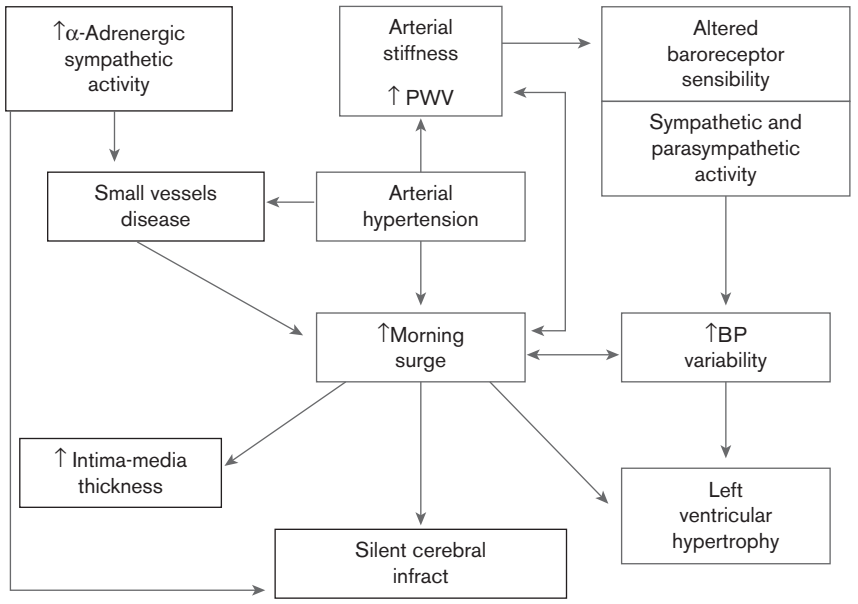
DPB, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure.

Fig. 1



Morning surge (MS) relationship with left ventricle mass (LVM), left ventricular index (LVI=LVM/BMI), blood pressure variability and the orthostatic pressor response.

Fig. 2

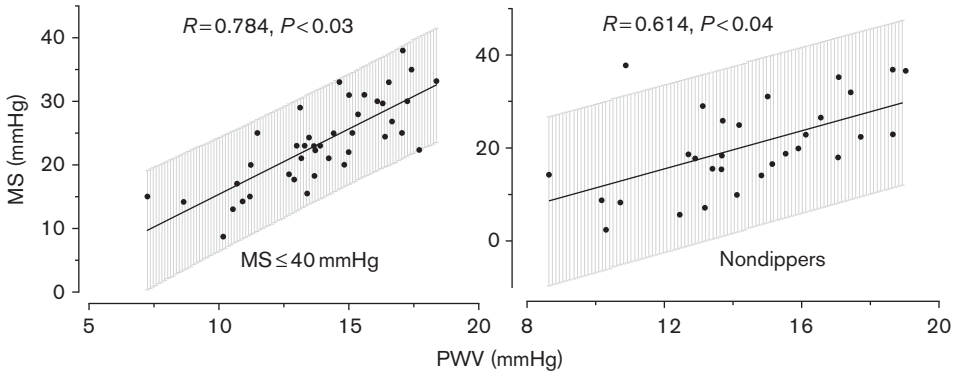


Morning surge was closely correlated to pulse wave velocity (PWV) and blood pressure (BP) variability in all patients. Morning surge and high blood pressure variability are known to cause left ventricular hypertrophy, whereas arterial stiffness alters baroreceptor sensitivity, which in turn affects blood pressure variability, perpetuating a vicious cycle.

Discussion

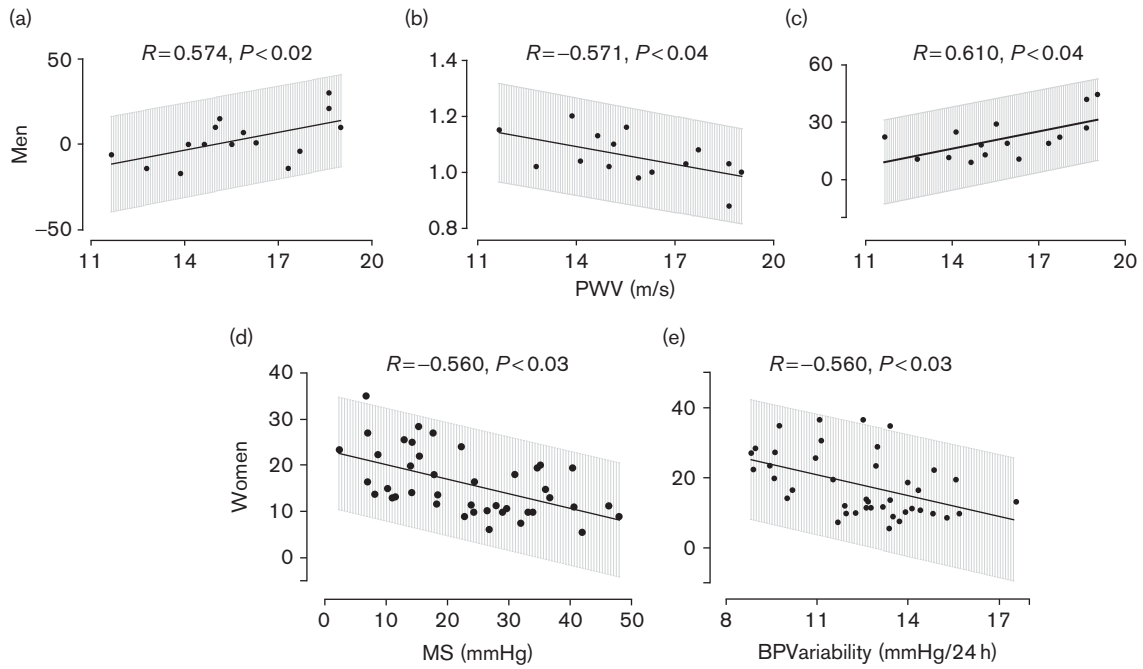
MS in BP was correlated to LVM, left ventricular index (LVI = LVM/BMI), the orthostatic pressor response, and BPVar. From a mathematical point of view, MS–BPVar correlation should be expected, whereas it is biologically reasonable that MS may relate to LVM and LVI, which

Fig. 3



Morning surge (MS) relation to pulse wave velocity (PWV).

Fig. 4



Sex-related differences in the interplay of autonomic function with morning surge (MS), blood pressure variability (BPVar), and pulse wave velocity (PWV). PWV correlation with the orthostatic pressor response (a), the immediate heart rate response to standing ('30 : 15'') (b), and the heart rate variation during deep breathing ('I:E') (c) in men. Heart rate variation during deep breathing ('I:E') correlation with MS (d), and BPVar (e) in women.

reflect cardiovascular target organ damage. These observations are in agreement with published data showing that high MS values may cause progression of cardiovascular remodeling, which in turn may predict future cardiovascular morbidity and mortality [17]. Previously, MS has been associated with cardiovascular remodeling in elderly hypertensive patients being treated by antihypertensive medications [18]. In agreement with others, we observed that the magnitude of MS was related to the severity of hypertensive target organ damage [19,20].

All patients in our study showed orthostatic hypertension (only one patient had orthostatic hypotension), in agreement with a previous report involving elderly patients [21]. The fact that orthostatic hypertension (easily detected by BP monitoring) has been proposed to be a high-risk factor for cardiovascular events in elderly hypertensives is of clinical importance [21]. The increase in orthostatic BP is selectively abolished by α-adrenergic blocking, indicating that α-adrenergic activity is the predominant pathophysiologic mechanism of orthostatic hypertension [9].

A strong correlation was observed between PWV and MS for MS values of 40 mmHg or less. This cutpoint resulted from the calculation of 'mean MS value + 1 SD', which, by definition, equals the 84th percentile of the total population. PWV was also correlated with MS values in nondippers, who, interestingly, had MS values of 40 mmHg or less as well [22].

Sex influenced some bivariate associations. In men, PWV values were related to the outcome of three autonomic tests (the orthostatic pressor response, heart rate variation during deep breathing, and the immediate heart rate response to standing), whereas one autonomic test (heart rate variation during deep breathing) was related to MS and BPVar in women. These observations suggest that deregulation of cardiac autonomic reflexes in elderly hypertensive patients could be more related to arterial stiffening in men and with MS (and BPVar) in women. In addition, cardiac autonomic reflexes would be more widely affected in men than in women and would mainly involve an impairment in parasympathetic modulation. Nevertheless, these hypotheses need to be contrasted in a larger number of participants.

Neither the PWV nor the orthostatic pressor response could fully account for MS changes, indicating that additional factors contribute to the increase in BP in the early hours after awakening.

Left ventricular hypertrophy was directly proportional to the increase in BPVar. However, as this was a cross-sectional observation, this finding cannot be interpreted in terms of causal links between MS (or BPVar) and organ damage.

From the seminal papers by Kario *et al.* [2,9,13], higher morning BP surge is accepted as an independent risk factor of atherosclerotic events irrespective of ambulatory BP values and nocturnal BP falls (dipping). MS in BP has also been identified as the strongest independent predictor of silent and clinical cerebrovascular disease in elderly hypertensive patients [2,13] in association with increased α-adrenergic sympathetic activity [23]. Moreover, surge in morning BP is a destabilizing factor of atherosclerotic plaque that is related to inflammation-induced plaque ruptures and increased intima-media thickness [6].

Arterial stiffening associated with hypertension reduces baroreceptor sensitivity, which is evidenced by deviation from the normal response in parasympathetic and sympathetic tests. A correlation between MS and PWV was observed neither in normotensive nor in hypertensive patients.

As previously mentioned, MS and BPVar (which involves autonomic alterations) were closely related to each other. In turn, MS and high BPVar are known to induce left ventricular hypertrophy [3,14].

In the recent prospective study by the IDACO group, a MS above the 90th percentile significantly and independently predicted cardiovascular outcome and might have contributed to risk stratification by ABPM [3]. In this study, using the 84th percentile as the breakpoint (mean value of MS + 1 SD), we found that MS and PWV were reciprocally related in all elderly patients (> 65 years) whose MS values were 40 mmHg or less (Fig. 3).

This value is higher than that used by Kario *et al.* [2], in the pioneer paper, where they compared the risk of silent and clinical cerebrovascular diseases in the top decile (≥ 55 mmHg) of the systolic sleep-through MS with the risk in the other patients. This value was also higher than that reported by Wizner *et al.* [24] (≥ 35 mmHg in Europeans and South Americans and ≥ 43 mmHg in Asians).

Conversely, as suggested in the study by the IDACO group [3] a sleep-through or preawakening MS in SBP less than 20 mmHg is probably not associated with an increased risk of death or cardiovascular events.

Ambulatory BPVar measured as the SD of the overall 24-h BP recording has been widely used and is positively related to organ damage and predicts worsening over time [14]. In the present study, BPVar was linearly dependent on MS in all patients ($P < 0.0001$). In nondippers, reliable correlations ($P < 0.001$) were observed for BPVar with PWV and for LVM with BMI.

As it has been widely demonstrated that MS is an independent predictor of mortality and cardiovascular events, in the present study, we show that various factors causing structural damage (i.e. left ventricle hypertrophy) are present in the elderly independent of established hypertension [25] and are related to each other.

MS may cause anatomical damage to the large arteries if the pressure load during the morning period repeatedly exceeds the buffering capacity of the arterial walls [6,26,27]. Thus, rupture of elastin fibers, disarrangement, and hypertrophy of the arterial muscular layers due to an exaggerated or persistent pressure on the arterial wall [13,16] may induce plaque rupture [6,28]. These factors might be especially important in atherosclerotic arteries [13,26,28], in the presence of oxidative stress [29], and in elderly patients with altered baroreflexes [16,23]. We have recently reported that barochemoreceptors are target organs in spontaneously hypertensive rats [30,31] and in hypertensive patients who died from stroke. These structures showed moderate-to-severe atrophy and fibrosis. Loss of the characteristic chief cells (> 50%) and of the argyrophilic Grimelius staining granules at the glomus level suggested a decrease in the catecholamine content. The arterioles reaching the glomus showed severe fibrointimal proliferation, disruption of the internal elastic lamina, luminal narrowing, and luminal thrombi. Damaged nerve

endings (S-100 +) were observed at the media layer of the carotid sinus [16].

In conclusion and in terms of clinical implications, the most important aspect in this study was that the extent of MS was partly associated with PWV (arterial stiffness) and/or orthostatic BP/heart rate changes (autonomic function). Namely, the higher the PWV and/or the extent of autonomic function impairment, the larger the MS may be.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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