MASKED HYPERTENSION: CURRENT SCENARIO

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ABSTRACT
Masked hypertension is an emerging clinical entity with under-recognized prevalence and increased cardiovascular risk. With widespread availability of self-home monitoring of blood pressure and use of ambulatory blood pressure monitoring as gold standard, more and more evidence of its detection and prognostic implications is budding. The relationship of masked hypertension with target organ damage is well known. However, the need to identify it early and subtype it is important in preventing cardiovascular morbidity and mortality. In this review, we intend to define masked hypertension, its prevalence and causal mechanisms and subjects at-risk, subtypes, prognostic implications and rationale for its treatment.

INTRODUCTION
Blood pressure (BP) measurement techniques have always been an issue of controversy. Initial studies were based on BP measurement in a medical environment, using an auscultatory method with mercury or an aneroid sphygmomanometer. High BP variability led to the development of out-of-office BP measurement techniques like self home BP monitoring (HBPM) and ambulatory BP measurement (ABPM). These complementary methods allow clinicians to identify four types of BP status: true normotension (normotensive by both methods), sustained hypertension (SH) (hypertensive by both methods), white-coat hypertension (WCH) (hypertensive based on clinic BP and normotensive by HBPM or ABPM) and masked hypertension (MH) (normotensive by clinic BP and hypertensive by HBPM or ABPM). Thomas Pickering in 2002 proposed the term ‘masked hypertension’. The other terms which have been used for this entity are reverse white-coat effect, isolated clinic normotension, isolated ambulatory hypertension, and masked uncontrolled hypertension.

DEFINITION OF MH
Precisely speaking, MH is defined as untreated hypertensive patients with a clinic BP < 140/90 mmHg and HBPM or daytime ABPM > 135/85 mmHg. In patients treated with antihypertensive drugs, a normal BP in the office associated with a high BP out-of-office does not identify MH as subject has already been diagnosed hypertensive.

INCIDENCE AND PREVALENCE OF MH
The data on incidence of MH is scarce. Only one Japanese study of 649 subjects, who were initially normotensive with conventional and HBPM measurements, had incidence of MH to be 11% after a follow-up period of more than eight years (Table 1). The prevalence of MH has varied in various cross-sectional studies depending on the study population, settings, definition of MH and technique of BP measurement. It ranged between 8-38%. A meta-analysis showed a prevalence of 16.8% based on 28 studies. Recently, the working group for the study of MH in Spain (ESTHEN) did a prospective study of a cohort of 302 hypertensive patients followed in 75 hypertension units. Mean age was 56.2 years and 56% were male. Prevalence of MH was 48% (95% CI: 42-53). In a French study of a community-based sample of 1,814 participants aged 75 years or older, the frequency of MH was 16% in the overall sample and 41% in participants with a normal OBP. Lurbe et al. reported that a
BP pattern of MH persisted in 40% of pediatric population over a 3-year period. [8] In one mixed (untreated and treated hypertensive patients) study of prevalence of MH, ABPM and OBP readings were repeated in a subgroup of patients (82 of the initial 1494 patients), the prevalence of MH tended to increase from 8% to 18% (P = 0.06). This apparent increase was due to a significant decrease in OBP between two sessions, with no change in ABPM.9

Another issue of concern is reproducibility of MH. Evidence is limited on this subject. A recent study by Viera et al. showed that prevalence rates of MH based on office-daytime ABPM pairings were 54% and 53%, with agreement of 73% (κ = 0.47; 95% confidence interval (CI) 0.21-0.72). MH was less prevalent (43% and 35%) using HBPM-office pairings, with agreement of 69% (κ = 0.34; 95% CI 0.06-0.62). They concluded that MH appears to have fair-to-moderate reproducibility, favoring the hypothesis that office blood pressure (OBP) measurement systematically fails to identify some patients who should be treated as hypertensive.10

The big question is whether HBPM or ABPM identify the same phenomenon? In the Pressioni Arteriose Monitorate E Loro Associazioni (PAMELA) study, the prevalence of MH in untreated subjects as assessed by HBPM and ABPM was essentially the same (8-10%). Nevertheless, only 45% of the subjects with MH defined on the basis of high 24-hour systolic ABPM had systolic MH and only 57% had diastolic MH on HBPM. In another study of 438 subjects, 150 of the subjects with MH defined on the basis of high 24-hour systolic ABPM had systolic MH and only 57% had diastolic MH on HBPM.11 In another study of 261 Finnish patients, HBPM and ABPM detected 10.6 and 11.4% of MH, respectively. Only 59% of patients diagnosed as masked hypertensive with ABPM measurement also had MH on HBPM. Their agreement in the diagnosis of MH is only moderate. The results suggested that HBPM can be used to diagnose MH, but this diagnosis is not analogous with that made with ABPM.13 Though results appear to be dissimilar in various studies, however, within a given population, ABPM and HBPM identify MH in plausibly similar fashion.

### CAUSAL MECHANISMS OF MH

The mechanisms of MH can be divided into two groups of factors, reduced OBP and increased ambulatory BP. The reduced OBP in relation to ambulatory BP is often attributed to a phenomenon of ‘regression-to-mean’, wherein OBP have been consistently lower than ambulatory BP among normotensive patients.1 The absence of diagnostic labeling may explain lower OBP noted in patients with MH.12 Second, are the factors which selectively augment ambulatory BP. These include male gender, alcohol consumption, obesity, smoking, physical activity, and psychosocial factors like anxiety, interpersonal conflicts and job stress.13-15 It is well known that exaggerated BP response to exercise (EBPR) is a predictor of future hypertension. To investigate the relationship between these two entities, Kayrak et al. evaluated 61 normotensive subjects with EBPR with ABPM. The prevalence of MH among subjects with EBPR was 41%. In multivariate logistic regression analysis, the diastolic BP measured at peak exercise was detected as an independent predictor of MH in subjects with EBPR.16 Because of these factors, health care providers should rely on anxiety-neutral approaches such as ABPM or HBPM. Though, there is no convincing data, but, Pickering believed strongly that prehypertensives are the ones who progress to MH and SH.17

### SUBTYPES OF MH

MH can be sub-classified according to the pattern of ambulatory BP and causal mechanisms. The detection of subtypes and their causal mechanisms might have prognostic and therapeutic implications in long-run. Various subtypes include morning hypertension, daytime hypertension, and nighttime hypertension.21

**Morning hypertension**

It is the most common subtype of MH. There is a physiological
rise in BP in early morning (morning surge) with fall in late morning and early afternoon. It is possible that if OBP readings are taken in late morning, this circadian change may cause MH. Renin system activation and sympathetic activation occurs in early morning. The other reason for morning hypertension is use of short acting antihypertensive agents in the morning which fail to provide adequate 24-hour BP control. The prognostic significance of morning surge in BP remains obscure because of conflicting results in different studies. More and more data is forthcoming to correlate morning surge with dipping status in affecting the cardiovascular (CV) and cerebrovascular outcomes.

Daytime hypertension

It is plausibly caused by lifestyle-modifiable factors like job stress, cigarette smoking and increased physical activity. In an Italian study, of 1488 consecutive outpatients referred for routine clinical evaluation of suspected or established arterial hypertension, the risk of MH was higher in men than in women (RR 1.14;95%CI,1.01-1.28) and was higher in current smokers (RR 1.16; 95% CI, 1.04-1.30). Another study found that patients with MH exhibit lower levels of anxiety in the office than those with WCH. Yamasue et al. showed that job strain was responsible for higher rates of MH noted amongst Japanese workers compared with retirees, thus implicating psychosocial stress as a cause of MH. Cavelaars et al. showed that increasing physical activity from a very low level (e.g. watching television) to a moderate level (e.g. shopping) caused an average response of systolic blood pressure (SBP) of 11.6 mmHg and of diastolic blood pressure (DBP) of 7.0 mmHg. All these factors result in daytime hypertension.

Nighttime hypertension

Non-dippers may cause MH. This pattern is often seen in obese, those taking high salt intake, sleep apnea, chronic kidney disease, and with autonomic dysfunction. Many of these patients also show continuum to morning hypertension. The prognostic implications of this are still under investigation as data is confounding. A recent study of 2627 patients, nondippers (n = 1,039) had a highly significant morning surge—as data is confounding. A recent study of 2627 patients, of 11.6 mmHg and of diastolic blood pressure (DBP) of 7.0 mmHg.24 All these factors result in daytime hypertension.

TARGET ORGAN DAMAGE

MH has been associated with increased target organ damage (TOD) than in subjects with normotension. In a pioneer study in 1999 of 234 normotensives, 64 sustained hypertensives, and 61 masked hypertensives, Liu et al. showed that patients with MH were older with higher body mass index, blood glucose and creatinine levels. Left ventricular mass index (LVMI) and relative wall thickness were higher by 13g/m² (95% CI: 8-18) and by 0.03 (95% CI: 0.01-0.04) respectively. They had more prevalent carotid plaque (28%) than true normotensives (15%) (P<0.05); those with MH were not dissimilar to sustained hypertensives. In PAMELA study of 3200 Italian men and women, the prevalence of left ventricular hypertrophy was lower in subjects with MH (14%) than with SH (26%), but significantly higher than in patients with true normotension (4%). There is evidence for endothelial dysfunction in masked hypertensives. Kotnis et al. in his study f 1535 untreated individuals found that masked hypertensives on average had higher LVMI and carotid intima media thickness (CIMT) than normotensives. Manios et al. recently showed in his 807 subjects that prehypertensive patients with MH had higher (p<0.01) CIMT values (0.712mm; 95%CI: 0.698-0.725) than actual prehypertensives (0.649mm; 95% CI: 0.641-0.656) and normotensives (0.655mm; 95% CI: 0.641-0.670) even after adjustment for baseline characteristics. Normotensives and actual prehypertensives did not differ significantly regarding CIMT values (p>0.05). After adjusting for potential confounders, (including demographic characteristics, vascular risk factors, and OBP) prehypertension with MH was independently (p<0.01) associated with a 0.06mm increment in CIMT (95% CI: 0.03-0.09). In another study of 165 subjects, the CIMT and relative LV wall thickness (RWT) were greater in the masked nocturnal hypertension group than in the normotensive group (CIMT: 0.76+/-0.20 vs. 0.64+/-0.14 mm, p<0.05; RWT: 0.50+/-0.14 vs. 0.41+/-0.10, p<0.05). In a study of 50 African-Americans by Veerabhadrappa et al., subjects in the MH sub-group had a higher high-sensitivity C-reactive protein (hs-CRP) (P = 0.04) and diminished endothelial function (P = 0.03) compared to the true-prehypertensive sub-group (OBP: 120/80-139/89 mm Hg and ABPM: daytime <135/85 mm Hg or night-time <120/70 mm Hg). Regression analysis showed that endothelial function was inversely related to hs-CRP amongst the masked-hypertensive sub-group (R(2) = 0.16; P = 0.04). MH was identified in 58% of African Americans which suggests that a masking phenomenon may exist in a sub-group of prehypertensives who also seem to have a diminished endothelial function that could be mediated by an elevated subclinical inflammation leading to the increased CV disease. Yoon et al. in a recent study of 1019 patients showed that waist and hip circumferences and the level of fasting glucose were higher in patients with MH than in patients with WCH (p = 0.008, 0.016, 0.009, respectively). Metabolic risk factors were more frequent in patients with WCH, MH, and uncontrolled hypertension than in patients with controlled hypertension. Heart damage was more frequent in MH than in WCH (P = 0.03). In another recent study, Ishikawa et al. in 129 participants showed that masked hypertensive participants defined by 24-hour ABPM (n=13) had a higher serum glucose level (126 vs. 96 mg/dL, P=0.001) and urinary albumin-creatinine ratio (38.0 vs. 7.5 mg/g Cr, P<0.001) than the normotensive participants (n=74).
However, a few studies have not demonstrated a consistent relationship between TOD and MH. A transverse analysis of PAMELA cohort provided no evidence of a correlation between left ventricular mass and MH. In a French study of 150 subjects, no significant differences in LV mass index were seen between MH and normotensives (81.1±21.7 g/m² vs. 79.3±16.7 g/m²; P=0.99) and no differences in CIMT (664±107 µm vs. 626±75 µm). However, masked hypertensives had higher pulse wave velocities than normotensives (9.58 ±1.55 m/sec vs. 8.59 ±1.38 m/sec; P<0.05).  

### PROGNOSTIC ILLATION

Data from various studies suggest that MH portends risks for CV morbidity and mortality similar to that of SH and much higher than true normotension (Table 2). In a Swedish longitudinal study of 578 untreated elderly men, 72 comorbid events (2.37 per 100 person-years at risk) occurred over 8.4 years of follow-up. MH was an independent predictor of CV morbidity after adjustment for smoking, diabetes and cholesterol levels (HR: 2.77; 95% CI: 1.15-6.68). In a prospective study of 1700 Danish subjects, the relative risk of CV mortality (95% CI) associated with 10 mm Hg increments in systolic and 5 mm Hg increments in diastolic ABPM were 1.51 (1.28 to 1.77) and 1.43 (1.26 to 1.61). The corresponding figures for all cause mortality were 1.18 (1.06 to 1.31) and 1.18 (1.09 to 1.28). The relative risks of CV mortality were lower for OBP, and OBP did not predict all cause mortality. When ambulatory and office blood pressures were entered in the same multivariate models, only the ambulatory blood pressures were significant predictors of all cause mortality and CV mortality. The relationship between ambulatory blood pressures and risk of mortality was log-linear, with no indication of a threshold. Mancia G et al. studied 2051 subjects between ages 25 and 74 years and followed them for more than 12 years. They showed that the frequency of CV mortality as 1.1% in normotensives and 4.1% in masked hypertensives. The all-cause mortality rate was 5.7% for normotensives and 12.8% for masked hypertensives. In International Database on Ambulatory Blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) study of Scandinavian and Japanese population involving 7030 subjects, the incidence of fatal combined with nonfatal CV events amounted to 863 (228 deaths, 326 strokes and 309 cardiac events). Adjusted hazard ratios for all cardiovascular events were 1.62 (95% CI = 1.35-1.96; P = 0.0001) for MH and 1.80 (95% CI = 1.59-2.03; P < 0.0001) for SH.

There are three systematic reviews evaluating prognostic implications of MH. Borbie et al. in their meta-analysis of six studies about prognostic relevance of MH showed that compared to normotension, the overall adjusted HR was 1.92 (1.51-2.44) for MH. Fagard et al. examined seven clinical studies involving 11,502 subjects and 912 first CV events. The overall adjusted HR of MH vs. normotension was 2.00 (95% CI: 1.58-2.52). A recent meta-analysis by Pierdomenico et al. included eight studies with pooled population of 7,961 subjects who experienced 696 events. The overall adjusted HR was 2.09 (1.55-2.81; P = 0.0001), for MH vs. normotension and 2.59 (2.0-3.35; P= 0.0001) for SH vs. normotension. Thus CV risk is significantly higher in MH than in normotension. The authors felt that probably MH is largely undetected and untreated in the population. Thus, the HR between MH and normotension observed in various studies, in which a greater proportion of subjects with MH were treated, most likely under-calculates the risk of MH itself in the population in general.

### CLINICAL IMPLICATIONS

The CV risk of MH is almost comparable to that of SH. With the evidence from numerous clinical trials to treat hypertension to prevent CV morbidity and mortality, as well as prevention of TOD, it seems reasonable for masked hypertensives to undergo lifestyle changes and possibly drug treatment. In recent study of 262 treated hypertensive outpatients followed for one-year, out of 79 MH patients initially, 62.0% remained as MH, while 32.9% turned out to be normotensive a year later.

The best practically feasible method for identification of MH remains to be established. At present, though ABPM is ideally the gold standard method for identifying MH, HBPM correctly classifies most cases of MH even in children, and adolescents. A recent study in 84 patients, however, showed that a 30-minute automated OBP appeared to agree well with daytime ABPM and has the potential to detect MH. Systolic and diastolic blood pressures differed from 0 to 2 mm Hg (95% CI: -2 to 2 mm Hg and from 0 to 3 mm Hg) between mean 30-minute OBP and daytime ABPM, respectively. The limits of agreement were between -19 and 19 mm Hg for systolic and -10 and 13 mm Hg for diastolic blood pressures. This is potentially a novel approach which could prove useful in diagnosing MH.

The other issue relates to screening for MH. Since it is not feasible to screen population at large, there needs to be targeted screening for at risk subjects. (Figure 1) Even with
data emerging for antihypertensive treatment, there are still no consensus guidelines. However, an algorithm 43 could help in diagnosing and following masked hypertensives till such evidence becomes available (Figure 2).

CONCLUSION
MH is a clinical entity which needs to be assessed in at-risk population. The availability of self-monitoring of BP at home and ABPM would lead to its identification. Once identified, adequate management strategies should be instituted. The issue that needs to be answered is what BP goals and parameters are acceptable in this population and how aggressively these goals need to be met. Till date, the outcome gains are still indecisive. Until a substantial evidence to answer all these queries is available, masked hypertensives should not be devoid of benefits of antihypertensive treatment.

REFERENCES


