Hypertension Research (2023) 46:778–780
https://doi.org/10.1038/s41440-023-01182-5

COMMENT

# Masked hypertension: how not to miss an even more silent killer

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**Keywords** Detection · Masked hypertension · Out-of-office · Prediction · Screening

Received: 7 December 2022 / Revised: 19 December 2022 / Accepted: 21 December 2022 / Published online: 16 January 2023


The term "masked hypertension" (MH) was introduced by Thomas Pickering in 2002 [1] to describe a hypertension phenotype characterized by diagnostic disagreement between office and out-of-office blood pressure (BP) measurements [1, 2]. MH refers to untreated individuals with normal office (OBP) but elevated out-of-office BP [home (HBP) and/or ambulatory (ABP)], while "masked uncontrolled hypertension" (MUCH) refers to a similar diagnostic disagreement but among individuals treated for hypertension [2]. These intermediate hypertension phenotypes reflect certain BP variability patterns and require confirmation with repeated standardized office and out-of-office BP evaluations [2].

MH has gained interest for three important reasons. First, it is not rare, and depending on its definition and BP measurement methodology, it has been reported to affect 10–20% of individuals attending hypertension clinics [2]. Second, MH is not an innocent phenomenon and is accompanied by an adverse cardiovascular prognosis that is close to that of sustained hypertension [2]. Third, the term "masked" implies diagnostic difficulty, requiring out-of-office BP evaluation [2]. Although current guidelines highlight the importance of the accurate diagnosis of hypertension, the classification of hypertension and the BP goals of treatment are largely based on OBP measurements [2]. In this context, MH may remain undiagnosed and may be proven to be an "even more silent killer" than office hypertension.

Alves et al., in their recent paper in the *Hypertension Research* journal, attempted to address the issue of the optimal screening strategy for MH [3]. In a cross-sectional nationwide study of 686 medical centers in Brazil that included 22,000 treatment-naïve individuals with normal OBP, OBP and HBP measurements were used to investigate different methodologies for detecting MH. They showed that the implementation of the MH screening algorithms recommended by the European Society of Cardiology/European Society of Hypertension (ESC/ESH), the American College of Cardiology/American Heart Association (ACC/AHA), and the Brazilian Society of Cardiology (BSC), which are mostly based on high-normal OBP status, could lead to misclassification and misdiagnosis of MH in a considerable proportion of individuals. The authors developed a risk score for MH screening based on logistic regression models using five clinical variables [(systolic and diastolic OBP, age, sex and body mass index (BMI)] known to be associated with MH and easily obtained in clinical practice. After external validation in a cohort of 2,807 subjects, the authors concluded that MH phenotype prediction was more accurate using their risk score than when following the guideline-proposed algorithms.

Male sex, BMI and current smoking status have been identified as significant determinants of MH [4]; however, borderline elevation of OBP with levels between the normal and high OBP range appears to be the strongest determinant of MH [2, 4, 5]. This OBP range is variably defined in different guidelines as "high-normal BP" by the ESC/ESH, "elevated BP" by the ACC/AHA, or "prehypertension" by the BSC (Table 1). Alves et al. showed that the OBP level-driven screening strategy for MH detection has limited diagnostic accuracy. Among participants deemed as having MH by ESC/ESH and BSC criteria, only 59.1% and 53.2% had OBP levels at 130–139/85–89 mmHg (high-normal or prehypertension), respectively. Moreover, among participants with MH by the ACC/AHA criteria, 73.7% had OBP levels at 120–129/75–79 mmHg (elevated BP). Thus, 30–50% of individuals with MH would not have been characterized as high risk for MH by current guidelines' proposed screening methods and would probably remain undiagnosed and untreated. These

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**Table 1** Proposed screening strategies for masked hypertension

| | Strategies/Variables used to indicate high probability for MH |
|---|---|
| ***Guidelines strategies*** [3] | |
| BSC, 2020 | • OBP 130–139/85–89 mmHg |
| ESC/ESH, 2018 | • OBP 130–139/85–89 mmHg<br>• OBP < 130/85 mmHg with HMOD or at high total cardiovascular risk |
| ACC/AHA, 2017 | • OBP 120–129/75–79 mmHg |
| ***Other strategies*** | |
| Alves et al. (present study) [3] | • Risk score generated from multivariable logistic regression analysis<br>• Based on 5 clinical variables (systolic/diastolic OBP, age, sex, BMI) |
| Hung et al. [9] | • Machine learning-based predictive models<br>• Based on 33 candidate variables (demographics, OBP parameters, antihypertensive treatment usage, biochemical profiles) |
| Booth JN 3rd et al. [10] | • OBP index equation<br>• Based on OBP (OBP index = systolic OBP + 1.3*diastolic OBP) |
| Sheppard et al. [11] | • PROOF-BP equation<br>• Based on 10 variables (demographics, OBP parameters, medical history, antihypertensive treatment use) |

*ACC/AHA* American College of Cardiology/American Heart Association, *BMI* body mass index, *BSC* Brazilian Society of Cardiology, *ESC* European Society of Cardiology, *ESH* European Society of Hypertension, *HMOD* hypertension mediated organ damage, *OBP* office blood pressure, *MH* masked hypertension, *PROOF-BP* Predicting Out-of-Office Blood Pressure in the Clinic

findings are in line with those of an analysis of a database from Greece, Finland and the UK, which showed that among 445 treated and untreated individuals with MUCH and MH assessed using both HBP and ABP monitoring, 55% had high-normal OBP, 35% had normal (120–129/80–84 mmHg) OBP, and 10% had optimal OBP levels (<120/80 mmHg) [5]. Thus, almost half of the individuals with MH had normal or even optimal OBP levels (ESC/ESH criteria). Due to this imperfect predictive potential of high-normal OBP status, alternative approaches for MH screening have been considered (Table 1).

Although the findings of the study by Alves et al. are praiseworthy, there are some key points that need to be addressed [3]. An important methodological issue is that OBP and HBP measurements were not performed according to the guidelines' proposed protocols. OBP was measured twice at a single office visit, and HBP was monitored for 4 days. The results of the study would have been different if OBP was measured at more visits and the average of the second and third reading was used and HBP was monitored for 7 days with the first day readings discarded, which is the optimal recommended schedule [2, 6]. The optimal assessment of measurement methods would probably result in lower OBP and HBP levels, which could affect the MH classification in selected cases.

Another important factor that influences the accuracy of MH diagnosis and was not considered in the study by Alves et al. is the impact of using 24-h ABP monitoring. Had ABP monitoring been used instead of HBP monitoring, these results would probably differ since among younger individuals, ABP identifies more cases with MH than HBP monitoring and fewer cases among older individuals [5]. A recent study including 445 individuals with MUCH and MH showed that half of them had elevated ABP but not HBP or the reverse [5]. Age appeared to be an important determinant of these "partial" phenotypes (isolated increased ABP or HBP), with isolated ambulatory MH being more common among younger individuals and isolated home MH among older individuals [5]. Alves et al. also reported increasing age to be a significant determinant for MH diagnosis, with positive regression coefficients for higher age subgroups [3]. If ABP was used instead of HBP, these coefficients would probably indicate an inverse association of age with ambulatory MH diagnosis. The same might have been observed with sex, since female sex was shown to be a significant determinant of isolated ambulatory MH [5]. This implies that the MH score proposed by the authors would probably be inappropriate for MH prediction when ABP is used instead of HBP. Moreover, in a recent study among 445 individuals with MUCH detected by ABP or HBP using the same BP device, the diagnostic agreement between the two methods was 30% [7].

Partial MH phenotypes appear to be associated with higher cardiovascular risk than normotension but lower cardiovascular risk than "dual" MH (confirmed by both ABP and HBP) [8]. In this context, the optimal approach would be to implement both ABP and HBP. If both methods were considered in the study by Alves et al., the prevalence of dual MH would have been significantly lower than that observed using solely HBP monitoring. Moreover, age would probably fail to predict the dual MH phenotype. Finally, dual MH was also associated with established cardiovascular disease in a recent analysis [5], which supports the ESC/ESH recommendation to specifically suspect

MH in all individuals with OBP below the hypertension threshold when there is evidence of target organ damage or their total risk is high (Table 1). Data on established cardiovascular disease and total cardiovascular risk were not available in the study by Alves et al. and require further validation regarding their predictive role for MH diagnosis.

Although OBP may be misleading in a considerable proportion of individuals, it will probably remain the cornerstone for the evaluation and management of hypertension in many settings, as the routine implementation of HBP and ABP monitoring may not be feasible. Alves et al. suggested an interesting approach for MH screening, which takes into consideration not only OBP levels as proposed by most guidelines but also simple and easily obtainable clinical variables. This approach should not convey the wrong message that any screening technique is able to replace the imperative need for out-of-office BP monitoring, especially in individuals with high-normal OBP or those with high total cardiovascular risk. Nevertheless, this approach serves as a promising tool to enhance the detection of MH in settings where HBP or ABP monitoring are not widely available.

## Compliance with ethical standards

**Conflict of interest** The authors declare no competing interests.

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