White-coat hypertension and masked hypertension: an update

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ABSTRACT

White coat hypertension and masked hypertension are two conditions with a controversial role in the beginning and the progression of the cardiovascular disease. We focused our attention on the definition, the epidemiology, the pathophysiology and the clinical consequences of these two conditions, with an attention also on the management. This review was based on the papers found on PubMed and MEDLINE up to August 2015. The search terms used were *white coat hypertension, masked hypertension* in combination with *epidemiology, management and pathophysiology*.

Introduction

The precise quantification of blood pressure (BP) is an essential step to reach the largest number of correct diagnosis of arterial hypertension (AH) and consequently to optimize the anti-hypertensive therapy. Since the invention of the first sphygmomanometer in 1896, Riva-Rocci observed the inaccuracy of that method for a correct BP determination:[1] the simple appearance of a doctor was accompanied by an immediate rise in BP in some patients. Years later Pickering called this phenomenon *white coat hypertension* (WCHT).[2] The introduction of fully-automated BP measurement during the 24 h (ambulatory blood pressure monitoring, ABPM) allowed to observe the entire circadian BP profile, highlighting how BP could be normal in physician office and elevated at home, especially during the nocturnal period.[3] This last observation was named *masked hypertension* (MHT).[4]

WCHT is defined as office BP persistently ≥140 mmHg systolic, ≥90 mmHG diastolic, or both, whereas out-of-office BP is within normal (<130/80 mmHg for 24-h mean BP, or <135/85 mmHG for home BP).[5-7] Medical environment triggers this *alarm reaction*,[8] through the hyperactivation of sympathetic nervous system.[9] It peaked 2-4 min after the start of the visit and continued throughout the duration of the physician's visit.[10] For this reason, international guidelines recommended to record at least two ABPM to confirm the diagnosis of WCHT and to determine the possible development of sustained hypertension.[11] Further WCHT can be divided into true WCH, when both home BP values and ABPM values are normal, and partial WCHT, when only one of these out-of-office measurements is normal.[5]

If WCHT can determinate an overdiagnosis of AH, on the other hand some subjects present normal office BP values in contrast to pathological 24-h BP profile on ABPM or altered home BP. This *reverse white-coat effect* or MHT[12,13] is related to a worse cardiovascular (CV) prognosis[14] and also to the development of a target organ damage (TOD) comparable to sustained hypertension patients[15] (Table 1). Both WCHT and MHT are examples of how the correct evaluation of BP profile is a difficult challenge and how their better knowledge can lead to a more precise diagnosis and consequently to a proper treatment of AH.

Epidemiology

The prevalence of WCHT and MHT is not completely clear. AS a confounding factor several studies showed different values for normal BP. Regarding

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WCHT, Pickering and co-workers in 1988 reported a prevalence of 21 in 292 patients (7.2%);[2] in subsequent years other studies showed various frequencies, ranging from 15.1% in the Finn Home Study, which involved 1540 untreated subjects aged 44 to 75 years,[16] to 15-45% of the *Pressioni Arteriose Monitorate E Loro Associazioni* (PAMELA) study, a Mancia's large population trial which assessed the CV and all-cause mortality over 16 years in 2051 patients aged 25-74 years.[12] Lately, the 2014 position paper on ABPM estimated a WCHT prevalence of 15-30%.[7]

Among subjects older than 80 years, the Hypertension in the Very Elderly Trial (HYVET) showed a 50% prevalence of the WCHT.[17] However it is well known that the office BP and mean ambulatory BP difference increases with age and it is unlikely that the definition of WCHT is appropriate over 80 years. Conen and colleagues[18] recently demonstrated that the prevalence of WCHT exponentially increased from 2.2% to 19.5% from those aged 18 to 30 years to those aged ≥70 years. WCHT is also more prevalent among female gender.[19] Otherwise, smoking habit seems to be a protective factor.[20]

The exact prevalence of MHT was achieved with the introduction of ABPM that showed a diagnostic sensitivity higher than home BP monitoring (HBPM).[21] Indeed analysis from PAMELA reported a prevalence of 9%;[22] other studies reported frequencies ranging from 10.2%[23] to 23%,[24] reaching even 48%.[25] It might be fair to say that since the WCHT is more common in the elderly, consequently MHT should gradually decline with age.[26,27] However, the increasing prevalence of reduced nocturnal BP dipping among older patients,[28] could alter this assertion. The prevalence is around 10% among children and young adults.[29] Overall MHT is more prevalent in male gender and past smokers.[24] Other risk factors are high normal office BP, the overweight and a higher education level.[30] Also, it was showed how middle-age athletes have a higher prevalence of MHT31 (Table 2).

Pathophysiology

The physiological mechanisms that underlie WCHT and MHT are quite different. Utilizing microneurography, a methodology which measures the muscles and skin sympathetic nerve traffic, Grassi and co-workers demonstrated that subjects with WCHT presented pronounced activation of skin nerves and associated sympathetic inhibition of muscle nerve-traffic when physicians either took BP measurements or were present during these measurements.[32] Researchers indicate that this response is similar to a *defense reaction* that has been demonstrated in animal models when they react to emotional stressors and is largely dependent by diencephalic areas.[33]

The partial inhibition of these responses could underlie the reduced prevalence of WCHT among tobacco users.[34] Therefore, emotional factors such as anxiety or stress may be responsible for this microneurographic response and the origin of WCHT.[35] Patients with WCHT showed higher levels of anxiety compared with both normotensive individuals and patients with sustained hypertension.[36] However, research has also showed that patients who are prone to WCHT do not hyperreact to all types of emotional stimuli. Instead, they only react to emotional stimuli that have been associated with a physician's office or the physician.[37] This situational anxiety was further investigated in a study conducted by Ogedegbe and co-workers: patients who experience WCHT presented high anxiety at physicians' offices as a result of previous negative or painful experiences with the medical office or physician.[38] Results from this study also indicated that patients who had expectations of high BP when being measured experienced elevated

Table 1. Comparison between different blood pressure (BP) measurement methods among BP profiles.

	Office BP	HBPM	ABPM
True normotension	Normal	Normal	Normal
Sustained hypertension	Elevated	Elevated	Elevated
White-coat hypertension	Elevated	Normal	Normal
Masked hypertension	Normal	Elevated	Elevated

BP, blood pressure; HBPM, home blood pressure monitoring; ABPM, ambulatory blood pressure monitoring.

Table 2. Prevalence of white-coat hypertension and masked hypertension among different studies.

	Prevalence (%)
White-coat hypertension	2.2-50
Masked hypertension	9-48

BP. This is caused by an anxiety related to their expectations, rather than being caused by a persistent trait anxiety of the patients.[39]

WCHT seems to be a condition with an impaired baroreflex of vagal, but not of the sympathetic, CV system with a consequent hyperadrenergic state similar to that detected in subjects with sustained hypertension.[40]

About MHT, it is better to focus the attention not only on an etiologic mechanism but also on the methodological topic: as we said before, with the introduction of HBPM first and after the ABPM fully-automated devices, it was possible to analyze the entire circadian BP profile far from medical environment. For example, Mann *et al.* reported that smoking habit elevates the mean diurnal systolic BP despite a similar clinic BP between smokers and non-smokers,[41] leading to an undertreatment.[42] Other factors associated with high diurnal BP are alcohol intake[43] and physical activity.[44] ABPM is usually performed during a normal day, including the working period. As showed by Pieper and colleagues,[45] working environment can significantly change BP, both in normotensive and hypertensive subjects.[46,47] Also during the night period some factors interfere with the entire circadian BP profile. Aydin and coleagues[48] demonstrated that subjects exposed to a higher noise at night showed a higher morning BP. A similar relief was found with sleep deprivation.[49]

The possible role in MHT of sympathetic nervous system alteration leading to an isolated nocturnal hypertension was present more frequently in particular groups of patients, such as diabetics[50] (Table 3).

Clinical consequences

The prognostic value of WCHT is still under debate. If National Institute for Health and Clinical Excellence (NICE) guidelines did not stress this topic,[51] the European Society of Cardiology/European Society of Hypertension (ESC/ESH) guidelines[5] underline the importance of subjects with WCHT when compared to normotensives. Several cross sectional studies investigated the association between WCHT and asymptomatic TOD. The results are conflicting: if some studies showed that subjects with WCHT, when compared to normotensives, had an increased TOD like left ventricular hypertrophy (especially in elderly),[52] diastolic dysfunction,[53,54] increased intima-media thickness (IMT) and kidney damage (for example proteinuria),[55,56] other studies found no associations.[57] Further, the increased degree of TOD showed in some studies did not have prognostic significance.[58,59] Longitudinal studies did not clarify these discrepancies. In two large studies, the incidence of CV events was similar in WCHT subjects when compared to normotensive subjects[60,61] or sustained mild hypertension.[62] These data were also confirmed by a meta-analysis published in 2007.[63] However, other data demonstrated that WCHT is not clinically benign. A Danish study, with a ten-year follow-up, demonstrated that WCHT was associated with a significant increase in CV risk when compared to normotensive subjects. However, this risk was lower with respect to the CV risk of subjects with sustained hypertension.[64] The PAMELA study showed similar results, with an increase of hard endpoint such as total mortality and CV mortality in subjects with WCHT when compared with normotensive subjects. However, when subjects with WCHT were divided into two subgroups, those with true WCHT and those with partial WCH, the significance of these outcomes was maintained only in the second subgroup. The PAMELA study also clearly showed that WCHT increased the risk of sustained hypertension.[12] Several factors could explain the increased CV risk of WCHT subjects. These patients, when compared to normotensive subjects, demonstrated more metabolic risk factors, a higher BP variability, a well-known independent risk factor for CV events.[65] Furthermore, when compared to normotensives, WCHT subjects showed home and ambulatory BP measurements in the upper normotensive range.[65,66]

Instead, regarding MHT, recent meta-analysis showed how this phenomenon is undoubtedly associated with a higher left ventricular mass index[67] and with a greater IMT,[68,69] when compared with normotensive subject. The alteration in those two indicators in MHT is similar to that observed in sustained hypertension.[69] In addition, beyond IMT thickening, there was an increased incidence of carotid plaque stenosis.[70] This is the possible reason for the prognostic overlap between MHT and sustained hypertension.[71,72] The Masked Hypertension Study also showed that MHT determines during follow-up diastolic dysfunction such as sustained hypertension.[73] Further, Lurbe and colleagues, in a cohort of 272 subjects aged 6-18 years showed that subjects with MHT (n=39)

Table 3. Conditions associated with white-coat hypertension and masked hypertension.

	WCHT	MHT
Predisposing factors	Female gender Non smoking habit Anxiety Old patient	Male gender Smoking habit Overweight Night noise High normal BP Diabetes mellitus Young patient

WCHT, white-coat hypertension; MHT, masked hypertension; BP, blood pressure.

presented a higher risk of sustained hypertension during time, and this risk was higher in male patients.[74]

Although clinic BP is in the normal range in subjects with MHT, optimal values (<120/80 mmHg) are related to a lower prevalence of this alteration with a lower presence of TOD[75] and also with a lower incidence of MHT during a long follow-up period.[76] However, this cut-off value lead to an high false-positive rate.[77] Home BP measurement could be useful in the diagnosis and in the prognostic stratification, also for the nocturnal period,[78] but ABPM seems to be the best method to make an accurate diagnosis.[79,80] In addition, the Ohasama study demonstrated, in a cohort of 843 subjects of the general population who performed ABPM, that the nocturnal BP values were the best predictor of future chronic kidney disease.[81] In the Japan Morning Surge Home Blood Pressure (J-HOP) Study, Kario *et al*. developed a more comfortable device with respect to traditional ABPM device focused on the night time BP values of 02:00, 03:00, 04:00 a.m., which showed in 2562 subjects a strict correlation between nighttime BP values and TOD.[82] However, traditional ABPM devices remain the gold standard also for the evaluation of the night time period.[83]

In conclusion, both WCHT and MHT increased the risk to produce sustained hypertension and TOD.[66] However, several data showed a worse prognosis in subjects with MHT: in the Finn Home Study subjects with MHT or sustained hypertension presented a higher TOD when compared to normotensives or subjects with WHT.[84,85]

Management

When the physician made a diagnosis of WCHT, he should investigate the existence of metabolic risk factors, the presence of TOD, with meticulous follow-up. The first approach is lifestyle interventions. For those with CV risk factors and TOD, a pharmacological approach could be considered as a first-line treatment.[86]

Interestingly, the European Lacidipine Study on Atherosclerosis (ELSA) recently demonstrated that anti-hypertensive treatments in WCHT subjects reduced office BP similar to subjects with sustained hypertension, whereas it did not have any consistent lowering effect on 24 h, daytime and nighttime BP.[87] By contrast, subjects with sustained hypertension had both office and ambulatory BP reduction. This is the only available trial in which all the subjects underwent office and ambulatory BP measurements before and at yearly intervals during a 4-year anti-hypertensive treatment period. The ELSA trial did not give information about the eventual protective role of anti-hypertensive treatment in WCHT patients. The results of a large database[88] and of the Systolic Hypertension (SystEur) trial[89] showed that in WCHT subjects the pharmacological treatments did not lower the CV risk. However, these two trials only 1 on-treatment ambulatory BP was available. Furthermore, in the SystEur substudy the number of patients and events was too small to give sufficient statistical power.[90] Third in the large database there are no ambulatory BP baseline values.[89] By contrast, a big meta-analysis showed that the treatment of office BP levels resulted in a reduction of CV events, regardless of the ambulatory and home BP values of the studies subjects.[90] However, further randomized trial are needed for clarifying the best management of WCHT.

On the other hand, an incorrect diagnosis and treatment of MHT lead clearly to a worse CV prognosis.[91] Consequently it is fundamental to identify those subjects with a higher risk of MHT, in order to start an adequate therapy and assure an optimal BP control.

Angeli and colleagues proposed a diagnostic algorithm to identify patients with high risk of MHT in order to make ABPM only for those at high risk: subjects with pre-hypertension, smokers, high alcohol consumption, male gender, diabetes, obesity and environmental stress.[92] The high prevalence of MHT in diabetes, particularly due to an elevated BP during the night period,[93] with *reverse dipping* pattern,[94] can be limited with an adequate chronotherapy: American Diabetes Association (ADA) guidelines suggest to administer at least one anti-hypertensive medication at bedtime.[95] Further, in the International Database in Ambulatory blood pressure in relation to Cardiovascular Outcomes showed a difficult in BP control in diabetes subjects with MHT, with worst outcomes, so the clinician may pay particular attention in BP control of this group.[96] Despite the increased adoption of HBPM and clear utility for diagnosis, as demonstrated in obese patients,[97] ABPM remain the best method to correctly assess the cardiovascular prognosis also at follow-up.[98]

Conclusions

WCHT and MHT are two opposite phenomena, which represent an incorrect quantification of the patient's BP profile, leading often to an inappropriate treatment with consequences on CV prognosis. WCHT is a situation of higher risk when compared to normotensives, caused by an hyperadrenergic state, with a high prevalence which increases with age. By contrast, MHT can be also in young patients an important source of morbidity, mainly determined by an underestimation of BP control during the 24 h.

Both MHT and WCHT are often associated with metabolic risk factor, odds ratio, and the development of sustained hypertension, but MHT seems to be a condition with a worse prognosis. In daily clinical practice the identification and the management of these two conditions, especially through ABPM but

also with HBPM, is of crucial importance for patient's lifetime CV risk.

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