Review

Masked Hypertension: Lessons for the Future

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Abstract

Masked hypertension (MH) is a commonly overlooked phenotype of hypertension in practice. Lifestyle factors and conditioned stress response specific to out of clinic blood pressure readings may be the mechanisms leading to this phenomenon. 24-hour ambulatory blood pressure monitoring or home blood pressure monitoring in an out of office setting are required for its reliable diagnosis. MH has a high risk of progressing to sustained hypertension with comparable cardiovascular and mortality risk. In this review, we discuss current evidence-based perspectives on definition, pathological mechanisms, risk factors, screening, clinical implications, and treatment of MH.

Introduction

Blood Pressure (BP) is a fluctuating phenomenon that was historically quantified exclusively by static measurements in the physician's office. Variability of BP values when the subject's measurement was done in a medical environment using mercury or aneroid sphygmomanometer led to the advent of out of office BP measurement techniques. The validity of office blood pressure measurement (OBPM) was first questioned by Ayman and Goldshine in a landmark paper published in 1940 which revealed differences between office blood pressure and home blood pressure readings before treatment, signifying the role of home blood pressure monitoring (HBPM) to improve the precision of diagnosis and treatment of hypertension.[1] In 1962, the first device for non-invasive ambulatory blood pressure monitoring (ABPM) was developed by Hinman and colleagues.[2] Subsequent pioneering work by Sokolow et al showed that ambulatory blood pressure values correlated more with cardiovascular damage compared to casual office BP values and established the role of ABPM in hypertension management.[3,4] The spectrum of BP values measured across different modalities of measurement led to the identification of four BP phenotypes (Figure 1):

1. Normal or Controlled BP - Normotensive BP measured in office and in out of office setting.

2. Whitecoat hypertension (WCH) -High office BP but normal out of office BP.

3. Masked hypertension (MH) – Normal office BP but high out of office BP.

4. Uncontrolled or sustained hypertension (SH) – High office and out of office BP.

BP that is normal at a physician's office but higher in other settings is known as Masked hypertension (MH). Pickering first coined the term masked hypertension for the entity which was previously referred to as reverse white-coat effect, isolated clinic normotension, isolated ambulatory hypertension.[5,6] It is a commonly overlooked phenotype of systemic hypertension.

Pathomechanisms

Mechanisms leading to MH may be classified into two groups which may not be mutually exclusive:[7]

1. Low office BP relative to ambulatory BP – The exact cause of low office BP compared to ambulatory BP is unknown. But extrapolating our understanding that WCH may in part be a conditioned anxiety response that is relatively specific to the clinic setting, the reverse could be true in MH, where the anxiety or stress response is higher out of the doctor's office. Office BP in some elderly hypertensives measured after meals may show significant post-prandial reduction leading to a diagnosis of MH.[8]

2. Selectively high ambulatory BP – Lifestyle factors such as smoking, alcohol, physical inactivity, interpersonal

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	Office BP **HIGH**	Office BP **NORMAL**
Out Of Office BP **HIGH**	Sustained Hypertension	Masked Hypertension
Out Of Office BP **NORMAL**	White Coat Hypertension	Normal Blood Pressure

Figure 1 - Blood Pressure Phenotypes

conflicts, mental anxiety, and job stress could selectively increase ambulatory BP. Sedentary, obese individuals may have poor exercise tolerance through daily activity showing pre-hypertensive BP values in office when measured at rest. Exaggerated BP response to exercise (EBPR) is also associated with MH. Kayrak et al studied sixty-one normotensives with EBPR by ABPM. The prevalence of MH in subjects with EBPR was 41%. Diastolic BP measured at peak exercise was an independent predictor of MH in subjects with EBPR.[9] Because of these factors, measurement of BP should rely on anxiety neutral approaches like automated office blood pressure (AOBP) in office and ABPM or HBPM out of office.

Incidence, Prevalence & Risk Factors

Data on the incidence of MH is scarce. In the Ohasama study from Japan, which included 649 normotensive subjects by conventional and HBPM measurements, the incidence of MH requiring treatment was found to be 11.3% after a follow-up of 8 years.[10] This correlated with the more recent study by Trudel et al where 1836 normotensive patients by ABPM were followed for 2.9 years with the cumulative incidence of MH at 10.3%.[11] Current data on the prevalence of MH is highly variable due to differences in ethnicity of study groups, the heterogeneous definition of MH, and measurement tools used (ABPM/HBPM/Daytime/Nocturnal/24 Hour ABPM) for its diagnosis. Overall, the prevalence of MH in the general population ranges from 8.5% to 16.6%.[12] The prevalence increased to 30.4% in populations with high normal clinic BP.[12] In a systematic review by Thakkar et.al, the prevalence of MH was significantly higher in patients of African ethnicity with prevalence as high as 52.5% in African-Americans as compared to lower values in patients of Korean (5.7%) and Omani (6%) descent.[13] The presence of comorbidities also influenced the prevalence of MH, with 30% in obstructive sleep apnea (OSA), 13.3% to 66.4% in diabetes, 7% to 32.8% in chronic kidney disease (CKD), 15% in haemodialysis and 16% to 39% in renal transplant recipients.[13]

In a prospective study, risk factors for MH identified are male gender, age > 40 years, body mass index (BMI) > 27, smoking, and alcohol intake > 6 drinks/week.[14] Interestingly, people with a habit of smoking, substance abuse, and alcoholism had a high prevalence of MH as they are often abstinent when visiting doctors and record lower or normal clinic BP.[13] Another issue for accurate estimation of MH prevalence is the reproducibility of MH in subsequent measurements. There is limited evidence in this aspect. De la Sierra et al reported the reproducibility of MH diagnosis over a median period of 3 months was only 47%.[14] In this study, the authors concluded that MH phenotype is reproducible only in the short term and frequently shift towards SH in the long term.[15]

Screening

The 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) blood pressure guidelines suggest screening for MH in these populations:

1. Individuals with clinic systolic blood pressure (SBP) 130-139 mmHg or diastolic blood pressure (DBP) 85-89 mmHg.

2. Patients with hypertension-related target organ damage (arterial stiffening, peripheral vascular disease, retinopathy, proteinuria, CKD, left ventricular hypertrophy (LVH).

3. Subjects with high cardiovascular risk (calculated 10-year systematic coronary risk evaluation of >5%). The method of out of clinic measurement is by validated HBPM device or ABPM.[16]

Diagnosis

Accurate diagnosis of MH hinges on the reliable measurement of the clinic and out of clinic BP measurement. In a systematic review and meta-analysis by Roerecke et al, AOBP, when recorded with the patient sitting alone in a quiet place, is more accurate than office BP readings in routine clinical practice and similar to awake ambulatory BP readings with mean AOBP negating white coat effect.[17] Health care providers must ensure clinic BP measurement using a device validated by British and Irish Hypertension Society[18] and manually exclude conditions with pulse irregularity like atrial fibrillation as automated devices may not measure BP accurately in these conditions.[19] An appropriate cuff size to the person's arm should be used. In individuals who have normal BP (<140/90 mmHg) during clinic measurement may be stratified into 3 categories:

1. Optimal office BP (<120/80 mm Hg)

2. Normal BP (120-129/80-84 mm Hg)

3. High normal BP (130-135/85-89 mmHg)[16]

In persons with high normal BP, a possibility of MH should be considered and an out of office BP measurement by HBPM or ABPM should be pursued. In all categories, focused evaluation with history, physical examination, and diagnostics for hypertension mediated target organ damage (HMOD) should be done. Basic screening tests include the 12-lead electrocardiogram (ECG) to look for LVH, urine albumin to creatinine ratio (ACR), blood creatinine and estimated glomerular filtration rate (eGFR) to detect possible renal disease and optic fundoscopy to detect hypertensive retinopathy.[16]

Cardiovascular (CV) risk has to be estimated based on risk factors using the QRISK3 score to assess 10-year CV risk.[9] Individuals with high CV risk (>5%) should be further evaluated with out of office BP measurements to screen for MH. The National Institute for Health and Care Excellence (NICE) guidelines of 2019 for diagnosis and management of hypertension in adults define MH as normal blood pressure (<140/90 mm Hg) during a clinic visit, but higher than 140/90 mm Hg when measured outside the clinic using average daytime ambulatory blood pressure monitoring (Day-ABPM) or average HBPM measurements.[19]

Classification

The positive difference between office and out of office BP measurements further identifies 3 subtypes of MH.

1. Masked Effect – BP in an untreated subject measured with ABPM or HBPM is higher than the corresponding normal clinic BP but within the target. A study from the Netherlands in healthy volunteers by Aksoy et al showed that home BP can be significantly higher compared to office BP although both values can remain in normotensive range.[20]

2. Masked Hypertension - BP in an untreated subject measured with ABPM or HBPM is higher than the corresponding normal clinic BP and target out of office BP threshold.

3. Masked Uncontrolled Hypertension (MUCH) – BP in patients on antihypertensive treatment where office BP is on target and out of office BP is not on target.

MH can also be classified based on ABPM into two types [21]

1.Masked daytime hypertension – This pattern is observed in individuals with job stress, smoking, poor exercise tolerance, or heavy alcohol consumption.

2. Masked night-time hypertension- This is seen in the context of OSA, diabetes, CKD, sleep deprivation, or metabolic syndrome.

Many patients with MH will show both daytime and night-time MH. Among the out of office BP measurement modalities, there is little evidence to determine whether HBPM, ABPM, or both should be used for accurate diagnosis of MH. HBPM is more readily available, easier to perform, and easier to monitor. ABPM is cumbersome and more costly, though 24-hour ABPM is the gold standard for out of office BP measurement. Out of office BP measurement should be done preferably by ABPM. If ABPM is unsuitable or the person is unable to tolerate it, HBPM should be offered for diagnosis of hypertension.[19] When using ABPM, at least 2 measurements per hour should be taken during the persons waking hours and the average value of at least 14 measured values noted during the persons usual awake hours should be used to diagnose hypertension.[19]

When using HBPM, it must be ensured that for each BP recording 2 consecutive measurements are taken at least 1 min apart with a person seated. Additionally, HBPM should be recorded for at least 4 days and ideally 7 days with BP recordings twice daily in the morning and in the evening. If hypertension is not diagnosed by the clinic and out of office BP measurement, but target organ damage is evident, consider work up for alternative causes of target organ damage. BP should be measured annually in adults with type 2 diabetes, and at least every 5 years or more frequently in persons without hypertension or target organ damage. Preventive lifestyle advice should be reinforced.

There are considerable variations among various guidelines regarding the technique of out of office measurement of BP and the threshold values for the diagnosis of hypertension. (Figure 2) In contrast to the NICE UK 2019 and American College of Cardiology/American Heart Association (ACC/AHA) 2017 hypertension guidelines which prefer day BP, the ESC/ESH 2018 consider either day, night, or 24 hours mean BP for diagnosis of hypertension. In a study by Anstey
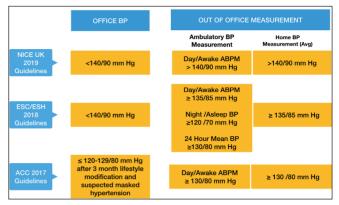

Figure 2 - Definition of Masked Hypertension

et al which evaluated the overlap between HBPM and ABPM for diagnosis of MH, majority of untreated hypertensive subjects had hypertension by ABPM with an associated increase of left ventricular mass index (LVMI) compared to a diagnosis of hypertension by HBPM which did not correlate with increased LVMI suggesting that ABPM is essential for identifying individuals with MH who are at high CV risk.[22] Inferences from the Jackson Heart Study suggest that night time BP is an overlooked component of 24-hour ABPM which correlated not only with MH more than day-ABPM, but also the progression of CKD and poor CV outcomes in the African-American population.[23,24]

In summary, based on current evidence, ABPM is the preferred out of office method to screen for MH with emphasis on considering night ABPM measurement in individuals with African ancestry.

Adverse outcomes

Observations from the Finn-Home study revealed MH phenotype had the highest risk of progression to SH compared to normotension or WCH during an 11 year follow up.[25] Robust data from meta-analyses support MH association with increased risk of CV events, target organ damage, and mortality which is comparable to the risk of having SH. Re-analyzed cross-sectional analysis of several studies showed that patients with MH have higher left ventricular (LV) mass often comparable to SH.[26] This correlation was also found in patients treated with antihypertensive medications. Meta-analyses by Cuspidi et al showed that MH is also associated with increased LVMI and increased carotid intima-media thickness which is a presumed indicator of early atherosclerosis.[27,28]

In a systematic review and meta-analysis by Palla et al,[29] CV events and all-cause mortality were higher in patients with MH compared to normotension and WCH. Though composite CV events were low in MH compared to SH, the all-cause mortality due to MH did not show a significant difference compared to SH.[29] In patients who underwent treatment with antihypertensives, there was no significant difference in composite CV events and all-cause mortality between the patients with MH and SH. However, in treated patients, MH was associated with higher rates of CV events compared with normotension and WCH.[29]

A large observational cohort study from Japan which included 4261 hypertensive outpatient participants, where MH was defined based on HBPM and median follow-up was for 3.9 years, showed that MH was associated with greater risk of stroke compared to a group with controlled BP independent of CV risk factors like urine ACR and circulating B-type natriuretic peptide levels.[30] Analysis of the Dallas Heart Study showed an increase in aortic pulse wave velocity, cystatin C and urine ACR in persons with MH and conferred a 2.03 times increased risk of CV events compared to normotensives at 9-year median follow-up after adjusting for traditional CV risk factors.[31]

Clinical implications in special patient groups

Diabetes – The prevalence of MH is higher in patients with diabetes compared to those without diabetes.[32] In untreated diabetics followed for a median duration of 11 years, the adjusted risk for CV events for masked hypertensive patients was higher, compared to sustained normotensive subjects (HR: 1.96; 95% CI: 0.97–3.97; P=0.059) and similar to untreated stage 1 hypertensives (HR: 1.07; 95% CI: 0.58–1.98; P=0.82) but less than stage 2 hypertensives (HR: 0.53; 95% CI: 0.29–0.99; P=0.048).[32]

CKD – Cross sectional data from the Chronic Renal Insufficiency Cohort (CRIC) study by Drawz et al[33] showed MH measured by ABPM was independently associated with low estimated glomerular filtration rate (eGFR -3.2ml/min/1.73m2 ; 95% CI – 5.5 to -0.9 ml/min/1.73m2), greater LVMI (2.52 g/m2.7; 95% CI, 0.9 to 4 g/m2.7), pulse wave velocity (+0.92 m/s; 95% confidence interval,0.5 to 1.3 m/s) and higher proteinuria (+0.9 unit higher in log2urine protein; 95% CI, 0.7 to 1) compared with controlled BP.

Persons of African ethnicity – The Jackson Heart Study showed a high prevalence of MH in African Americans. Specifically, isolated nocturnal hypertension was noticed in 19% subjects by ABPM with mean office BP of 124/76 mm Hg.[34] They also had greater left ventricular mass and 3 times higher odds of left ventricular hypertension compared to normotensives.[34]

Outcomes of Masked Uncontrolled Hypertension (MUCH)

In a meta-analysis by Pierdomenico et al, patients with MUCH had a significantly higher risk of CV events and all-cause mortality compared to those with controlled hypertension.[35] The prognostic effect of MUCH was similar, whether the measurement was done by ABPM or HBPM. The overall adjusted hazard ratio was 1.80 (95% CI, 1.57–2.06) for MUCH versus controlled hypertensives.

Treatment

MH is a high-risk phenotype of hypertension and should not be left untreated. Unfortunately, many patients with MH have been excluded from hypertension trials due to normal office BP values leading to a paucity of data regarding the best way to treat MH. There have been no prospective clinical trials to evaluate the effect of treating MH and its impact on CV events and mortality. However, consistent evidence pointing to CV risk in patients with MH suggests prompt treatment of MH despite lack of evidence.

It is reasonable to consider pharmacological management in identified MH patients after optimizing their metabolic profile by treating the modifiable risk factors like obesity, diabetes, OSA, avoidance of alcohol, smoking, addressing work-related issues if any, and psychosocial factors. Another approach is to use antihypertensives to reduce ambulatory BP despite the absence of elevated office BP and monitor response to treatment by periodic ABPM.

Retrospective analyses of JMS-1 (Japanese Morning Surge-1) study and J-TOP (Japanese Morning Surge -Target Organ Protection) study showed treatment of MH targeting morning home BP was associated with regressions in surrogates of target organ damage like urine ACR, pulse wave velocity and LVMI over 6 months.[36] Effective CPAP in patients with OSA was shown to reduce MH.[37] The Spanish Registry Study which followed 2115 treated hypertensive patients for 4 years noted that night time, but not daytime SBP predicted CV events (hazard ratio per SD increase, 1.45: 95% CI, 1.29–1.59) suggesting the need for good nocturnal BP control.[38] Inferences from Spanish registry study and Jackson Heart Study show isolated nocturnal hypertension as a variant of MH and poor control of nocturnal BP is twice more common than daytime ABPM control and favour the importance of using 24-hour ABPM to monitor BP control during treatment both during daytime and night especially in high-risk patients.[39]

A double-blinded placebo-controlled randomized controlled trial (RCT) by Hare et al studied the impact of fixed-dose spironolactone (25 mg daily) in 115 untreated individuals without hypertension but with a hypertensive response to exercise (exercise SBP >210 mm Hg in men or >190 mm Hg in women, or DBP >105 mm Hg).[40] In the subgroup analysis of the 40% of participants with MH by daytime ABPM using a cut off of 135/85 mm Hg, the spironolactone group showed significantly greater reductions in exercise systolic BP (–10.0±12.9 vs 0.3±8.7 mm Hg, P<0.01) and 24-h ambulatory pulse pressure (–2.4±4.7 vs 2.1±8.4 mm Hg, P<0.05). However, no difference in LVMI reduction was observed between the spironolactone and placebo groups after 3 months.

Several ongoing clinical trials are investigating the impact of antihypertensive treatment in MH. Results are awaited from an RCT evaluating the effect of anti-hypertensives on the clinic and ambulatory BP, proteinuria, and target organ damage in patients with MH (ClinicalTrials.gov NCT02142881). Another large multicentric, randomized, 4-year prospective study aims to understand MH treatment based on office and out of office ABPM measurements and differences in outcome with a focus on cardiovascular (LVMI), and renal (Urine ACR) endpoints and events including all-cause mortality, CV morbidity, and mortality, cerebral morbidity and mortality (ClinicalTrials.gov NCT02804074). An interventional trial from China aims to study the role of allisartan isoproxil in the treatment of MH for target organ protection (ClinicalTrials.gov NCT02893358).

Conclusion

MH is often an occult phenotype of hypertension, the possibility of which should be considered in individuals with high normal office BP, lifestyle risk factors, and African ethnicity. 24-hour ABPM is the preferred method for diagnosis and comprehensive long-term management of MH. Individuals with MH are at high risk for progressing to SH with an equal risk of target organ damage and CV risk. RCTs to identify the optimal degree of day and night-time BP control which translates to a reduction in the CV and target organ damage risk are currently lacking and are required for future perspectives.

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