

Masked Hypertension: a common diagnostic issue in clinical practice

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Abstract

Out-of-office blood pressure measurement is necessary for the diagnosis of the white coat and masked hypertension phenomena. The terms masked hypertension for untreated subjects and masked uncontrolled hypertension for treated ones are used to define subjects with low office and elevated out-of-office blood pressure. The masked hypertension phenotypes are more common in younger males with high-normal office blood pressure. Both conditions are associated with increased cardiovascular risk compared to normotensives or controlled hypertensives. The reliable diagnosis and the optimal management of masked hypertension is important, yet only recently this was clearly recommended in hypertension guidelines. Masked hypertension detected only by ambulatory blood pressure monitoring and not by home monitoring, or the reverse, is not uncommon. Such cases are often miss-diagnosed in clinical practice and both ambulatory and home blood pressure monitoring are needed for accurate diagnosis and efficient cardiovascular prevention.

Keywords: masked hypertension, diagnosis, hypertension, home blood pressure, ambulatory blood pressure, cardiovascular risk

Introduction

Out-of-office blood pressure (BP) evaluation is now regarded as indisputable for the accurate diagnosis and management of hypertension [1,2]. Thus, the

white coat hypertension and masked hypertension (MH) phenomena cannot be identified, unless out-of-office BP monitoring methods are applied with 24-hour ambulatory (ABP) or home blood pressure monitoring (HBP). Office blood pressure (OBP) is an established screening method for hypertension detection, yet an imperfect one as it typically misses all cases with MH which are falsely characterized as normotensive [3]. Thus, the BP level and the cardiovascular (CV) risk are underestimated and necessary antihypertensive treatment is not offered [4].

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Definitions

MH is defined as office normotension and out-of-office hypertension in untreated subjects, whereas in subjects treated for hypertension who have low OBP but elevated out-of-office BP a more suitable term is masked uncontrolled hypertension (MUCH), implying that post treatment OBP is normalized but out-of-office BP remains elevated [1,2]. For practical reasons MH is often used to describe both MH and MUCH phenotypes.

There is a significant heterogeneity among studies and guidelines on the definition of out-of-office hypertension. Both HBP and ABP are proposed for diagnosing MH, yet it is not clear whether both of them are needed, or if abnormality in only one of them is adequate for MH diagnosis. A study which investigated this issue showed disagreement in the diagnosis of masked hypertension using HBP or ABP in 23% of cases for systolic BP and 30% for diastolic [4]. MH can be ‘dual’ or ‘isolated’ on the basis of ABP and HBP levels. In dual MH both ABP and HBP are abnormal, whereas in isolated ABP MH OBP and HBP are normal with the abnormality identified only by ABP monitoring. Conversely, isolated HBP MH is defined as normal OBP and ABP with BP abnormality identified only by HBP monitoring [5,6].

ABP monitoring is considered as the gold standard for out-of-office BP evaluation. However, it is not clearly stated whether 24-hour, daytime or nighttime ABP, or any combination of them should be considered for MH diagnosis. Anstey et al. used all these three ABP parameters for MH definition, while other studies used only 24-hour ABP, or only

daytime ABP [5,6]. A logical consideration would be that the most representative indice of ABP should be preferred for MH definition. This indice is the one that includes measurements taken during the entire 24-hour period, which is average 24-hour ABP (Table 1).

Epidemiology

MH is common among both treated and untreated subjects. Almost 10-20% of subjects attending hypertension clinics who eventually have low OBP have out-of-office hypertension, namely MH [7]. In large datasets of subjects treated for hypertension the prevalence of MUCH is about 30% [8,9].

Several factors may be responsible for the BP measurement methods disagreement which results in the MH phenomenon. The most important factor seems to be age [10]. A study that evaluated 462 children, adolescents and adults demonstrated a dynamic relationship between age and the office – out-of-office BP difference, and indicated that MH is more likely to be detected in younger subjects [10]. Daytime ABP was higher than OBP and HBP in children, whereas as age approached the third decade daytime ABP and HBP tended to have the same values, both being lower than OBP. In subjects ≥ 60 years daytime ABP tended to be lower than HBP and OBP [10].

Apart from age, there are other important determinants of MH. In a meta-analysis of 70 studies (86,167 subjects) male gender, smoking, increased body mass index and increasing systolic OBP were shown to be related with increased risk of MH [11].

Table 1. Phenotypes of masked hypertension.

Blood pressure (mmHg)	Dual MH	Isolated Ambulatory MH	Isolated Home MH
Office	<140/90	<140/90	<140/90
24h Ambulatory	$\geq 130/80$	$\geq 130/80$	<130/80
Home	$\geq 135/85$	<135/85	$\geq 135/85$

MH, masked hypertension.

Table 2. Determinants of masked hypertension.

	Any MH	Isolated Ambulatory MH	Isolated Home MH
Younger age	↑	↑	↓
Male gender	↑	-	-
Smoking	↑	-	-
Increased BMI	↑	-	-
High-normal BP	↑	-	-
High CV risk	↑	-	-

MH, masked hypertension; BMI, body mass index; BP, blood pressure; CV, cardiovascular.

High CV risk, due to diabetes mellitus, peripheral artery disease, chronic kidney disease, obstructive sleep apnea, or left ventricular hypertrophy, also predicts MH diagnosis [12,13] (Table 2).

MH detected only by ambulatory (isolated ABP MH) or only by home BP monitoring (isolated HBP MH) is not uncommon. Anstey et al. showed that only 1/3 of subjects had MH identified by using both ABP and HBP measurements. The vast majority of subjects (61%) had isolated ABP MH [5]. In a retrospective analysis of cross-sectional data in treated or untreated adults from Greece, Finland and UK, 445 out of 1,971 subjects (23%) had MH. Among subjects with MH, 215 had MH by using both ABP and HBP measurements (48%), 132 had isolated ambulatory MH (30%) and 98 had isolated home MH (22%) [6]. Again age came out as a crucial factor, predicting not only office versus out-of-office BP disagreement, but also the differences between the two out-of-office BP measurement methods. Age appears to be the most important determinant with isolated ambulatory MH being more common in younger subjects and isolated home MH in older ones [6] (Table 2). Possible explanation of this phenomenon is that younger subjects have more intense physical activity and experience more job strain and high responsibility duties than older ones, resulting in higher daytime ABP than HBP

levels [14]. On the other hand, elderly subjects experience more often orthostatic hypotension events, resulting in lower daytime ABP values and may find self-monitoring of BP more stressful resulting in higher HBP levels [15].

Prognostic relevance

The prognostic relevance of MH and MUCH has been well established through population-based outcome studies using either ABP and/or HBP measurements. In some studies MH has been associated with increased CV risk and worse CV outcomes even compared to sustained hypertension. This phenomenon reflects the difficulty of MH detection, which often remains undiagnosed and therefore inadequately treated.

In a meta-analysis of 7,030 subjects from Belgium, Denmark, Japan and Sweden, hazard ratio (HR) for all CV events was 1.62 (95% CI 1.35-1.96; P<0.0001) for MH compared to normotension [16]. Similarly, in a cohort of 4,939 treated elderly hypertensive patients the HR for all CV events was 2.06 (95% CI, 1.22-3.47) for MH compared to controlled BP [17]. Similar results have been found in other cohorts and population-based studies [18-20].

MH is strongly associated not only with CV event incidence but also with total mortality compared to normotension or well controlled OBP hypertension. A general population study in Greece with 19-year follow-up showed that MH was associated with increased risk of death versus normotensive participants [20]. Similar results were reported by the PAMELA study in Italy [21]. Impressive results were derived from the Spanish ABP monitoring registry, where 63,910 hypertensive patients in primary care were recruited from 2004 through 2014 and were assessed with OBP and ABP. MH was more strongly associated with all-cause or CV mortality (HR, 2.83; 95% CI, 2.12-3.79) than sustained hypertension (HR, 1.80; 95% CI, 1.41-2.31) [22]. Thus, the prognostic relevance of MH regarding CV events and CV or total mortality remains highly relevant even in treated hypertensives (MUCH). Treated patients with uncontrolled out-of-office BP carry increased CV risk when compared to well controlled (both in office and out-of-office BP measurements) hypertensives [23].

Diagnosis

Given the clinical relevance of MH and MUCH, the timely detection and treatment of these conditions is of vital importance for CV disease prevention. However, there is no clear consensus on the optimal approach for MH diagnosis and follow-up in untreated and treated individuals [1,2]. Recent guidelines recommend the use of any out-of-office BP monitoring method (ABP or HBP) when MH is suspected. In fact, out-of-office BP monitoring is suggested in case of high-normal OBP, or in case of normal BP and increased total CV risk. However, in a recent study among 445 subjects with MH, 55% had high-normal OBP, 35% normal and 10% optimal OBP, implying that OBP within the high-normal range predicts only half of subjects with MH, the other having lower OBP levels. Thus, guidelines suggesting that the investigation for MH is necessary in subjects with OBP within the high-normal OBP range and not at lower OBP levels should probably be reconsidered [6].

As mentioned above, if only HBP or only ABP is used for the definition of out-of-office hypertension,

then there is the risk of misdiagnosing isolated ABP or isolated HBP MH, respectively. Given the recent evidence showing that MH detected by either method carries the same detrimental CV risk, both methods are necessary to exclude MH in subjects with office normotension [6].

Conclusions

Hypertension has been characterized through literature as the “silent killer” due to the fact that it remains asymptomatic and often is discovered only after a CV event has occurred. MH and especially MUCH which are not rare conditions, are even more difficult to be detected in routine clinical practice. This difficulty lies in the fact that most general practitioners in primary care setting base their therapeutic decisions exclusively on OBP measurements. In terms of population screening, OBP remains a basic tool for BP evaluation. However, the out-of-office BP measurement methods should be more systematically integrated in routine BP evaluation in primary care. For the complete evaluation of the BP profile and behavior both HBP and 24-hour ABP monitoring are required, which provide complementary and not fully interchangeable information.

Conflict of interest

The authors confirm that there are no conflicts of interest.

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