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ORIGINAL ARTICLE

The role of blood pressure variability in misdiagnosed clinic hypertension

Amos Cahan[1], Iddo Z Ben-Dov[2], Judith Mekler[1] and Michael Bursztyn[1]

Blood pressure (BP) assessment may be vulnerable to bias by increased BP variability. Uncertainty in determining BP control is inherent to the clinic setting. We analyzed a registry of 3949 patients referred for ambulatory BP monitoring. The difference between clinic and ambulatory readings was plotted against ambulatory BP variability, assessed by standard deviation. In addition, BP variability of patients with clinic and awake ambulatory hypertension was compared with that of patients with controlled BP and sustained hypertension, respectively. The average clinic–ambulatory systolic BP difference was $5 \pm 17/3 \pm 9$ mm Hg. Patients with >10-mm Hg systolic difference had higher systolic ambulatory BP standard deviation (14.9 ± 4.2 mm Hg) compared to patients with a difference of 0 to 10-mm Hg (standard deviation 12.5 ± 3.7 mm Hg). Patients with masking (negative clinic–ambulatory BP difference) also had comparatively higher standard deviation (14.4 ± 4.9 mm Hg $P<0.0001$). Greater ambulatory BP variability carried increased risk for both false diagnosis of hypertension (odds ratio (OR): 2.09, 95% confidence interval (CI): 1.58–2.76), and missed clinic diagnosis of hypertension (OR: 1.86, 95% confidence interval: 1.48–2.33). The former was more striking in women, in whom high variability carried greater odds for false diagnosis of hypertension (OR: 2.76, 95% confidence interval: 1.96–3.89). Thus, clinic misjudgment of BP control may stem in part from high BP variability. Women with high BP variability are more susceptible to hypertension misdiagnosis. It is possible that high BP variability contributes to the increased cardiovascular risk related to both masked hypertension and white coat hypertension.
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Keywords: blood pressure variability; gender differences; masked hypertension; white coat hypertension

INTRODUCTION

Patients with white coat hypertension (WCH), also referred to as having 'isolated clinic hypertension', have higher than normal clinic blood pressure (BP) with normal home BP readings or ambulatory BP monitoring (ABPM). This phenomenon, shown to increase in prevalence with age,[1] may be confined to the clinic setting as recently reported.[2] However, it may reflect a generalized tendency to raise BP intermittently (for example, as an enhanced stress response), both in clinic and in normal daily life. It has been shown, for example, that the fraction of patients in an outpatient clinic who had isolated ambulatory hypertension (normal in-clinic readings with abnormally high ABPM), namely masked hypertension (MH), declined with repeated clinic BP measurements.[3] The question whether the white coat and masking phenomena are linked with increased BP variability remains to be answered;[4] considerable data links increased BP variability to worse prognosis in patients with elevated BP or controlled hypertension,[5–10] whereas several studies suggest that prognosis of patients with WCH and MH is worse than that of subjects with 'truly' normal BP.[11–13] Recently, both WCH and MH have been shown to predict sustained hypertension in subsequent ambulatory monitoring.[14]

Our hypothesis in this study was that large differences between clinic and ambulatory BP, found among patients with both MH and WCH, can be associated with increased ambulatory BP variability. In addition, we aimed to quantify the risk of inaccurate assessment of BP control in the clinic (under- or overestimation) in patients with high BP variability.

METHODS

Study population

Data were extracted from records consecutively collected in our ABPM service database, from 1991 through 2005. Both treated and non-treated patients were included, except those <16 years old, pregnant women and subjects with poor quality ABPM (<50 valid measurements). Patients were referred for standard clinical indications at the discretion of the referring physician (mainly by primary care practitioners, who have been shown to use ABPM for appropriate indications).[15]

ABPM and definitions

The 24-hour ABPM was executed with Spacelabs 90207 (Spacelabs Healthcare, Issaquah, WA, USA). Before 1999, we used Accutracker II (SunTech Medical Inc., Morrisville, NC, USA), as previously described.[16] The Accutracker II has been validated by intraarterial BP monitoring during exercise and at rest.[17,18]

[1]Hypertension Unit, Department of Medicine, Hadassah–Hebrew University Medical Center, Jerusalem, Israel and [2]Laboratory of RNA Molecular Biology, The Rockefeller University, New York, NY, USA
Correspondence: Dr A Cahan, Hypertension Unit, Department of Medicine, Hadassah–Hebrew University Medical center, Mount Scopus, PO Box 24035, Jerusalem 91240, Israel.
E-mail: amoscahan@yahoo.com
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The monitor was mounted on the nondominant arm between 0800 hours and 1000 hours and removed 24 hours later. Recordings were made every 20 min between 0600 hours and midnight and every 30 min between midnight and 0600 hours. A mercury sphygmomanometer was initially attached to the monitor via a Y-connector to verify agreement between the two modes of measurement (within a range of 5 mm Hg). Cuff size was selected according to measured arm circumference: ⩽24-cm pediatric cuff, 24- to 32-cm standard adult cuff and >32-cm large adult cuff. The average of two to three initial clinic (sphygmomanometer) measurements, taken by a trained technician after the subject had been in a sitting position for 5 min, was considered the patient's clinic BP.[19] Clinic BP was considered optimal, high normal or high at <130/80 mm Hg, 130–139/80–89 mm Hg and 140/90 mm Hg, respectively. Clinic hypertension was further classified as grade I (<160/100 mm Hg), grade II (<180/110 mm Hg) or grade III (180/110 mm Hg or higher). Ambulatory awake BP was considered normal or high at <135/85 mm Hg or 135/85, respectively. Sleep, including daytime naps (reported in 31%), was logged in a diary. Daytime sleep was not included in the awake BP average. Normal sleep BP was considered <120/70 mm Hg.[20,21] The overall 24-h normality definition was <125/80 mm Hg.[22] On the basis of combined clinic and awake ambulatory BP (aABP) readings, patients were classified as having controlled BP (normal clinic and awake BP; namely, both normotensives and controlled hypertension), or as having clinic hypertension (high clinic BP with normal awake BP; either WCH or white coat uncontrolled hypertension), aABP hypertension (high awake BP with normal clinic BP in patients with MH or masked uncontrolled hypertension) or sustained hypertension (both high clinic and high awake ambulatory BP). For each patient, we subtracted the awake systolic ambulatory BP (aABP) from the clinic systolic BP to define the clinic–aABP difference, a measure of discrepancy between the two settings and a proxy measure of the white coat and masking phenomena.[19] Variability of aABP was estimated using standard deviation (s.d.) and the coefficient of variation (CV=100*s.d./average aABP).

Data analyses

To characterize the association between the clinic–aABP difference and the variability of ambulatory systolic BP, the study population was split according to predetermined clinic–aABP difference cutoffs: between 0 and −10 mm Hg (masking), <−10 mm Hg (extreme masking) between 0 and 10 mm Hg (neutral difference) and >10 mm Hg (white coat effect (WCE)). Baseline characteristics including treatment for hypertension were compared across these categories. We further categorized the study population according to tertiles of awake systolic BP variability (CV). We used a logistic regression model to examine the odds of WCH and MH according to aABP variability. The models also included variables for age, gender, treated hypertension and diabetes, body mass index, systolic aABP and a dummy variable for the BP monitor—Spacelab 90207 or Accutracker II. The interaction term monitor*BP variability was introduced when significant. We also examined the interaction of ambulatory BP and gender with the appropriate multiplicative term. General linear models were used to estimate covariate-adjusted ambulatory BP variability. Data are expressed as mean ± s.d., unless otherwise specified. Two-sided nominal $P<0.05$ was considered significant. PASW Statistics 17.0 (SPSS, Chicago, IL, USA) was used for statistical analysis.

RESULTS

During a 15-year period, 3949 patients aged 16–93 years underwent valid ambulatory monitoring in our service. The study population characteristics are shown in Table 1. In all, 58% of the patients had treated hypertension. Average clinic BP and aABP were 147 ± 22/85 ± 13 mm Hg and 142 ± 16/82 ± 11 mm Hg, respectively. The average difference between clinic BP and aABP was 5 ± 17/3 ± 9 mm Hg.

Systolic BP variability and the clinic–ambulatory difference

Awake ambulatory systolic BP variability was higher in patients with large differences between the clinic and aABP, both positive and negative (Table 1). Patients with a positive (>10 mm Hg) clinic–aABP difference (that is, WCE) had higher unadjusted systolic BP variability (s.d. 15 ± 4 mm Hg, CV 10.5 ± 2.8%) compared with patients with a difference of 0–10 mm Hg (s.d. 12 ± 4 mm Hg, CV 8.9 ± 2.5%). Patients with a marked negative difference (beyond 10 mm Hg) also had high systolic BP variability (s.d. 17 ± 5 mm Hg, CV 11.1 ± 3.3%) compared with those with moderate negative difference (−10–0 mm Hg; s.d. 13 ± 4 mm Hg, CV 9.2 ± 2.9%, both Bonferroni-corrected *P*-values <0.0001). In a parallel analysis by deciles of the clinic–awake ambulatory difference a similar pattern was found in treated and non-treated patients (Figure 1). Accordingly, compared with patients with controlled BP and sustained hypertensive subjects, patients with clinic hypertension and hypertension according to aABP had higher systolic aABP variability (Figure 2).

A similar pattern was noted when 24 h systolic BP variability was compared across categories of clinic–ABP difference (Figure 3); Patients with a large positive or negative difference had higher

Table 1 Demographic characteristics of the study population split according to the magnitude of the clinic–awake ambulatory systolic blood pressure difference (*n*=3949)

		Clinic–awake systolic BP difference (mm Hg)				
	All patients (n=*3949*)	*I* <−*10* (n=*671*)	*II* ⩾−*10*–<*0* (n=*976*)	*III* ⩾*0*–*10* (n=*965*)	*IV* >*10* (n=*1337*)	P-*value*
Age (years)	55 (range, 16–93)	52 ± 17	50 ± 16	54 ± 16†	61 ± 14*†‡	<0.0001
Gender (% females)	53	47	47	52	63	<0.0001
Body mass index (kg m^{-2})	27.2 (range, 12–50)	27.4 ± 4.7	27.1 ± 4.4	27.3 ± 4.5	27.2 ± 4.6	0.517
Clinic BP (mm Hg)	147 ± 22/85 ± 13	131 ± 16/81 ± 13	136 ± 16*/84 ± 12*	145 ± 16*†/86 ± 12*†	165 ± 20*†‡/89 ± 12*†‡	<0.0001
Awake BP (mm Hg)	142 ± 16/82 ± 11	150 ± 17/84 ± 11	141 ± 16*/83 ± 11*	140 ± 15*/82 ± 10*	142 ± 16*‡/80 ± 10*‡	<0.0001
Awake heart rate (b.p.m.)	74 ± 12	76 ± 12	76 ± 11	74 ± 11*†	71 ± 11*†‡	<0.0001
Treated hypertension (%)	58	55	49	55	68	<0.0001
Treated diabetes (%)	9	9	7	8	10	0.014
s.d. of awake systolic BP (mm Hg)	14.1 ± 4.5	17 ± 5	13 ± 4*	12 ± 4*	15 ± 4*†‡	<0.0001
CV of awake systolic BP (%)	9.9 ± 3.0	11.1 ± 3.3	9.2 ± 2.9*	8.9 ± 2.5*	10.5 ± 2.8*†‡	<0.0001

Abbreviations: BP, blood pressure; b.p.m., beats per minute; CV, coefficient of variation.
P-values were derived from analysis of variance or χ^2-tests, as appropriate. Bonferroni adjustment for multiple comparisons: $^{*}P<0.05$ *vs.* group I; $^{\dagger}P<0.05$ *vs.* group II; $^{\ddagger}P<0.05$ *vs.* group III.

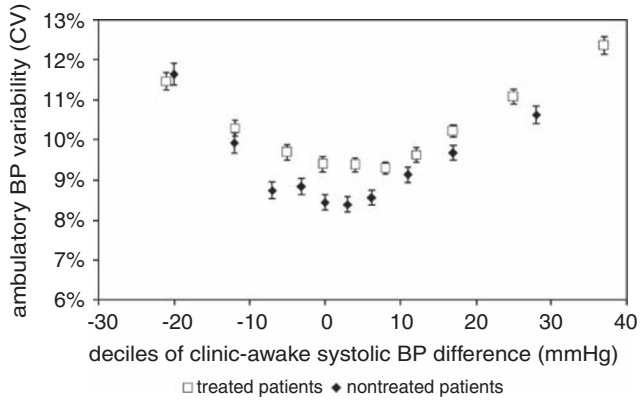

Figure 1 Unadjusted systolic aABP variability according to deciles of systolic clinic–aABP difference in nontreated (black diamonds) and treated patients (open squares). The R^2 values for the quadratic fit-lines (not shown) were 0.916 (non-treated patients) and 0.964 (treated patients). aABP, awake ambulatory blood pressure; BP, blood pressure; CV, coefficient of variation.

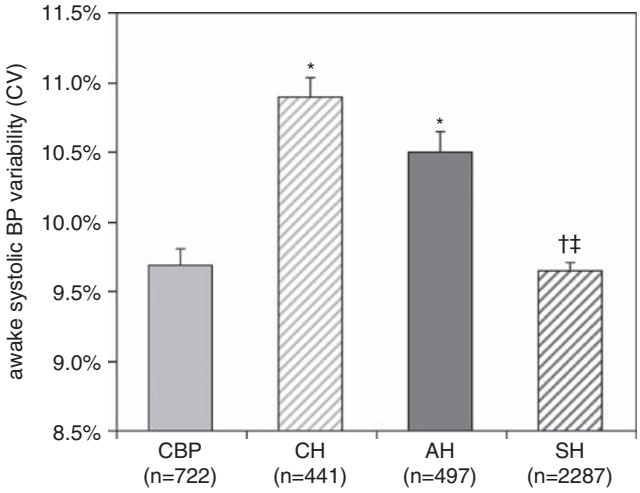

Figure 2 Unadjusted awake systolic blood pressure (BP) variability by BP categories. Controlled BP (CBP), clinic hypertension (CH), awake hypertension (AH) and sustained hypertension (SH). Overall *P*-value (analysis of variance) <0.0001. In *post hoc* analyses (Bonferroni); $^{*}P<0.0001$ for the comparison with CBP; $^{\dagger}P<0.0001$ for the comparison with CH; $^{\ddagger}P<0.0001$ for the comparison with AH.

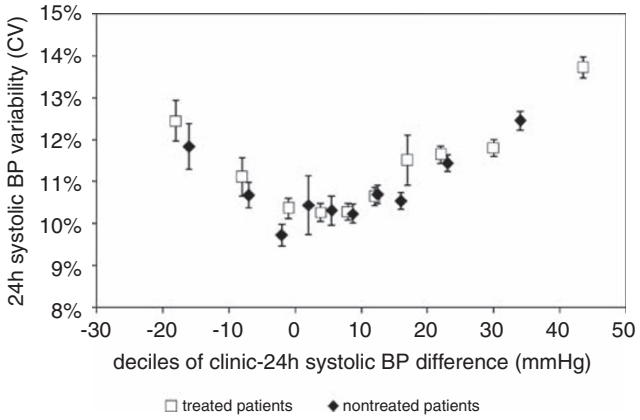

Figure 3 Unadjusted systolic 24 h ambulatory blood pressure (BP) variability according to deciles of systolic clinic–24 h ambulatory BP difference in non-treated (black diamonds) and treated patients (open squares). CV, coefficient of variation.

variability than patients with a difference <10 mm Hg (15.1 ± 3.7, 14.3 ± 4.9 and 12.4 ± 3.3 mm Hg, respectively). Differences were significant after Bonferroni correction ($P<0.0001$). Patients receiving antihypertensive treatment had a clinic–ABP difference similar to that of untreated patients (Figure 3).

Age- and gender-adjusted systolic aABP variability was virtually the same in diabetics and non-diabetics (s.d. 14.0 mm Hg, standard error 0.1 mm Hg and s.d. 14.1 mm Hg, standard error 0.2 mm Hg, respectively).

Systolic BP variability and the clinic–ambulatory difference in patients with normal *vs.* high ambulatory BP

In models computing BP variability according to the systolic clinic–awake ambulatory difference, a significant interaction was noted with awake ambulatory BP. Thus, determinations of the link between systolic BP variability and the clinic–ambulatory BP discrepancy were conducted separately in patients with normal ($<135/85$ mm Hg) or high awake ambulatory BP. In Figure 4, a mirror image shows that systolic BP variability increases with the degree of clinic hypertension in patients with normal ambulatory BP, whereas the opposite is true in patients with ambulatory hypertension.

As we hypothesized, increased systolic BP variability was involved with inaccurate clinic diagnosis of BP control in patients with both normal and high ambulatory measurements. In patients with normal awake BP, having ambulatory systolic BP variability in the upper tertile (*vs.* lower two tertiles) conferred odds ratio (OR) of 1.63 (95% confidence interval (CI) 1.26–2.11) toward a false-positive diagnosis of hypertension according to clinic measurement, after adjustment for age (exponential term), gender, body mass index and treatment status for hypertension and diabetes. Conversely, in patients with high awake BP, having ambulatory systolic BP variability in the upper tertile associated with OR of 1.86 (95% CI 1.52–2.28) toward a false-negative diagnosis of normal BP in the clinic. With CV of awake systolic BP as a continuous variable, the results for WCH were blunted (Table 2). Nonetheless, in view of the fact that women are more susceptible to WCH, we reanalyzed data according to gender (Table 3). Among subjects of both sexes with high clinic BP, higher variability predisposed to aABP hypertension (not shown). However, there was a gender-dependent relationship between variability and clinic hypertension (interaction *P*-value <0.05). Women with normal ambulatory BP and high (third tertile) variability had a markedly increased risk of being falsely diagnosed with hypertension compared to women with less variable BP (OR: 2.36, 95% CI 1.67–3.34). On the other hand, in men with normal ambulatory BP, high systolic BP variability was not associated with an increased risk of clinic hypertension (OR: 0.98, 95% CI 0.58–1.64).

DISCUSSION

Our results indicate that patients with WCH or MH, as well as white coat uncontrolled hypertension or masked uncontrolled hypertension, have increased daytime systolic BP variability which is not confined to the clinic setting. This higher systolic BP variability may reflect an enhanced stress response to external stimuli, and not isolated clinic reaction. Alternatively, these patients' high systolic BP variability may be intrinsic. It should be noted, however, that the clinic–aABP

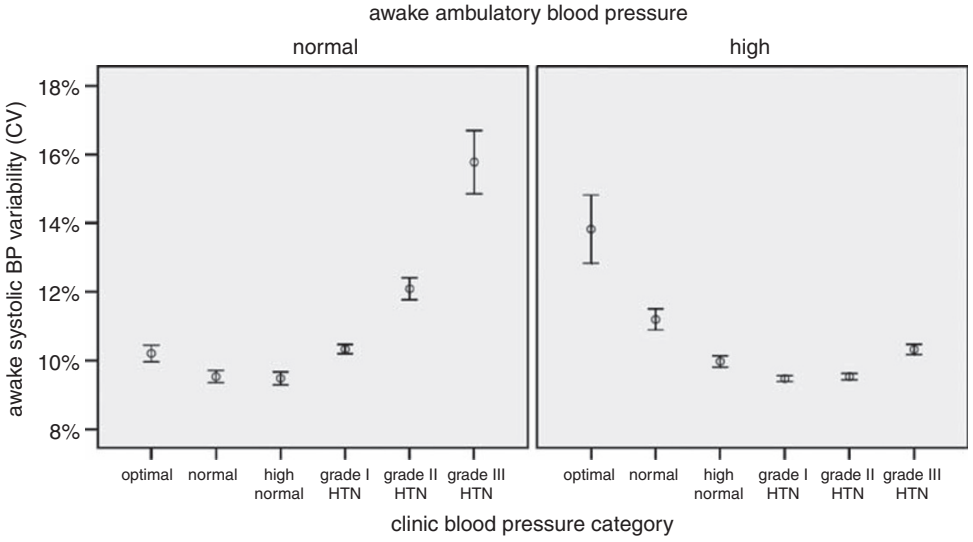

Figure 4 Unadjusted awake systolic ambulatory blood pressure (BP) variability in patients with normal (<135/85 mm Hg, left panel) or high (⩾135/85 mm Hg, right panel) awake BP by clinic BP categories: optimal <120/80 mm Hg; normal <130/85 mm Hg; high normal <140/90 mm Hg; grade I HTN <160/100 mm Hg; grade II HTN <180/110 mm Hg; grade III HTN ⩾180/110 mm Hg. CV, coefficient of variation; HTN, hypertension.

Table 2 Clinical predictors of misdiagnosed blood pressure status by categories of ambulatory blood pressure

		Normal awake BP (n=1166)		*High awake BP (n=2783)*	
Predictor	*Unit*	*OR for WCH*	P-*value*	*OR for MH*	P-*value*
CV (awake systolic BP)	1%	1.04 (0.98–1.10)	0.228	1.16 (1.11–1.22)	<0.0001
Age	5 Years	1.16 (1.10–1.22)	<0.0001	0.88 (0.85–0.91)	<0.0001
Gender	F/M	1.30 (0.97–1.73)	0.074	0.83 (0.67–1.03)	0.086
Treated hypertension	Yes/no	0.96 (0.70–1.31)	0.798	1.09 (0.86–1.39)	0.454
Treated diabetes	Yes/no	1.08 (0.61–1.91)	0.788	0.92 (0.62–1.35)	0.662
BMI	1 kg m^{-2}	0.99 (0.96–1.02)	0.406	1.00 (0.97–1.02)	0.676
Awake systolic BP	10 mm Hg	2.62 (2.08–3.32)	<0.0001	0.56 (0.50–0.63)	<0.0001
Awake diastolic BP	10 mm Hg	1.54 (1.22–1.94)	<0.0001	0.64 (0.56–0.73)	<0.0001

Abbreviations: BP, blood pressure; BMI, body mass index; CV, coefficient of variance; F, female; M, male; MH, masked hypertension; OR, odds ratio; WCH, white coat hypertension.
The multivariable models also included a variable for the type of monitor used (Spacelab *vs.* Accutracker) and an interaction term for the BP monitor and BP variability

Table 3 Clinical predictors of white coat hypertension or white coat uncontrolled hypertension by gender

		Men (n=1839)		*Women (n=2110)*	
Predictor	*Unit*	*OR for WCH*	P-*value*	OR for WCH	P-*value*
CV (awake systolic BP)	1%	1.02 (0.95–1.10)	0.588	1.20 (1.13–1.28)	<0.0001
Age	5 Years	1.15 (1.07–1.25)	<0.0001	1.22 (1.14–1.31)	<0.0001
Treated hypertension	Yes/no	0.99 (0.58–1.68)	0.957	0.95 (0.65–1.40)	0.804
Treated diabetes	Yes/no	0.96 (0.36–2.58)	0.934	1.17 (0.58–2.34)	0.660
BMI	1 kg m^{-2}	0.96 (0.90–1.01)	0.137	1.00 (0.96–1.03)	0.828
Awake systolic BP	10 mm Hg	3.05 (1.99–4.64)	<0.0001	2.32 (1.74–3.08)	<0.0001
Awake diastolic BP	10 mm Hg	1.33 (0.90–1.97)	0.154	1.72 (1.29–2.32)	<0.0001

Abbreviations: BP, blood pressure; BMI, body mass index; CV, coefficient of variation; OR, odds ratio; WCH, white coat hypertension.
The multivariable models also included a variable for the type of monitor used (Spacelab *vs.* Accutracker).

difference is only a very crude indication of the WCE measured by beat to beat recordings.

The less anticipated variability step-up among patients with isolated ambulatory hypertension (MH or masked uncontrolled hypertension) may theoretically stem from a more active lifestyle of these patients, suggested in part by the higher prevalence of younger men and higher awake heart rate.[22] Alternatively, such as in case of patients with clinic hypertension, highly variable BP may be an inherent characteristic.

We found that patients with small clinic–aABP difference also had low systolic BP variability (Figure 2). This indicates that regression toward the mean cannot fully account for the relationship between the clinic–aABP difference and systolic BP variability. The positive linear correlation between the clinic–aABP difference and clinic systolic BP[23] and the U-shaped relation between BP variability and the clinic–aABP difference (Figure 1) are actually a different graphic representation (accounting for the absolute clinic–aABP difference) of the same phenomenon. It should be emphasized that, though absolute differences in BP variability between patients with WCH (or white coat uncontrolled hypertension) and MH (or masked uncontrolled hypertension) compared with other patients were rather small, comparable differences in variability have been linked to increased cardiovascular mortality.[10]

We also found that higher systolic aABP variability may interfere with accurate BP-related diagnoses based on clinic readings. Patients with highly variable systolic BP have higher odds of being diagnosed with either WCH or MH compared with patients with smaller systolic BP variability. This may mediate the poorer prognosis reported with masked, and to a lesser extent WCH, underlying the importance of ABPM as a tool for the unequivocal diagnosis of hypertension.

Our results show that women with higher awake systolic BP variability are more prone to be misdiagnosed with hypertension compared with men. One explanation for this could be the reported greater prevalence of anxiety among women,[2] and the more prominent effect of anxiety on BP in women.[24] Nevertheless, the absent consequence of highly variable BP on the odds of clinic hypertension misdiagnosis in men is surprising and suggests a hypothetic BP lowering effect of the clinic setting in this population. Unlike a recent report,[25] in which an association was reported between the presence of diabetes and increased BP variability, we found that the adjusted s.d. of awake systolic BP was similar in patients with and without diabetes mellitus, not supporting diabetes as a predictor of WCH (Table 3). Indeed, previously,[26] after adjustment for confounders we had found patients with diabetes to have a lesser white coat and a greater masking effect.

Our study is limited in the sense, that clinic BP was taken on a single occasion, not at three separate visits as due, that we used an indirect definition of WCE (based on clinic BP readings taken by a technician) which may underestimate the true WCE,[22] and its relation to masking effect has not been described. The questionable reproducibility of the clinic–aABP difference is another potential source of inaccuracy.[27,28] It seems possible that in the case of clinic non-responders with high systolic BP variability, computation of the clinic–aABP difference based on repeated ABPM would give inconsistent values, providing an explanation for unsatisfactory reproducibility. The referred population of patients, some being treated (with variable ABP control), some untreated, is another limitation, although subgroup analysis by hypertension treatment did not change the results. We did not have data on other parameters known to affect variability such as smoking, menopausal status, obstructive sleep apnea, left ventricular hypertrophy and so on.

The strengths of our study are its size, and a consistent mode of performance that takes into account patients activity report so that no daytime sleep (reported in almost a third) is included in the awake ABP data. Such an inclusion artifactually dampens aABP level and increases its variability.[29]

Our findings indicate that high ambulatory BP variability may hamper accurately diagnosing clinic hypertension based upon a small sample of clinic readings. This is especially important considering the under recognition of MH, which affects about 10% of the population.[1,2,30] Thus, a more liberal use of ABPM may be warranted. Further research is necessary to evaluate the causal relationship between greater aABP variability and worse prognosis in patients with masked and WCH.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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