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Uncontrolled hypertension in older patients: markers and associated factors to masked and white-coat effect

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Abstract

Background Hypertension is the main risk factor for cardiovascular diseases, affecting more than half the elderly population. It is essential to know if they have proper control of hypertension. The aim of this study was to identify the associated factors to masked uncontrolled hypertension and false uncontrolled hypertension in older patients. **Methods** Two-hundred seventy-three individuals (70.1 ± 6.7 years-old) had blood pressure (BP) measured at the office and by ambulatory BP monitoring (ABPM), with the definition of controlled group (C), individuals with high office BP and adequate ABPM, called white-coat effect group (WCE), uncontrolled (UC), and subjects with appropriate office BP and elevated ABPM denominated masked effect group (ME). Age, body mass index, diabetes, pulse pressure (PP) and BP dipping during sleep were evaluated (Kruskal-Wallis test and logistic regression models). **Results** Age was higher in UC than in C and ME ($P < 0.01$), and 24-h ABPM PP was lower in C (48 ± 7 mmHg) and WCE (51 ± 6 mmHg) than in UC (67 ± 12 mmHg) and ME (59 ± 8 mmHg) ($P < 0.01$). Sleep systolic BP dipping was lower in ME than in C ($P = 0.03$). Female gender was associated with a greater chance of being of ME group, which showed a higher PP and lower BP dipping during sleep. **Conclusions** In older individuals, office BP measurements did not allow the detection of associated factors that would permit to differentiate WCE from UC group and C from ME group. ABPM favored the identification of a higher PP and a lower BP dipping during sleep in the masked effect and uncontrolled groups.

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Keywords: Ambulatory blood pressure monitoring; Hypertension; Masked effect; The aged; White coat effect

1 Introduction

Hypertension is the main risk factor for cardiovascular diseases, affecting more than half the elderly population. Considering the wide variation of blood pressure (BP) among the elderly during the 24-h period, ambulatory BP monitoring (ABPM) represents a particularly useful method for this population. BP obtained by ABPM shows better association with cardiovascular risk than office measurements.[1–3]

An individual on treatment for hypertension can be considered to be uncontrolled if only the office BP is taken into account, but may be controlled in ABPM, a false uncontrolled hypertension, fact related to the white coat effect (WCE). In this circumstance, there is no or low increase in cardiovascular risk, perhaps because the patients are under treatment for hypertension.[4–6] The risk of this situation is the prescription of more medications, with a higher risk of postural hypotension and reduced quality of life.

On the other hand, treated hypertensive individuals can have BP controlled in the office and high BP levels in 24-h ABPM, with a masked uncontrolled hypertension, condition that is explained by the masked effect. The cardiovascular risk of individuals who show this false control of BP has been shown to be high. Bobrie, *et al*.,[7] published a longitudinal follow-up for 3.2 years of hypertensive elderly people, which revealed a 3.4% rate of cardiovascular events among controlled subjects, 7.6% among uncontrolled individuals, and 8.9% among uncontrolled subjects with a masked effect. Greater thickening of the media and intima layers of the carotids, a greater concentric left ventricle hypertrophy[8,9] and early renal damage[8,10] were also observed in treated individuals with a high BP only outside the office.

Thus, knowing if the patients are controlled inside and outside the office is of fundamental importance. Although ABPM is the gold standard for the follow-up of hyperten-

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sive individuals under treatment, it is expensive and not widely available. Thus, the aim of this study was to identify associated factors and possible markers that point out individuals with a masked effect and elderly subjects with white coat effect, besides evaluate the prevalence of incorrect diagnosis based only in office evaluation.

2 Methods

Two-hundred and seventy-three hypertensive individuals aged 60 years or more were selected for the present study. The subjects regularly took antihypertensive medication(s), with no changes in prescriptions over the last two months, were regularly followed up at Public Health Services, were in good general condition and had no debilitating diseases. Exclusion criteria were alcohol abuse (more than 105 g alcohol per week), a diagnosis of renal failure, and uncontrolled hypothyroidism or hyperthyroidism as reported in their medical records. The procedures carried out in the study were authorized by the local Research Ethics Committee and all subjects gave written informed consent to participate.

The individuals were submitted to a general clinical examination and measurements of weight, height and body mass index (BMI). BP was measured on both arms by the auscultatory method using a mercury column sphygmomanometer, with phases I and V of the Korotkoff sounds being considered for the identification of systolic and diastolic arterial pressure, respectively. The measurements were made on two office visits separated by an interval of about one week, between 7: 00 and 10: 00 am. Three measurements were made on each arm during each visit, with the subjects resting in the sitting position for five minutes, with a two-minute interval between measurements. The mean BP obtained in the upper right limb was used for all subjects since no important differences (> 5 mmHg) were observed between the measurements obtained in the two arms of each volunteer.

ABPM was performed by installing a monitor (SPACELABS MEDICAL, model 90207) on the no dominant upper limb, permitting BP measurements and their recording over a period of 24 h. The instrument was programmed to obtain measurements at 15 min intervals during the period from 07: 00 to 23: 00 and at 30 min intervals from 23: 00 to 07: 00 of the subsequent morning.

The measurements were rejected when they showed systolic blood pressure (SBP) of less than 80 mmHg or more than 250 mmHg and diastolic blood pressure (DBP) of less than 40 mmHg or more than 140 mmHg and the recordings were considered to be valid for interpretation when they showed that 80% or more of the measurements were successfully made. The participants were instructed to maintain their habitual daily activities during the period of measurement and to maintain their no dominant upper limb in a loose and relaxed position, whenever possible, during each measurement. Diaries were supplied to the volunteers for a detailed description of their activities.

The mean values of all valid BP measurements (24-h ABPM) were calculated, as well as the mean values of the BP measurements obtained during the period when each individual reported to be awake on the basis of his diary (Awake ABPM) and of the measurements obtained during sleep (Sleep ABPM). The values considered to be abnormal in the present study were mean BP above 130/80 mmHg, 135/85 mmHg and 120/70 mmHg for 24-h, awake and sleep BP, respectively.[11] The difference between awake BP and sleep BP was calculated for each individual, characterizing SBP and DBP dipping during sleep. The percentage of BP dipping was also calculated for SBP and DBP.

The difference between SBP and DBP, called pulse pressure (PP), was calculated for the office measurements, for 24-h ABPM, awake ABPM and sleep ABPM. Values of more than 60 mmHg for the office measurements and more than 50 mmHg for ABPM measurements were considered to be altered.

Individuals with office BP lower than 140/90 mmHg and 24-h ABPM lower than 130/80 mmHg were defined as controlled (C); individuals with office BP of 140/90 mmHg or higher and 24-h ABPM lower than 130/80 mmHg were defined as WCE group; individuals with normal office BP and high 24-h ABPM as masked effect (ME) group; and individuals with elevated BP as determined by the two methods were defined as uncontrolled group (UC).

The nonparametric Kruskal-Wallis test was used to compare quantitative variables between groups. When this test was significant or borderline, the Dunn post-test was applied.

The simple and multiple logistic regression model was used to identify the factors associated with the groups under study[12] in order to obtain the crude and adjusted odds ratio (OR), respectively. The OR was adjusted for age, BMI, diabetes and PP.

All analyses were carried out using the SAS software version 9.0, with the level of significance set at $P < 0.05$.

3 Results

Two-hundred and seventy-three elderly hypertensive subjects under treatment, aged 60 to 91 years, met the inclusion criteria proposed. Mean age was 70.1 ± 6.7 years. There was a predominance of women (72.16%) and 11.7%

of the subjects had a diagnosis of diabetes. The descriptive characteristics of the participants were given in Table 1.

BMI was less than 26.9 kg/m^2 (normal or low weight) in 38.5% of the subjects, 27–29.9 kg/m^2 in 33% (overweight) and ≥ 30 kg/m^2 (obesity) in 28.5%.

Considering only the office measurements of systolic BP, 60.8% of the subjects were controlled when the 140 mmHg limit was used. When the 150 mmHg limit recently proposed by the Eighty Joint National Committee (JNC-8) was used, 75.1% were controlled. The office DBP measurement was below 90 mmHg in 84% of the subjects.

Office PP was below 60 mmHg, a value considered adequate, in 66% of the subjects, whereas in ABPM, with the normal limit below 50 mmHg, only 36% of the subjects were adequate in 24-h ABPM, 38% in awake ABPM and 37% in sleep ABPM.

Regarding SBP dipping during sleep compared to Awake SBP, 30% of the subjects showed BP elevation or maintenance during this period, 47% showed attenuated dipping (<10%), only 21% showed appropriate dipping (10%–20%), and 2% showed exacerbated dipping (> 20%). Regarding DBP, the values were 26%, 30%, 38% and 6%, respectively.

The percentage of elderly subjects classified as C was 41.4% (n = 113), WCE was 15.4% (n = 42), UC was 24.2% (n = 66), and ME was 19% (n = 52) (Table 1).

The groups studied did not differ in terms of gender, BMI (normal, low, overweight, obesity) or in terms of the prevalence of diabetes. Subjects in the UC group were older than C and ME subjects (P < 0.01). However, there is no difference between UC and WCE, groups with high blood pressure in the office. Figure 1 illustrates the age distribution among the groups. The number of antihypertensive drugs used was similar for all groups. Office PP was similar for C and ME and for WCE and UC (Figure 2).

PP obtained during 24-h ABPM was lower in group C (48 ± 7 mmHg) than in group UC (67 ± 12 mmHg) and ME (59 ± 8 mmHg) (P < 0.01). Similarly, PP was lower in the WCE group (51 ± 6 mmHg) than in the UC and ME groups (P < 0.01) (Figure 3). PP obtained during wake ABPM and sleep ABPM followed the same pattern.

SBP dipping was lower in group ME than in group C (2% ± 9% *vs*. 5% ± 12%, P = 0.03) and DBP dipping was lower in group UC than in group C (5% ± 9% *vs*. 10% ± 9%, P = 0.01). In group ME, 46.1% of the subjects showed SBP elevation during sleep, the same occurring in 23% of group C, 25.8% of group UC and 35.7% of group WCE (Table 2). Regarding DBP, most individuals showed appropriate dipping during sleep, except for group UC, in which attenuated dipping was predominant (Table 2).

Table 1. Clinical characteristics of the study sample.

Characteristics	C, n = 113	WCE, n = 42	ME, n = 52	UC, n = 66	Total, n = 273
Age, yrs	68.7 ± 6.1	71.4 ± 6.8	68.7 ± 6.0	72.9 ± 7.3	70.1 ± 6.7
Female, %	77.2%	70.0%	75.4%	63.4%	72.2%
BMI, kg/m^2	28.2 ± 0.1	26.8 ± 4.3	28.8 ± 4.1	27.0 ± 5.0	27.8 ± 4.4
NAHD	1.6 ± 0.7	1.9 ± 1.0	1.5 ± 0.8	1.5 ± 0.7	1.6 ± 0.8
Diabetes, %	10.9%	10.0%	13.1%	12.7%	11.7%
Office SBP, mmHg	120 ± 10	152 ± 10	127 ± 9	160 ± 15	136 ± 21
Office DBP, mmHg	73 ± 9	89 ± 14	75 ± 9	86 ± 13	79 ± 13
Office PP, mmHg	47 ± 10	63 ± 15	51 ± 9	74 ± 18	57 ± 17
24 h S ABPM, mmHg	117 ± 7	120 ± 10	139 ± 8	147 ± 14	129 ± 16
24 h D ABPM, mmHg	69 ± 7	68 ± 8	80 ± 9	80 ± 8	74 ± 10
24 h PP ABPM, mmHg	48 ± 7	51 ± 6	59 ± 8	67 ± 12	55 ± 11
Awake S ABPM, mmHg	119 ± 8	121 ± 11	140 ± 8	149 ± 14	130 ± 16
Awake D ABPM, mmHg	71 ± 8	70 ± 9	82 ± 9	82 ± 8	76 ± 10
Awake PP ABPM, mmHg	48 ± 8	52 ± 6	58 ± 8	67 ± 12	53 ± 12
Sleep S ABPM, mmHg	113 ± 13	116 ± 12	137 ± 13	144 ± 16	126 ± 19
Sleep D ABPM, mmHg	64 ± 8	65 ± 8	77 ± 10	77 ± 9	70 ± 11
Sleep PP ABPM, mmHg	49 ± 12	51 ± 7	60 ± 9	67 ± 12	56 ± 13
Nocturnal SBP dipping, %	6% ± 14%	4% ± 8%	2% ± 9%	3% ± 8%	4% ± 10%
Nocturnal DBP dipping, %	7% ± 7%	6% ± 9%	6% ± 10%	5% ± 9%	7% ± 9%

Data are presented as mean ± SD unless other indicated. ABPM: ambulatory blood pressure monitoring; BMI: body mass index; C: control; D: diastolic; DBP: diastolic blood pressure; S: systolic; SBP: systolic blood pressure; ME: masked effect; NAHD: number of antihypertensive drugs; PP: pulse pressure; UC: uncontrolled; WCE: white coat effect.

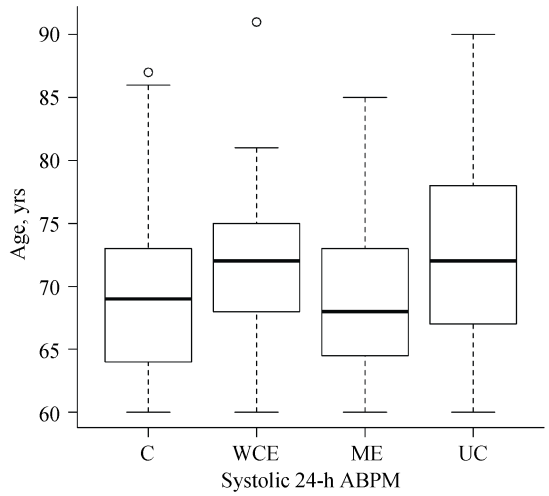

Figure 1. Box-plots representing age distribution in the C, WCE, ME and UC groups, obtained from systolic arterial pressure in ABPM (24-h). UC *vs*. C and UC *vs*. ME; $P < 0.01$. No difference between C and ME, and between UC and WCE. ABPM: ambulatory blood pressure monitoring; C: control; ME: masked effect; UC: uncontrolled; WCE: white coat effect.

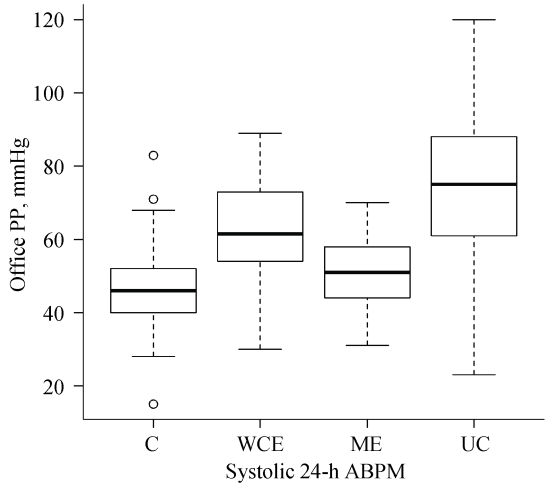

Figure 2. Box-plots representing office PP distribution in the C, WCE, ME and UC groups, obtained from systolic arterial pressure in ABPM (24-h). C *vs*. WCE, C *vs*. UC, WCE *vs*. ME and UC *vs*. ME; $P < 0.01$. No difference between C and ME, and between UC and WCE. ABPM: ambulatory blood pressure monitoring; C: control; ME: masked effect; PP: pulse pressure; UC: uncontrolled; WCE: white coat effect.

Table 3 presented the association between ME and selected factors using group C as reference. Female sex was found to be associated with a greater chance of ME.

The associations between WCE and selected factors are presented in Table 4 using group UC as reference. There was no significant association when the model was adjusted.

4 Discussion

The high risk of using only mean office BP values to follow-up elderly individuals is not simply to obtain higher percentages of control, but also to have poorly evaluated individuals. According to our results, subjects with supposedly controlled office BP have a chance of about 30% of actually being uncontrolled, with a masked effect. Overall, one third (34%) of patients were falsely classified based only on office BP measurements. In a previous study also conducted on elderly subjects, it was observed that, if only office BP had been used, 42% of individuals considered as uncontrolled, with controlled BP in ABPM, would not have been identified.[13]

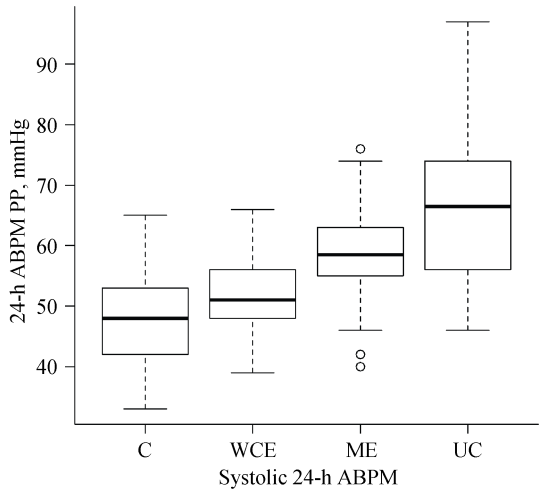

Figure 3. Box-plots representing PP distribution during 24-h ABPM in the C, WCE, ME and UC groups, obtained from systolic arterial pressure in ABPM (24-h). C *vs*. ME, C *vs*. UC, WCE *vs*. ME and WCE *vs*. UC, $P < 0.01$. No difference between C and WCE, and between ME and UC. ABPM: ambulatory blood pressure monitoring; C: control; ME: masked effect; PP: pulse pressure; UC: uncontrolled; WCE: white coat effect.

In most subjects, PP obtained by ABPM was higher than recommended, differing from what was observed for office PP. PP measured outside the office is better correlated with cardiovascular risk than office PP.[14] Analysis of the established groups revealed a lower PP in C and WCE, than in ME or UC subjects in terms of 24-h, awake and sleep ABPM. Thus, PP obtained during ABPM indicates a lower cardiovascular risk for C and WCE subjects and a higher cardiovascular risk for ME and UC subjects, in agreement with other studies that have assessed cardiovascular risk in these groups.[7,8,10]

Considering the present sample as a whole, only 21% had normal SBP dipping during sleep, with a 10% to 20% fall, while the percentage of DBP dipping was 38%. Analysis of the various groups showed that SBP dipping was lower in ME than in C subjects. This is an evidence of higher cardiovascular risk in the ME group, since a lower dipping is associated with a higher risk.[15,16] In addition,

Table 2. Distribution of the type of nocturnal systolic blood pressure dipping.

Type of dipping	24-h ABPM classification				
	C	WCE	ME	UC	Total
Reversed (S)	26 (23.0%)	15 (35.7%)	24 (46.1%)	17 (25.8%)	82
Attenuated (S)	50 (44.3%)	17 (40.5%)	19 (36.5%)	42 (63.6%)	128
Normal (S)	34 (30.0%)	9 (21.4%)	8 (15.5%)	7 (10.6%)	58
Exacerbated (S)	3 (2.7%)	1 (2.4%)	1 (1.9%)	0	5
Reversed (D)	21 (18.6%)	11 (26.2%)	19 (36.5%)	20 (30.3%)	71
Attenuated (D)	33 (29.2%)	12 (28.5%)	10 (19.2%)	26 (39.4%)	81
Normal (D)	47 (41.6%)	17 (40.5%)	22 (42.3%)	18 (27.3%)	104
Exacerbated (D)	12 (10.6%)	2 (4.8%)	1 (0.02%)	2 (3.0%)	17
Total	113	42	52	66	273

Data are presented as *n* (%) or *n*. Comparison of subgroups: $P < 0.01$ C *vs*. ME for systolic dipping and $P < 0.03$ for C *vs*. UC diastolic dipping. ABPM: ambulatory blood pressure monitoring; BP: blood pressure; C: control; D: diastolic; ME: masked effect; S: systolic; UC: uncontrolled; WCE: white coat effect.

Table 3. Factors associated with the masked uncontrolled hypertension (masked effect group) comparing to controlled BP.

Effect	Crude model			Adjusted model		
	Crude OR	95% CI	*P*-value	Adjusted OR	95% CI	*P*-value
Age	1.01	0.95–1.08	0.65	1.02	0.96–1.09	0.56
Gender F *vs.* M	3.81	1.24–11.74	0.02	3.93	1.26–12.21	0.02
BMI OW *vs.* LW-NW	1.12	0.43–2.91	0.82	1.15	0.42–3.17	0.79
BMI O *vs.* LW-NW	1.24	0.47–3.30	0.67	1.27	0.45–3.57	0.65
Diabetes Yes *vs.* No	1.80	0.60–5.39	0.29	1.78	0.56–5.62	0.33
PP A *vs.* N	0.73	0.19–2.80	0.65	0.55	0.13–2.40	0.43

A: abnormal (elevated); BMI: body mass index; BP: blood pressure; F: female; LW: low weight; M: male; N: normal (< 60 mmHg); NW: normal weigh; O: obesity; OW: overweight; PP: pulse pressure in office. Adjusted for age, gender, BMI, diabetes and PP.

Table 4. Factors associated with the false uncontrolled hypertension (white coat effect group) comparing to uncontrolled BP.

Effect	Crude model			Adjusted model		
	Crude OR	95% CI	*P*-value	Adjusted OR	95% CI	*P*-value
Age	0.95	0.89–1.01	0.12	0.95	0.88–1.02	0.18
Gender, F *vs.* M	0.35	0.14–0.92	0.03	0.41	0.15–1.17	0.10
BMI OW *vs.* LW-NW	0.67	0.24–1.85	0.44	0.62	0.20–1.94	0.42
BMI O *vs.* LW-NW	0.58	0.20–1.70	0.32	0.54	0.16–1.89	0.34
Diabetes Yes *vs.* No	1.11	0.30–4.16	0.88	1.20	0.28–5.12	0.81
PP A *vs.* N	0.39	0.16–0.94	0.04	0.44	0.16–1.17	0.10

A: abnormal (elevated); BMI: body mass index; BP: blood pressure; F: female; LW: low weight; M: male; O: obesity; OW: overweight; N: Normal (< 60 mmHg); NW: normal weigh; PP: pulse pressure in office. Adjusted for age, gender, BMI, diabetes and PP.

most ME subjects showed SBP elevation or maintenance during sleep. The reverse dipping pattern (BP elevation during sleep) is also associated with a higher cardiovascular risk. In a retrospective study, Kim, *et al*.,[17] detected a three times higher risk of death of cardiovascular origin in subjects with reverse dipping when compared to subjects with normal or attenuated dipping. In a prospective study on more than 3000 elderly subjects, Fagard, *et al*.,[18] reported a higher incidence of cardiovascular events with reverse dipping. In the current study, a lower DBP dipping was also observed during sleep in UC than in C subjects.

The groups studied here did not differ in terms of gender distribution, BMI or the prevalence of diabetes. UC subjects were older than C and WCE individuals. In a study of individuals aged 25 to 74 years, Abu-Saad, *et al*.,[19] detected an almost two-fold higher chance of hypertensive subjects with a known diagnosis to be uncontrolled every 10 additional years of age. It is known that the major cause of inadequate BP control is low adherence to pharmacological and non-pharmacological treatment.[20] Among the elderly, adherence to treatment may be impaired by various conditions which, although not inherent to age, are more prevalent in

this age range, such as cognitive deficit, depression, functional loss or coexistence of several diseases, with the need for multiple medications.

In the present study, the chance of a masked effect rather than controlled BP was three times higher among females than among males when office BP was within normal limits. Other studies, in contrast to the present one, have reported an association of male gender with masked hypertension; however, they studied younger samples and included untreated individuals.[21,22]

In the current study, comparing WCE to UC, both groups with high office BP, there was nothing that could differentiate WCE. It would be desirable to detect factors that may serve as an alert when office BP is elevated in order to identify the individuals that are controlled outside the office and would not need adjustment of their medication. A study conducted on 1087 hypertensive patients under treatment revealed that the PP measurement obtained by the doctor in the office showed a good correlation with SBP in the group who presented a WCE detected by ABPM. A value of 59.25 mmHg or higher for office PP was suggested to indicate a greater possibility of WCE in a patient, even though its sensitivity was only 52% and specificity 75%.[23] In the current study, both the WCE and UC groups showed high mean office values of more than 60 mmHg, with no significant differences between them.

Ben-Dov, *et al*.,[24] in a specific study of WCE, showed that this effect was higher on PP than on systolic BP (8.3% *vs*. 5.2%, $P \leq 0.0001$). Thus, although an important component of artery stiffness explains the increase in PP, a neurogenic mechanism is also involved. Supporting this statement, in the present study, individuals with WCE hypertension had a normal PP when evaluated by ABPM.

In a recent study, Sheppard, *et al*.,[25] analyzed multiple office measurements in an attempt to detect a pattern of pressure fall with repeated measures that might be of help for the identification of individuals more likely to have the WCE or the ME. Despite a high sensitivity, specificity and positive predictive value were low. Another study evaluated BP measurements obtained in the office but on a day preceding the visit, which were also ineffective in identifying individuals with WCE, suggesting that methods for BP measurements outside the office may be the best alternative since the WCE does not exist only in the presence of the doctor, but is also related to the environment.[26]

In conclusion, in older individuals, office BP measurements did not allow the detection of associated factors that would permit to differentiate WCE from UC group and C from ME group. There was only an association of female sex with a greater chance of being of ME group, but this information does not permit to exclude ABPM for the ideal evaluation of older subjects under treatment. ABPM favored the identification of a higher PP and a lower BP dipping during sleep in the ME and UC groups, providing information for a better understanding of these groups at high cardiovascular risk.

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