Chapter 10
Masked Hypertension: Does It Lead to CVD or CKD?

F. Wilford Germino

Introduction

"We also propose that the phenomenon might be called 'masked hypertension,' on the grounds that the hypertension is not detectable by the routine methods" [1].

With those words, previously awkward and clumsy terms such as "reverse white-coat hypertension" and "white-coat normotension" became merely historical descriptions of another phenotype of hypertension. This new term, coined barely more than a decade ago, afforded a clarity in its description that earlier terms did not.

The advent of 24-h ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HPM) added additional information and insight to the usual site of blood pressure (BP) measurement—the office blood pressure (OBP). These additional readings allowed the categorization of patients into four phenotypes:

1. *Normotensives*—those with normal OBP and ambulatory blood pressure (ABP)/home blood pressure (HBP)
2. *Sustained hypertensives*—those with elevated OBP and ABP/HBP
3. *White-coat hypertensives*—those with elevated OBP yet normal ABP/HBP
4. *Masked hypertensives*—those with normal OBP yet elevated ABP/HBP

Hypertension is well recognized as a major modifiable factor contributing to key end points—including stroke, cardiovascular disease (CVD), and chronic kidney disease (CKD). The identification and treatment of patients with hypertension clearly benefit patients with this condition. Traditionally, hypertensive patients were identified on the basis of casual blood pressure or OBP. These are the classic sustained hypertensives. Much of the data regarding attributable risk for CVD and CKD in hypertension are derived from this population. This is largely because they were

F. W. Germino (✉)
Department of Internal Medicine, Rush Medical College Rush University,
Orland Primary Care Specialists, 16660 S. 107th Avenue, Orland Park, IL 60467, USA
e-mail: wgermino@hotmail.com

M. R. Weir, E. V. Lerma (eds.), *Chronic Kidney Disease and Hypertension,*
Clinical Hypertension and Vascular Diseases, DOI 10.1007/978-1-4939-1982-6_10

diagnosed and classified as hypertensives based on OBP long before the widespread usage of HPM and ABPM in clinical trials. The advent of HPM and ABPM has confirmed that for many patients with elevated OBP, there is a persistency that extends to out-of-office readings now defined as sustained hypertension. But there is little doubt that at least some patients with isolated OBP elevation (white coat) were rendered into this category in the earlier studies. More recently, with greater use of out-of-office measurement, there has been not only greater interest but also greater need to ascertain where on the spectrum from normotensive to sustained hypertensive does the risk lie for these other previously difficult-to-categorize patients—those with elevated HBP in the presence of normal OBP and the reverse and those with normal HBP and elevated OBP. Recent observations revealing that white-coat hypertension is not a totally benign condition, but is associated with some long-term risk, have reinforced the concept that BP needs to be accurately measured in settings other than the clinic or office.

Defining a patient as hypertensive, warranting long-term treatment, needs demonstration that the measured BP is associated with not only long-term risk without treatment but also the reduction of that pressure results in improved outcomes. So where does masked hypertension exist in this continuum of BP? Is this condition associated with target organ damage (TOD), especially as it relates to CVD and CKD end points, and resembles the normotensive or the sustained hypertensive phenotype?

Cardiovascular and Cerebrovascular Risk

A pivotal study, utilizing the measurement of both OBP and ABP, compared normotensives, masked hypertensives (referred to as white-coat normotensives in the manuscript), and sustained hypertensives. They demonstrated a 20% prevalence of masked hypertension. Both masked hypertensives and sustained hypertensives had significantly higher left ventricular (LV) wall thickness and mass compared to normotensives. LV index (LVMI) was similar between masked (86 g/m^2) and sustained hypertensives (90 g/m^2) despite OBP differences of 35/16 mmHg and, as expected, there was a much narrower difference in the awake ABP (14/6 mmHg). Also, masked hypertensives evidenced greater carotid intimal medial wall thickness (cIMT), cross-sectional area, and higher prevalence of atherosclerotic plaque compared to sustained normotensives [2]. Additional studies also support these findings, demonstrating increased incidence in LV hypertrophy (LVH) [3, 4], LV mass index (LVMI) [3–5], LV wall thickness [3, 6], and cIMT [4, 5, 7]. Masked hypertension, compared to normotensive patients, is also associated with an increase in cardiovascular (CV) events [3, 6, 8–10]. The Ohasama study, using HBP measurement, detected greater risk of silent cerebrovascular lesions in both masked and sustained hypertension than in both white-coat and normotensive populations (see Table 10.1) [11]. In these trials, the data suggest that masked hypertension more closely resembles sustained hypertension than normotension.

Table 10.1 Higher risks associated with masked hypertension

LVH	LVMI	LV wall	cIMT	CV events	CVA	ESRD
Sega et al. [3]	Liu et al. [2]	**Sega et al.** [3]	Kotsis et al. [5]	Bobrie et al. [10]	Hara et al. [11]	Agarwal and Andersen [12]
Tomiyama et al. [24]	**Sega et al.** [3]		Hanninen et al. [4]	**Bjorklund et al.** [6]		
Pierdomenico et al. [19]	Kotsis et al. [5]		Hansen et al. [8]	Mancia et al. [9]		
Hanninen et al. [4]	Kuriyama et al. [23]		**Matsui et al.** [7]	Pierdomenico et al. [19]		
Pogue et al. [25]				Hansen et al. [8]		
				Franklin et al. [15]		
				Angeli [20]		

Bold-treatment naïve population
LVH left ventricular hypertrophy, *LVMI* left ventricular mass index, *LV* wall Left ventricular wall thickness, *cIMT* carotid intimal medial thickness, *CV* events cardiovascular events, *CVA* cerebrovascular accidents, *ESRD* end-stage renal disease
[a] Not all results are statistically significant, but may trend towards higher risk than referent normotension

The data for the masked hypertension and CKD are much more sparse. One study, albeit small, did demonstrate that patients with masked hypertension and CKD did exhibit an increased risk to the development of end-stage renal disease (ESRD) compared to normotensive patients [12]. Much of the available data, however, relate to the prevalence of masked hypertension in a CKD population [13, 14].

A large database of over 7000 individuals from four countries that included treated hypertensives examined outcomes based on both ABP and clinic BP. The adjusted hazard ratios for all CV events with normotensive as the referent were 1.22 (95 % CI = 0.96–1.53; $P = 0.09$) for white-coat hypertension (OBP ≥ 140/90 and ABP < 135/85 mmHg); 1.62 (95 % CI = 1.35–1.96; $P < 0.0001$) for masked hypertension (< 140/90 and ≥ 135/85 mmHg); and 1.80 (95 % CI = 1.59–2.03; $P < 0.0001$) for sustained hypertension (≥ 140/90 and ≥ 135/85 mmHg) [8].

More recently, an analysis of an 11-country International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) revealed that untreated diabetics with masked hypertension exhibited higher risk. During the median of 11 years of follow-up, using a composite CV end point (fatal and nonfatal stroke, transient ischemic attack (TIA), death from ischemic heart disease, sudden death, nonfatal MI, angina pectoris, coronary revascularization, fatal and nonfatal heart failure, and fatal and nonfatal peripheral artery disease), the adjusted risk for untreated masked diabetic patients was almost twice as high as normotensives (HR, 1.96; 95 % CI 0.97–3.97; $P = 0.059$) and similar to untreated stage 1 hypertensives (HR, 1.07;CI, 0.58–1.98; $P = 0.82$) and less than untreated stage 2 hypertensives (HR, 0.53; CI, 0.29–0.99; $P = 0.048$). A major limitation of these data is the relatively small numbers of patients and events in each group [15].

Table 10.2 Treatment status of masked hypertensives in outcome studies

Includes treated	Treatment naive
Bobrie et al. [10]	Bjorklund et al. [6]
Pierdomenico et al. [19, 20]	Franklin et al. [15]
Pogue et al. [25]	Selenta et al. [36]
Hara et al. [11]	Sega et al. [3]
Tomiyama et al. [24]	Matsui et al. [7]
Ohkubo et al. [37]	
Ben-Dov et al. [31]	
Uchida et al. [18]	
Kuriyama et al. [23]	
Hanninen et al. [4]	
Mancia et al. [9]	
Kotsis et al. [5]	
Hansen et al. [8]	

Limitations

Among the limitations affecting the calculations of the true prevalence of masked hypertension in CKD are several factors. From study to study, there are key differences in their methodology. These differences range from the timing of BP readings, the number of readings performed, and even the definition of what constitutes the threshold reading to confirm the diagnosis of hypertension in the CKD population. Further complexity is added by including within the analysis two, perhaps very different, populations—the treatment naïve and the currently treated. Only one utilized a treatment-naïve population [7] while others incorporated treated patients [16–20].

Traditionally, masked hypertension refers to treatment-naïve patients, but the definition has been expanded by many to include those patients who are treated with antihypertensive medications and whose patterns resemble those of masked hypertension–normal OBP with elevated HBP or ABP. These partially treated patients have been included, to at least some extent, in many of the studies assessing risk (see Table 10.2). The inclusion of these partially treated patients with the treatment-naïve masked hypertensives makes the assessment of true risk more difficult. The extent to which this influences the assessment of risk for TOD is unknown. Some authors believe that the definition of masked hypertension should be restricted to only those treatment-naïve patients—all others on treatment should be considered as patients with incomplete control of hypertension with partially treated sustained hypertension [21]. Others contend that the pattern of BP may be either sustained, masked, or white coat, all reflective of an underlying pattern of hypertensive phenotype.

The pretreatment patterns are not known for these patients. Were clinic BP readings less proportionally elevated than the HBP and ABP readings prior to treatment? Could these partially treated patients represent part of the spectrum of masked hypertension? Some data may suggest that. In a small prospective trial on nondiabetic

treated hypertensives, those patients who were able to achieve BP control in both OBP and ABP settings demonstrated reduction in LVMI and microalbuminuria, along with other indices. In contrast, those patients whose OBP was controlled, but not the out-of-office readings, demonstrated no such benefit [22]. These data have been confirmed by other authors in different CKD populations. Even in treated hypertensives whose OBP has achieved normalization, if HBP or ABP remain elevated, there exists an increased risk for adverse outcomes including increased LVMI in diabetics with CKD [23], carotid artery disease and LVH [24], LVH and cardiac events [19], and prevalence of LVH [24], and stroke [25]. The extent to which this simply represents the impact of hypertension load upon TOD is not known. Interestingly, in the African-American Study in Kidney Disease (AASK) of 61% of patients with controlled clinic BP, 70% demonstrated elevated BP outside the office setting—a masked pattern [26].

Home Versus Ambulatory Blood Pressure Measurement

Defining a patient as exhibiting masked hypertension requires measurement of blood pressure out of the usual office setting. It may be done with either self-measurement at home or with ABPM. There is no general agreement regarding the use of HPM or ABPM to diagnose masked hypertension. Sega and colleagues found only a 57 and 45% association between ambulatory and home diastolic BP (DBP) and systolic BP (SBP), respectively, suggesting that these measurements are not equivalent [3]. Others have suggested little difference [27]. A recent paper suggested that the method by which BP is measured in the office may also influence the diagnosis of masked hypertension. It appears that an automated measurement of office BP results in a lower prevalence rate of masked hypertension compared to the conventional manual readings. The manual method also results in a greater inconsistency from visit to visit [28]. This concern is addressed to some extent by the work of Ben-Dov and colleagues who found that 72% of patients initially classified as masked hypertension remained so upon repeat ABPM [29]. Work of Pickering et al. gave evidence that a single ABPM may not prove sufficient to phenotype hypertensive patterns [30].

There do seem to exist certain patient types who may have increased likelihood of exhibiting masked hypertension. Generally, these are males—some suggest younger, some older [2, 8]—with a history of cigarette smoking, exercise, job stress, and alcohol consumption [31–34], with a disproportionate number of diabetes. Additionally, the presence of high-normal SBP and DBP in the clinic accompanying some of the aforementioned factors may result in an elevated suspicion for the presence of masked hypertension, necessitating further evaluation [2, 4, 8, 33, 35]. Multivariate correction for these underlying factors does not suggest that they are responsible for the increased TOD demonstrated in these studies.

Prevalence

The determination of the prevalence of masked hypertension in the population is difficult to determine based on the literature. Estimates range from 8 to 20% in the general population up to 61% in treated patients [26, 34, 36–38]. Many of the factors in the discussion of CKD also loom regarding prevalence in the general population. Populations reported often include treatment-naïve as well as treated hypertensives. There is no single consistent method for clinic BP measurement, and often no universal agreement on abnormal BP levels, especially in diabetes mellitus (DM) and CKD. Also, there is some evidence that masked hypertension may be "unmasked" through the use of a low-intensity exercise stress test; a recent well-designed retrospective study suggests otherwise [39, 40]. The authors in the later study utilized both 24-h ABPM and at least two exercise stress tests and found not only no relationship to establish a diagnosis of masked hypertension but also poor reproducibility in the hyperdynamic response to exercise. It is not unrealistic to anticipate that persistent and chronic elevation of BP in an out-of office setting would result in increased risk for TOD—including CVD, CKD, and microalbuminuria. Masked hypertension may impact TOD simply because hypertension load is increased in this population as well as the sustained hypertensive.

Conclusions

The proper management of hypertension increasingly relies upon the measurement of BP beyond the traditional office setting. This becomes imperative not only for determining the proper phenotype of the hypertension but also for modification and adjustment of therapies. If clinicians and patients are unwilling to incorporate this in all patients under consideration for the diagnosis of hypertension or undergoing treatment, then what strategies might one use to find this often-difficult-to-discern phenotype? Certain patient types may have greater likelihood of presenting as masked hypertensives:

1. Patients who present in the office with normal OBP but evidence of TOD.
2. A high-normal or borderline hypertensive patient, especially if male, smoker, with a high-stress job, as well as other additional risk factors should be considered at higher risk for this condition and evaluated further.
3. Consider the out-of-office assessment in all patients with family history of hypertension and high-normal OBP.
4. Consider systematic evaluation for patients who report HBP being elevated despite normal OBP.
5. Consider the diagnosis in those patients who demonstrate a hypertensive response to exercise although this would not be diagnostic.

The measurement of BP outside the office can be expected to increase over the next decade to perhaps being the norm rather than the exception. With widespread use,

one can anticipate the ability to more clearly identify and treat these individuals, regardless of their baseline or posttreatment hypertensive phenotype. However, given the wide variability in BP levels with our current method of BP measurement, it is likely that some patients will remain undiagnosed and therefore untreated, and thus vigilance for evidence of TOD will remain part of the management of patients with both confirmed and suspected hypertension [41].

References

1. Pickering TG, Davidson K, Gerin W, Schwartz JE. Masked hypertension. Hypertension. 2002;40:795–6.
2. Liu JE, Roman MJ, Pini R, et al. Cardiac and arterial damage in adults with elevated ambulatory and normal office blood pressure. Ann Int Med. 1999;131:564–72.
3. Sega R, Trocino G, Lanzarotti A, et al. Alterations of cardiac structure in patients with isolated office, ambulatory or home hypertension: data from the general population (Pressioni Arteriose Monitorate e Loro Associazoni (PAMELA) study). Circulation. 2001;104:1385–92.
4. Hanninen MA, Niiranen TJ, Puukka PJ, Kesaniemi YA, Kahonen M, Jula AM. Target organ damage and masked hypertension in the general population: the finn-home study. J Hypertens. 2013;31:1–8.
5. Kotsis V, Stabouli S, Toumanidis S, et al. Target organ damage in "white coat hypertension" and "masked hypertension". Am J Hypertens. 2008;21:393–9.
6. Bjorklund K, Lind L, Zethelius B, Andren B, Lithell H. Isolated amulatory hypertension predicts cardiovascular mortality in elderly men. Circulation. 2003;107:1297–302.
7. Matsui Y, Egushi K, Ishikawa J, et al. Subclinical arterial damage in untreated masked hypertensive subjects detected by home blood pressure measurement. Am J Hypertens. 2007;20:385–9.
8. Hansen TW, Kikuya M, Thijs L, Bjorklund-Bodegard K, Kuznetsova T, et al. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7030 individuals. J of Hyperten. 2007;25:1154–64.
9. Mancia G, Bombelli M, Facchetti R, et al. Long-term risk of sustained hypertension in white-coat or masked hypertension. Hypertension. 2009;54:226–32.
10. Bobrie G, Chatellier G, Genes N, et al. Cardiovascular prognosis of 'masked hypertension' detected by blood pressure self-measurement in elderly treated hypertensive patients. JAMA. 2004;281:1341–9.
11. Hara A, Ohkubo T, Kondo T, et al. Detection of silent cerebrovascular lesions in individuals with "masked" and 'white-coat' hypertension by home blood pressure measurement: the Ohasama study. J Hypertens. 2009;27:1049–55.
12. Agarwal R, Andersen MJ. Prognostic importance of clinic and home blood pressure recordings in patients with chronic kidney disease. Kidney Int. 2006;69:406–11.
13. Kanno A, Metoki H, Kikuya M, Terawaki H, Hara A, et al. Usefulness of assessing masked and white-coat hypertension by ambulatory blood pressure monitoring for determining prevalent risk of chronic kidney disease: the Ohasama study. Hyperten Res. 2010;33:1192–8.
14. Bangash F. Agarwal R. Masked hypertension and white-coat hypertension in chronic kidney disease: a meta-analysis. Clin J Soc Neph. 2009;4:656–64.
15. Franklin SS, Thijs L, Li Y, et al. Masked Hypertension in diabetes mellitus: treatment implications for clinical practice. Hypertension. 2013;61:964–71.
16. Andersen MJ, Khawandi W, Agarwal R. Home blood pressure monitoring in CKD. Am J Kidney Dis. 2005;45:994–1000.
17. Minutolo R, Borrelli S, Scigliano R, Bellizzi V, et al. Prevalence and clinical correlates of white coat hypertension in chronic kidney disease. Nephrol Dial Transplant. 2007;22:2217–23.

18. Uchida H, NakamuraY, Kaihara M, Noril H, Hanayama Y, Makino H. The MUSCAT study: a multicenter PROBE study comparing the effects of angiotensin II type 1 receptor blockers on self-monitored blood pressure in patients with morning hypertension-study design and background characteristics. Kidney Inter. 2006;69:406–411
19. Pierdomenico SD, Lapenna D, Bucci A, et al. Cardiovascular and renal events in uncomplicated mild hypertensive patients with sustained and white coat hypertension. Am J Hypertens. 2004;17:876–81.
20. Pierdomenico SD, Lapenna D, Bucci A, DiTommaso R, et al. Cardiovascular outcome in treated hypertensive patients with responder, masked, false resistant, and true resistant hypertension. Am J Hypertens. 2005;18:1422–8.
21. Angeli F, Reboldi G, Verdecchia P. Masked hypertension: evaluation, prognosis and treatment. Am J Hypertens. 2010;23:941–8.
22. Cuspidi C, Negri F, Sala C, Mancia G. Masked hypertension and echocardiographic left ventricular hypertrophy: an updated review. Blood Press Monitor. 2012;17:8–13.
23. Kuriyama S, Otsuka Y, Iida R, et al. Morning blood pressure predicts hypertensive organ disease in patients with renal diseases: effect of intensive antihypertensive therapy in patients with diabetic nephropathy. Intern Med. 2005;45:1239–46.
24. Tomiyama M, Horio T, Yoshii M, et al. Masked hypertension and target organ damage in treated hypertensive patients. Am J Hypertens. 2006;19:880–6.
25. Pogue V, Rahman M, Lipkowitz M, Toto R, Miller E, et al. Disparate estimates of hypertension control from ambulatory and clinic blood pressure measurements in hypertensive kidney disease. Hypertension. 2009;55:20–7.
26. Verdecchia P, Angeli F, Gattobigio R, Borgioni C, et al. The clinical significance of white-coat and masked hypertension. Blood Press Monitor. 2007;12:387–9.
27. Verberk WJ, Thien T, deLeeuw PW. Masked hypertension, a review of the literature. Blood Press Monitor. 2007;12:267–73.
28. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Kaczorowski J. The Conventional versus Automated Meassurement of Blood Pressure in the Office (CAMBO) trial: masked hypertension sub-study. J Hypertens. 2012;30:1937–41.
29. Ben-Dov IZ, Ben-Arie L, Mekler J, Burstyn M. Reproducibility of white-coat and masked hypertension in ambulatory BP monitoring. Internat J Cardiol. 2007;117:555–9.
30. Pickering T, Schwartz J, Verdecchia P, et al. Prediction of strokes versus cardiac events by ambulatory monitoring of blood pressure: results from an international database. Blood Press Monitor. 2007;12:397–9.
31. Ben-Dov IZ, Ben-Arie L, Mekler J, Burstyn M. In clinical practice, masked hypertension is as common as isolated clinic hypertension: a predominance of younger men. Am J Hypertens. 2005;18:589–93.
32. Wing LM, Brown MA, Belin LJ, Ryan P, Reid CM. “Reverse white coat hypertension” in older hypertensives. J Hypertens. 2002;20:639–44.
33. Yoon HJ, Ahn Y, Park JB, et al. Are metabolic risk factors and target organ damage more frequent in masked hypertension than in white coat hypertension? Clin and Exp Hyper. 2010;32:480–5.
34. Ogedegbe G, Agyemang C, Ravenell JE. Masked hypertension: evidence of the need to rreat. Curr Hypertens Rep. 2010;12:349–55.
35. Mancia G, Facchetti R, Bombelli M, Grassi G, Sega R. Long-term risk of mortality associated with selective and combined elevation of office, home, and ambulatory blood pressure. Hypertension. 2006;47:846–53.
36. Selenta C, Hogan BE, Linden W. How often do office blood pressure measurements fail to identify true hypertension: an exploration of white coat normotension. Arch Fam Med. 2000;9:533–40.
37. Ohkubo T, Kikuya M, Metoki H, Assayama K, Obara T, Hashimoto J, et al. Prognosis of masked hypertension and white-coat hypertension detected by 24-h ambulatory monitoring. J Am Coll Cardiol. 2005;46:508–15.

38. Fagard RH, Cornelissen VA. Incidence of cardiovascular events in white-coat, masked and sustained hypertension versus true normotension: a meta-analysis. J Hypertens. 2007;25:2193–8.
39. Schultz MG, Hare JL, Marwick TH, Stowasser M, Sharman JE. Masked hypertension is "unmasked" by low-intensity exercise blood pressure. Blood Press. 2011;20:284–9.
40. Grossman A, Cohen N, Shemesh J, Koren-Morag N, Leibowitz A, Grossman E. Exaggerated blood pressure response to exercise is not associated with masked hypertension in subjects with high normal blood pressure levels. J Clin Hypertens (Greenwich). 2014;16:277–82.
41. Germino FW. Unmasking masked hypertension. J Clin Hypertens (Greenwich). 2014;16:267–8.