Επίκαιρο Άρθρο

White-coat and masked hypertension: evidence, clinical relevance and recommendations for clinical practice

Alejandro de la Sierra

ABSTRACT

The simultaneous use of office and out-of-office blood pressure (BP) measurement results in one-third of subjects showing discrepancies between measurements. In addition to normotension and hypertension (or sustained hypertension), white-coat hypertension (WCH: elevated values in the office with normal out-of-office BP) and masked hypertension (MH: normal office values with out-of-office BP elevation) are the two new derived phenotypes. Moreover, the terms white-coat uncontrolled hypertension (WCUH) and masked uncontrolled hypertension (MUCH) are used for defining the same situations in subjects under antihypertensive treatment.

WCH has a prevalence ranging from 15% to 40%, which depends on the population source, the quality of office measurement, and the criteria used for definition. Prevalence is higher in old females submitted to ambulatory blood pressure monitoring and when daytime BP is considered for the definition. If normal values of all 24-hour, daytime and nighttime BP is required, prevalence figures are considerably lower. WCH carries a lower cardiovascular risk in comparison to sustained or masked hypertension, while the risk can be similar or higher than normotension, depending on how strict is the criteria for diagnosis, absolute values of ambulatory BP, and the presence of other risk modifiers. Moreover, treatment decisions should consider all these aspects and individualized depending on the global risk.

MH also has a variable prevalence, higher in young males with high-normal office BP, occupational stress, sleep disorders, or documented organ damage. MH undoubtedly carries a higher cardiovascular risk in comparison with normal out-of-office BP and antihypertensive treatment, either initiation or intensification, seems reasonable for such patients. Evidence-based outcome data are required in order to support treatment recommendations for patients with WCH or MH.

INTRODUCTION

Clinical and therapeutical decisions related to blood pressure (BP) elevation have been classically based on the dichotomous phenotyping of normotension and hypertension, depending on the normality or elevation of BP measured at the doctor's office. This has always been considered as a pragmatic decision, as the relationship between blood pressure and cardiovascular mortality and morbidity is continuous and does not support a clear separation in such phenotypes. Consequently, the two most important clinical guidelines[1,2] currently disagree in the definition of the BP level required for defining a subject as hypertensive, with values of 130/80 mmHg or 140/90 mmHg.

In the last decades, the increasing use of out of office BP measurement, such as home BP and ambulatory BP monitoring (ABPM) has contributed to challenge this simplistic approach, with more than one third of subjects showing discordance in their categorization when using both office BP and out-of-office BP measurements (figure 1). Combining office BP with out-of-office BP, either home

Department of Internal Medicine Head, Internal Medicine Department Hospital Mutua Terrassa. University of Barcelona. Spain
✉ **Correspondence: Alejandro de la Sierra**, *MD, PhD, FESC, FAHA, Professor of Medicine Head*, Barcelona, Spain
Tel.: 34 937365000 • Fax: 34 937365037 • Email: adelasierra@mutuaterrassa.cat; aslerra@ub.edu

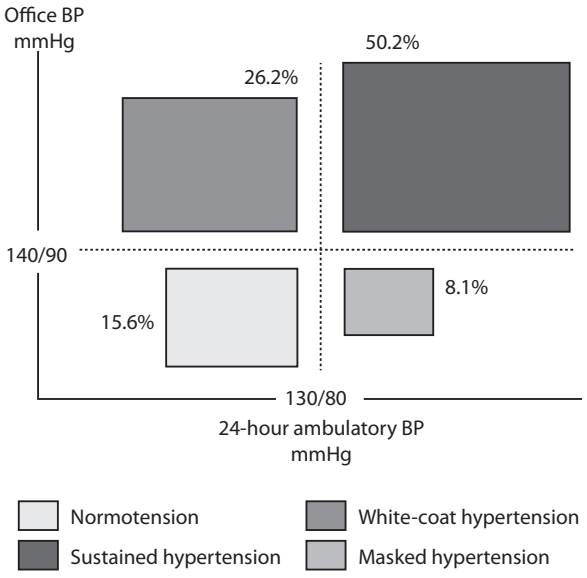

Figure 1. *Distribution of an untreated population submitted to Ambulatory Blood Pressure Monitoring in 4 phenotypes: normotension, sustained hypertension, white-coat hypertension, and masked hypertension. Data updated from reference 5.*

monitoring or ABPM, results in 4 different phenotypes, depending on the normality or not of either measurement. In addition to normotension and sustained hypertension (concordant normal or elevated BP by the two measurement methods), some patients have elevated BP at the office with normal home BP or ABPM, and are defined as having white-coat hypertension (WCH) or isolated office hypertension. In contrast, other group of individuals have elevated home BP or ABPM, while BP values measured at the office are normal, a category known as masked hypertension (MH). The prevalence, clinical features and recommendations for such 2 phenotypes are summarily discussed in this paper.

WHITE COAT HYPERTENSION

The phenomenon known as white-coat effect is the BP rise observed with the presence of the physician in the office[3]. It is usually accompanied by an increase in heart rate, suggesting that is driven by an alert reaction, and shows a large interindividual variability. WCH is conceptually defined as elevated BP in the office but normal out-of-office BP, while currently white-coat effect is usually considered as the difference in BP between office and out-of-office BP.

The definition is a little bit more complex when using ABPM, as white-coat effect and WCH can differ depending on which ambulatory BP is chosen for such definition. Classically, daytime BP has been considered for such phenotyping. The selection was based on the fact that both office and daytime BP are measured with the patient awake, and daytime BP is usually the highest BP estimate obtained by ABPM. However, there are also some differences, as office BP is measured while the patient is resting, while daytime BP depends on physical activity, showing a large interindividual variability. In addition, many patients with abnormal ABPM patterns, such as nocturnal isolated hypertension can be classified as having WCH if only daytime BP is considered. This is especially frequent in older subjects whose daytime BP can be low due to lack of physical activity.

The use of 24-hour BP contains both daytime and nocturnal BP. It has the advantage of being calculated with the highest number of measurements, thus showing a better reproducibility. More recently, it has been suggested that the definition of WCH must include normal values of all ABPM-derived estimates, including day, night, and 24-hour BP. This is currently recommended by the European Society of Hypertension working group[4], in its position paper released in 2013. The main advantage is that it clearly defines as white-coat hypertensives those subjects with undoubted normal ABPM. However, it requires a strict definition of the nocturnal period, tailored to patient's activity. Otherwise, an elevated mean night BP can be due to the contribution of BP measurements obtained while the patient is awake.

The prevalence of WCH is quite variable. It depends on the population source (general population, general hypertensive population, hypertensive population submitted for ABPM) and ranges from 15% to 40%[5]. Depending on which ABPM estimate is used for definition, it also modifies its prevalence, showing the highest when daytime BP is used and the lowest when considering the normality of all circadian periods[6].

To illustrate this issue, figure 2 shows different estimates of the prevalence of white-coat hypertension in 45020 untreated subjects from the Spanish ABPM Registry, most with elevated office BP. Prevalence of white coat hypertension ranged from

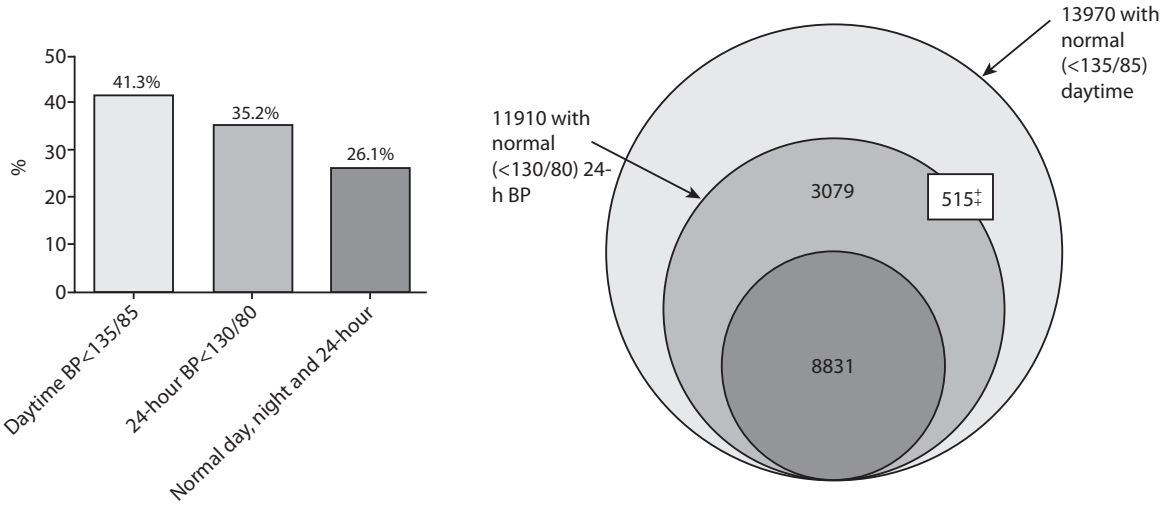

Figure 2. *Prevalence rates of white-coat hypertension in 33855 untreated subjects with office blood pressure ≥ 140/90 mmHg, depending on the ABPM estimate used for definition (left). Venn diagram of the distribution of subjects diagnosed as having white-coat hypertension by different estimates. The inner circle corresponds to patients with normal 24h, daytime, and nighttime BP. The circle in the middle corresponds to patients with normal 24-hour BP, and the external circle corresponds to those with normal daytime BP. 2575 patients with normal daytime BP had elevated 24-hour or nighttime BP. 3079 patients had normal 24-h BP but elevated night BP and 515 normal 24-h BP but elevated daytime BP. Data from reference 6.*

41% (considering those with daytime BP below 135/85 mmHg) to 26% (including only those with daytime BP < 135/85 mmHg, 24-hour BP < 130/80 mmHg, and nighttime BP < 120/70 mmHg). In addition, the figure includes a Venn diagram of such distribution. As seen, a substantial proportion of patients diagnosed of WCH by daytime BP had either 24-hour or nocturnal BP elevation. Moreover, even considering normal 24-hour BP, still a proportion of them showed elevation of nighttime BP[6].

The magnitude of white-coat effect and the prevalence of WCH is also dependent on the level of BP elevation and the quality of office BP measurement. In relation to the first aspect, differences between office and 24-hour systolic BP averaged 27 mmHg in patients with office BP above 140, whereas corresponding values for subjects with office SBP between 120 and 139 were 8 mmHg. In subjects with office SBP < 120 mmHg, 24-hour SBP was 6 mmHg higher than office BP (figure 3)[7].

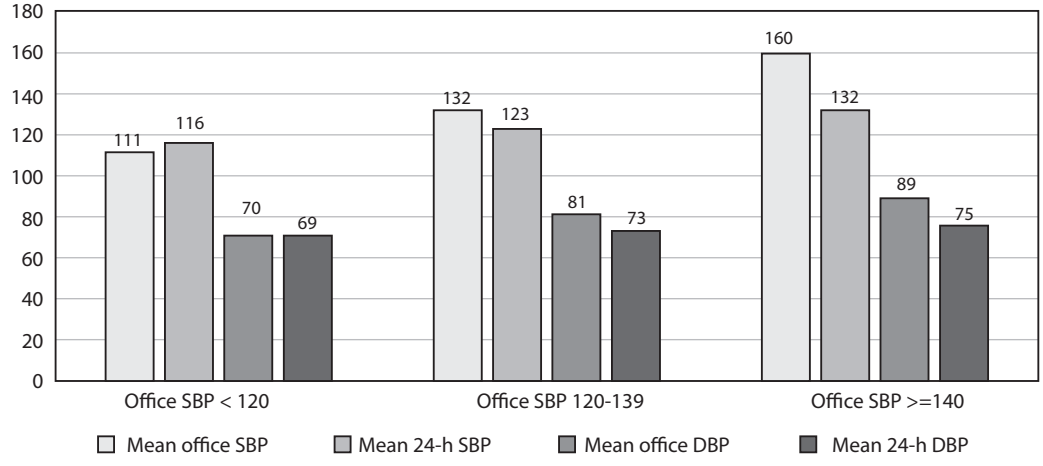

Figure 3. *Mean values of office and 24-hour systolic and diastolic BP depending on 3 categories of office systolic BP. As seen, office BP is considerably higher than 24-hour BP in those with office BP above 140 or between 120 1nd 139. In contrast, in those with office systolic BP lower than 120, office BP is higher than 24-hour BP. Data from reference 7.*

The quality of office BP measurement also contributes to the magnitude of white-coat effect. The use of non-standardized office BP measurement is usually associated with large differences between office and 24-hour BP, whereas the use of automated office BP (especially unattended) results in values close to mean daytime BP[8].

Some clinical characteristics are associated with the presence of white-coat hypertension, including older age, female gender, obesity, and absence of other cardiovascular risk factors and target organ damage[9]. However, the discriminant value of such clinical characteristics is very low, thus suggesting that ABPM (or home BP) should be more widely used to establish a precise classification of those patients.

The term white coat uncontrolled hypertension (WCUH) is also used for defining those patients under antihypertensive treatment with a white-coat effect, which translates in a lack of BP control in the office with normal home BP or ABPM. The situation is of particular importance in patients under the category of resistant hypertension (uncontrolled BP while on treatment with 3 or more antihypertensive agents), as this is a situation which requires special diagnostic and therapeutical procedures, such as intensive search for causes of secondary hypertension, treatment with second-line drugs, such as mineralcorticoid receptor antagonists or the new physical device treatments, such as renal denervation or baroreceptor stimulation. In a cohort of more than 8000 resistant hypertensive patients from the Spanish ABPM Registry, one third had normal 24-hour BP, defined as having white coat resistant hypertension[10].

One of the key aspects of WCH is the associated risk of cardiovascular disease. The prevalence of target organ damage is reduced in WCH with respect to sustained hypertension. In addition, the incidence of cardiovascular events is also reduced. These conclusions are of limited clinical value and probably only reflects that the predictive value of ABPM is superior to that of office BP. The important question is to determine if WCH is an innocent phenomenon, i.e. carries a risk not different from that of normotensive subjects. This issue has been extensively investigated in the past years, but results are conflicting. Differences in the methodology for defining WCH have also contributed to such conflicting results. In general, WCH have more metabolic disturbances and cardiac organ damage than normotensive subjects. Meta-analysis have also shown increased rates of cardiovascular events in comparison to normotensives[11], and results of the mortality study from the Spanish ABPM Registry cohort also demonstrated increase total and cardiovascular mortality in untreated subjects with WCH[12].

The picture is a little more complex due to several aspects. First, ambulatory BP in WCH, even normal by definition is usually higher than in normotensives. Second, as mentioned earlier, the definition of WCH based on the normality of daytime BP includes a proportion of patients with elevated nighttime BP, 24-hour BP, or both. Supporting this, two studies have demonstrated that the cardiovascular risk[13] and the prevalence of associated risk factors and organ damage[6] of WCH defined as having all daytime, nighttime, and 24-hour BP in the normal range was clearly reduced and approaching normotensive subjects, in comparison of WCH defined only by normal daytime or even 24-hour BP.

The presence of other cardiovascular risk factors also contributes to the risk of WCH. In one of the analyses of the IDACO cooperative group, WCH without other risk factors had rates of cardiovascular events similar to normotensive. In contrast, the WCH group at high risk (the presence of other cardiovascular risk factors) had event rates that doubled that of the normotensive group[14].

The decision regarding antihypertensive treatment in patients with WCH is not easy, due to the aforementioned uncertainities. Considering the prevalence of WCH, it is feasible to think that the benefit of antihypertensive treatment observed in most of the clinical trials in the past also affects WCH, as they would represent one third of patients included in such trials. This is obviously theoretical, as a subgroup analysis based on such categorization has not been carried out. Some of the clinical guidelines in the past suggested that antihypertensive treatment was unnecessary in WCH, as it was considered an innocent phenomenon. However, all the current knowledge runs against this conservative approach, although there is no clear evidence to support any decision. As mentioned, the mortality study of the Spanish ABPM Registry revealed that untreated WCH was associated with a higher risk of total and cardiovascular mortality with respect to normotensive subjects[12]. In contrast, in treated sub-

jects the risk associated with WCUH was minimally elevated and nonsignificant after adjustment for other risk factors. This is aligned with benefits observed in clinical trials and suggests that antihypertensive treatment is beneficial in WCH, at least in those with moderate to high cardiovascular risk.

In view of these considerations, the issue of antihypertensive treatment initiation in WCH is unresolved. However, some clinical considerations may help the decision. First, the quality of office BP measurement should be improved, with repeated measures, and if feasible, automated unattended measurements. Second, home BP or ABPM should be properly use, including one week of repeated measurements (home BP) and ABPM performed in a day with the patient engaged in his/her usual activities (ABPM performed on a resting patients can yield unusual low values and misdiagnose WCH). Third, a complete risk assessment including other cardiovascular risk factors and organ damage should be encouraged in order to establish patients's global cardiovascular risk.

The two most recent guidelines also show some differences in the recommendation of treatment for subjects with WCH. While the American guidelines[1] indicate lifestyle measures and annual monitoring, the European guidelines recommends considering antihypertensive treatment for WCH patients if target organ damage is present or cardiovascular risk is high[2]. None of these guidelines recommend uptitrating antihypertensive treatment in patients with white-coat uncontrolled hypertension.

MASKED HYPERTENSION

Masked Hypertension (MH) is defined as normal BP in the office with elevated home BP or ABPM. The same circumstance in treated subjects is known as masked uncontrolled hypertension (MUCH). The prevalence of MH and MUCH varies widely depending on the population screened[5]. From less than 10% in population-based studies to more than 30% in treated subjects with normal office BP submitted for ABPM[15]. The criteria for definition also modifies the rates of prevalence, being lower when elevated daytime BP is used for definition and higher when MH is defined as elevation of either daytime, nighttime, or 24-h BP[16], as stated by the European Society of Hypertension position paper[4].

Clinical associates with MH or MUCH include younger males, smokers, non-obese, with other metabolic risk factors, organ damage or overt cardiovascular disease[15,17]. As it happens with WCH, the predictive value of such clinical circumstances is poor and the most important challenge in MH is the detection of this condition, as it is relatively uncommon in clinical practice to perform ABPM in untreated subjects with normal BP or in apparently well-controlled treated hypertensives. Values of office BP in the high-normal range or repeated office measurements with alternate normal and elevated values, documented target organ damage, mental stress at work, or sleep disorders such as sleep apnea are some typical circumstances where MH can be suspected.

MH is undoubtedly associated with elevated cardiovascular risk, all-cause mortality and increased target organ damage[17,18]. Likewise, treated patients with MUCH have a worse prognosis in comparison to those controlled by means of ABPM. In the Spanish ABPM Registry[12] the overall and cardiovascular mortality associated with MH or MUCH were the highest of all different phenotypes, even superior to sustained hypertension. The explanation for this paradox finding is possibly related with a lack of treatment initiation or intensification in subjects with MH or MUCH, as treatment of such abnormalities are not included in most decision algorithms.

Therapeutic decisions in subjects with MH or MUCH are based on wise clinical judgement, as no evidence-based data are available. As stated before, some clinical circumstances may contribute to elevated out-of-office blood pressure, which can be modified. Smoking or excessive alcohol intake should be discouraged. Less frequently, but also important are sleep disorders, as nocturnal BP elevation is responsible of MH and MUCH more frequently than daytime BP[15,16], thus suggesting that treatment of such disorders may reduce nocturnal BP and consequently, MH.

It is reasonable to treat MH patients, especially if they have high cardiovascular risk or target organ damage. It is also reasonable to uptitrate drugs in MUCH patients in order to avoid future consequences of long-time out-of-office BP elevation. Recent guidelines[1,2] both recommend such treatment initiation or intensification. The main problem with such decisions is that treatment should be monitored by out-of-office BP. If MH or MUCH is

diagnosed by home BP, this is the preferred method for follow-up and future adjustments of treatment. If MH or MUCH is diagnosed by ABPM, especially by isolated nocturnal BP elevation with normal home BP, repeated ABPM is the only way to monitor treatment changes. In all cases, normalization of out-of-office BP is the final objective.

In conclusion, WCH and MH are two phenotypes with several particularities which require a specific evaluation. More information is required regarding mechanisms leading to such discrepancies between office and out-of-office blood pressure, along with a better standardized office measurement technique in order to avoid bias error[19]. The use of ABPM in future clinical trials of antihypertensive treatment, and consideration of such phenotypes in those trials are key features trying to better elucidate the best therapeutic option for patients with WCH and MH.

REFERENCES

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/ AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension* 2018; 71: 1269-1324.
2. Williams B, Mancia G, Spiering W, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. *J Hypertens* 2018; 36: 1953-2041.
3. Mancia G, Bertinieri G, Grassi G, et al. Effects of blood-pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet* 1983; 2: 695-698.
4. O'Brien E, Parati G, Stergiou G, et al, on behalf of the European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension position paper on ambulatory blood pressure monitoring. *J Hypertens* 2013; 31: 1731-1768.
5. Gorostidi M, Vinyoles E, Banegas JR, de la Sierra A. Prevalence of white-coat and masked hypertension in national and international registries. *Hypertens Res* 2015; 38: 1-7.
6. De la Sierra A, Vinyoles E, Banegas JR, et al. Prevalence and clinical characteristics of white-coat hypertension based on different definition criteria in untreated and treated patients. *J Hypertens* 2017; 35: 2388-2394.
7. De la Sierra A, Banegas JR, Divisón JA, et al. Ambulatory blood pressure in hypertensive patients with inclusion criteria for the SPRINT trial. *J Am Soc Hypertens* 2016; 10: 947-953.
8. Myers MG. Automated office blood pressure: the preferred method for recording blood pressure. *J Am Soc Hypertens* 2016; 10: 194-196.
9. Vinyoles E, Felip A, Pujol E, et al. Clinical characteristics of isolated clinic hypertension. *J Hypertens* 2008; 26: 438-445.
10. De la Sierra A, Segura J, Banegas JR, et al. Clinical features of 8295 patients with resistant hypertension classified on the basis of ambulatory blood pressure monitoring. *Hypertension* 2011; 57: 898-902.
11. Briasoulis A, Androulakis E, Palla M, Papageorgiou N, Tousoulis D. White-coat hypertension and cardiovascular events: a meta-analysis. *J Hypertens* 2016; 34: 593-599.
12. Banegas JR, Ruilope LM, de la Sierra A, et al. Relationship between clinic and ambulatory blood-pressure measurements and mortality. *N Engl J Med* 2018; 378: 1509-1520.
13. Asayama K, Thijs L, Li Y, et al. Setting thresholds to varying blood pressure monitoring intervals differentially affects risk estimates associated with white-coat and masked hypertension in the population. *Hypertension* 2014; 64: 935-942.
14. Franklin SS, Thijs L, Asayama K, et al. The cardiovascular risk of white-coat hypertension. *J Am Coll Cardiol* 2016; 68: 2033-2043.
15. Banegas JR, Ruilope LM, de la Sierra A, et al. High prevalence of masked uncontrolled hypertension (MUCH) in people with treated hypertension. *Eur Heart J* 2014; 35: 3304-3312.
16. De la Sierra A, Banegas JR, Vinyoles E, et al. Prevalence of Masked Hypertension in Untreated and Treated Patients With Office Blood Pressure Below 130/80 mm Hg. *Circulation* 2018; 137: 2651-2653.
17. Bobrie G, Clerson P, Menard J, et al. Masked hypertension: a systematic review. *J Hypertens* 2008; 26: 1715-1725.
18. Pierdomenico SD, Cuccurullo F. Prognostic value of white-coat and masked hypertension diagnosed by ambulatory monitoring in intially untreated subjects: an updated meta-analysis. *Am J Hypertens* 2011; 24: 52-58.
19. Stergiou G, Palatini P, Asmar R, et al. Blood Pressure Measurement and Hypertension Diagnosis in the 2017 US Guidelines: First Things First. *Hypertension* 2018; 71: 963-965.