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REVIEW PAPER

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Characteristics and control of the 24-hour ambulatory blood pressure in patients with metabolic syndrome

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Abstract

Asian countries are facing an increasing prevalence of metabolic syndrome (MetS), which may aggravate the burden of cardiovascular diseases in this region. MetS is closely associated with ambulatory blood pressure (BP). Patients with MetS, compared to those without, had a twofold higher risk of new-onset office, home, or ambulatory hypertension. Furthermore, the risk of new-onset MetS in patients with white-coat, masked and sustained hypertension was also doubled compared to normotensives. High-risk masked hypertension and blunted nighttime BP dipping are common in patients with MetS, suggesting perfect 24-hour BP control with long-acting antihypertensive drugs and early initiation of combination therapy might be especially important for patients with MetS.

1 | INTRODUCTION

Metabolic syndrome (MetS), which had been coined as "x syndrome"[1] and "syndrome of insulin resistance,"[2] is characterized as the clustering of multiple cardiovascular risk factors including central obesity, dyslipidemia, and elevated levels of fasting blood glucose and office blood pressure (BP).[3] Prior studies have demonstrated that MetS was associated with left ventricular hypertrophy, arterial stiffness, microalbuminuria, and long-term risk of cardiovascular morbidity and mortality.[4-6] Along with rapid economic development and urbanization, Asian countries are facing a significant epidemic of MetS. Around 20%-40% of the adult population were affected by MetS depending on the study population and the diagnostic criteria applied.[7] Tailored strategies for the prevention and management of MetS are required to reduce the associated cardiovascular disease burden in this region.

In the last three decades, ambulatory BP monitoring has been established and increasingly recommended as the method of choice for the assessment of BP.[8] It captures diurnal BP variations and allows identification of masked hypertension from office normotension and differentiating white-coat hypertension from office hypertension. Although the recommended definitions of the BP component of MetS still rely on office BP measurement, a closer association of MetS with the 24-hour ambulatory BP has been observed.[9,10] This article will concisely review the characteristics of the 24-hour ambulatory BP in patients with MetS and discuss the rational use of antihypertensive drugs in patients with MetS to achieve a perfect 24-hour BP control.[11]

2 | LITERATURE SEARCH

We searched PubMed for articles published in English from 2000 to 2020 on ambulatory BP monitoring and antihypertensive treatment in MetS, using the key word "metabolic syndrome" and the following terms related to ambulatory BP monitoring, including "ambulatory blood pressure," "white-coat hypertension," "masked hypertension," "dipping," "morning hypertension," and "morning blood pressure surge." In total, 603 articles were identified. After removal of duplicates and screening abstracts and references of the identified articles, 72 full-length articles were assessed. From these assessed articles, 38 (52.8%) were removed, because of outcomes not of interest (n = 20), data had been reviewed before[12] (n = 15) or incomplete data (n = 3). Finally, a total of 34 studies were included in the present review.

2.1 | A close relationship between MetS and ambulatory BP

There is a close relationship between MetS and ambulatory BP. Irrespective of the definition of MetS, patients with white-coat, masked and sustained hypertension had a higher prevalence of MetS compared to normotensives in both populations and patient cohorts (Table 1).[10,13-21] On the other hand, patients with MetS, compared with those without, had a higher 24-hour, daytime or nighttime BP, albeit not in all reports (Table 2).[22-28]

In the Pressioni Arteriose Monitorate e Loro Associazioni (PAMELA) study,[9] 193 (13.9%) patients with MetS according to the 2003 National Cholesterol Education Program Adult Treatment Panel (ATP) III criteria, compared to the 1201 patients without MetS, were older, and had higher office BP as well as 24-h and home BPs at baseline. After 10 years of follow-up, the age- and sex-adjusted risk ratios (95% confidence interval [CI]) of new-onset office, home, or ambulatory hypertension were, respectively, 3.52 (1.56-7.90), 2.94 (1.49-5.83), and 3.19 (1.75-5.79) ($p < .005$) in patients with MetS relative to those without.[9] Furthermore, the PAMELA researchers observed a greater age- and sex-adjusted incident risk of new-onset MetS in patients with white-coat hypertension (1.75 [1.01-3.04], $p = .0046$), masked hypertension (2.58 [1.26-5.30], $p = .009$), and sustained hypertension (2.14 [1.20-3.79], $p = .009$) defined with office and ambulatory BPs.[10] However, when hypertension was defined with office and home BPs, only patients with white-coat hypertension showed a greater risk of new-onset MetS (2.16, [1.28-3.63], $p = .003$). Similar associations were observed for single components of the MetS such as abdominal obesity and hyperglycemia.[10]

2.2 | High prevalence of masked hypertension in MetS

Masked hypertension is a special subtype of hypertension, characterized as out-of-office hypertension in the presence of a normal office BP and was associated with an adverse cardiovascular outcome.[8] One of the MetS components is an elevated office blood pressure of ≥130/85 mmHg, but quite a number of patients with MetS do not have hypertension based on office BP measurement according to the current hypertension guidelines in Asian countries. However, elevated office BP in the high normal range, increased waist circumference, and other components of MetS were significantly associated with a high risk of the presence of masked hypertension.[29]

In the Jackson Heart Study,[28] the prevalence of masked hypertension was compared between African Americans with and without MetS, who all had an office BP of <140/90 mmHg. Among the 359 participants not taking antihypertensive medication, the prevalence of masked hypertension was 62.3% and 43.6% among participants with and without MetS, respectively. After multivariate adjustment, the prevalence ratio of masked hypertension for MetS versus non-MetS was 1.38 (95% CI, 1.10-1.74). However, when the components of MetS were analyzed separately, only office BP of 130-139/85-89 mmHg was significantly associated with masked hypertension (OR, 1.90, 95%CI, 1.56-2.32). In the 393 participants who were treated with antihypertensive medication, there was no significant association between masked hypertension and MetS.[28]

TABLE 1 The prevalence of metabolic syndrome according to hypertension subtype

Study						OBP/ABP (N, %)			
First author, RefN	N	Population	Mean age (years)	Male sex (%)	Mets (n, %)	NBP	WCH	MHT	SHT
Baguet JP[13]	126	Patients with obstructive sleep apnea syndrome	48.2	84.9	34 (27.0)[a]	6 (15)	/	9 (24)	19 (41)
Konstantopoulou AS[14]	300	Outpatients in hypertension clinic	59.7	56.7	137 (45.7)[c]	/	48 (48)	41 (41)	48 (48)
Thomopoulos C[15]	328	Outpatients in hypertension clinic	48.0	52.4	69 (21.0)[a]	16 (12)	10 (17)	12 (29)	31 (30)
Hermida RC[16]	3344	Spanish subjects with normotension, untreated hypertension, or resistant hypertension	52.6	51.4	1915 (57.3)[a]	466 (44.0)	598 (64.1)	184 (52.1)	667 (66.8)
Afsar B[17]	309	Outpatients in nephrology clinic	55.3	67.0	86 (27.8)[a]	3 (3.5)	28 (25)*	9 (29)*	46 (57)*
Mancia G[18]	1921	Hypertensive patients in the ELSA trial	56.1	53.6	568 (29.6)[a]	/	77 (30.8)	/	491 (29.4)
Mancia G[19]	1256	Part of the general population of the PAMELA Study	46.4	46.5	107 (8.5)[a]	33 (3.8)	74 (19.8)*	/	/
Saeed S[20]	298	Ischemic stroke survivors	49.0	67.2	103 (34.6)[b]	19 (16)	/	12 (33)	72 (50)
Kenny IE[21]	323	Obesity patients without CVD	49.1	44.0	167 (51.7)[b]	19 (21.6)	/	30 (50.9)*	118 (67.3)*
Cuspidi C[10]	2024	The general population of the PAMELA Study	43.4	44.4	326 (16.2)[a]	/ (6.0)	/ (27.5)	/ (14.7)	/ (30.6)

Abbreviations: ABP, Ambulatory blood pressure; HBP, Home blood pressure; MetS, Metabolic syndrome; MHT, Masked hypertension; NBP, Normal blood pressure; OBP, Office blood pressure; RefN, Reference number; SHT, Sustained hypertension; WCH, White coat hypertension.

Definition of MetS applied:

[a]Adult Treatment Panel (ATP) III;

[b]American Heart Association/National Heart, Lung and Blood Institute guidelines((AHA/NHLBI);

[c]Not specified.

*$P < .05$ vs normotension

TABLE 2 Ambulatory blood pressure and dipping status in patients with and without metabolic syndrome*

Study	Without MetS							With MetS						
First Author, RefN	N	Mean age (Years)	Daytime BP (mmHg)	Nighttime BP (mmHg)	24-hour BP (mmHg)	Nighttime BP fall (%)	Non-dippers (%)	N	Mean age (Years)	Daytime BP (mmHg)	Nighttime BP (mmHg)	24-hour BP (mmHg)	Nighttime BP fall (%)	Non-dippers (%)
Hermida RC[22]	1588	50.9	128/81	115/68	124/77‡	10/16	39.5†	1764[a]	56.3	129/79	118/68	126/76‡	9/14	52.0†
Shivpuri S[23]	224	49.1	118/74	102/62	/	14/16		62[a]	51.4	124/75	108/65	/	13/13	/
Nazzaro P[24]	81	44.2	135/86	119/77	/	12/10	/	81[a]	47.3	142/88	125/79	/	12/10	/
Tadic M[25]	174	49.8	140/88	125/78	137/86	11/11	40.8†	144[a]	51.1	144/92	130/82	140/89	10/11	52.8†
Rhee MY[26]	332	45.4	/	/	115/75	/	/	131[c]	49.0	/	/	126/85	/	/
Yan B[27]	388	60.2	135/80	128/74	133/79	5/8	/	121[a]	59.8	139/81	133/76	138/80	4/6	/
Colantonio LD[28]	298	54.1	124/78	114/67	120/73	8/14	/	61[b]	56.0	128/77	119/68	125/73	7/12	/

Abbreviations: BP, Blood pressure; Mets, Metabolic syndrome; RefN, Reference number.

Definition of MetS applied:

[a]Adult Treatment Panel (ATP) III;

[b]The 2009 harmonized definition;

[c]Adult Treatment Panel (ATP) III and central obesity criteria for Korean.

*Studies published after the year of 2010 are listed.

†Non-dippers plus reverse dippers

‡48-h BP.

2.3 | Non-dipping BP pattern and morning BP surge in MetS

BP follows a circadian variation, being lower at night than during the day, and surging upon awakening and getting up in the morning. Four BP patterns consisting of dipping, non-dipping, reverse dipping, and extreme dipping are usually defined according to a night-to-day BP ratio of 0.8-0.9, 0.9-1.0, >1.0, and <0.8, respectively. Abnormal circadian BP variations, including non-dipping, reverse dipping, exaggerated morning BP surge, and morning hypertension, have been demonstrated to be associated with worse target organ damage and adverse cardiovascular outcome.[30,31]

Most previous studies found that non-dipping was more common among subjects with MetS than those without, and the prevalence of non-dipping increased with the number of the MetS components.[12,22,25] Table 2 lists the studies published after 2010.[22-28] In a meta-analysis which was published in 2010 and included 7 studies,[12] the overall relative ratio for non-dipping in patients with MetS (n = 352), in comparison with those without MetS (n = 326), was 1.19 (95% CI 1.03-1.374, p = .018). Among the 509 hypertensive patients (254 men and 255 women, 45 to 75 years old) enrolled from September 2013 to March 2014 in China,[27] 121 (23.8%) were defined as having MetS according to the NCEP ATP III definition. MetS was found in 42.9% and 24.6%, respectively, in patients with reverse dipping (n = 124) or without (n = 385). After multivariate adjustment for age, smoking, and other BP indices, only the reverse dipping (OR 2.298; p = .006) and 24-hour systolic BP (OR, 1.063; p = .021) were significantly associated with MetS in men. No BP indices were found to be associated with MetS in women. [27]

Few studies addressed the association between ambulatory morning BP surge and MetS. In 352 Portuguese with newly diagnosed hypertension but without diabetes,[32] MetS was defined based on the International Diabetes Federation 2005 criteria. The 140 patients with MetS, compared to the 212 controls matched for age and casual BP, had significantly higher ambulatory morning BP surge (28 *vs* 25 mmHg, p < .03). Among the 1087 South Korean hypertensive patients,[33] Bastos et al found that MetS was more common (p = .019) in patients with morning hypertension (97/173, 59.5%) defined as a self-measured home morning BP of ≥135/85 mmHg as compared to those without (415/914, 49.5%). Similar findings were observed in 181 Japanese with hypertension.[34]

2.4 | 24-hour ambulatory BP control in MetS

Since MetS is characterized by a high prevalence of masked hypertension, blunted nocturnal BP dipping, and exaggerated morning BP surge, it is important for patients with MetS to control 24-hour BP level and circadian BP variations. On the basis of lifestyle modifications (exercise and diet), long-acting antihypertensive drugs with long half-life are recommended in order to achieve perfect control of 24-hour BP.[11,31]

Current guidelines[35,36] recommend that renin-angiotensin system blockers, including angiotensin converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), are the first choice of antihypertensive drugs in patients with MetS. ACEIs and ARBs were more useful than other drugs in the prevention of new-onset diabetes mellitus which might be related to the alleviation of insulin resistance as suggested by several clinical trials, for instance Candesartan Antihypertensive Survival Evaluation in Japan (CASE-J) and the Valsartan Antihypertensive Long-term Use Evaluation (VALUE).[36] Calcium channel blockers and alpha-blockers can be added on if patients had an uncontrolled BP treated with a single drug. Asian patients with MetS are more salt-sensitive than non-MetS ones,[37,38] thereby reducing salt intake and a judicious use of diuretics in patients with MetS are preferred. As adverse metabolic effect associated with short-term exposure of atenolol and hydrochlorothiazide was common,[39] especially in those with abdominal obesity, vasodilating beta-blockers are recommended to counteract increased sympathetic tone in hypertensive MetS patients.[40] New hypoglycemic drugs, such as sodium-glucose cotransporter-2 inhibitors (SGLT2i), not only reduces blood glucose, but also improves 24-hour BP control, especially for patients with uncontrolled nocturnal hypertension,[41] which might also be desirable for patients with MetS. Many studies have shown that 50%-70% of hypertensive patients need two or more drugs to achieve the goal of BP reduction, initiation of antihypertensive treatment with a single-pill combination is therefore highly recommended by international guidelines.[42]

Between ACEIs and ARBs, no significant difference was found in their antihypertensive effect among patients with MetS in several small-sized clinical trials that used office BP measurement.[43,44] The Zofenopril in Advanced MEtabolic Syndrome (ZAMES) study is a multicenter, randomized, double-blind clinical trial conducted in Italy and Romania.[43] Totally 466 patients with Mets and hypertension (mean age 59 years, male 53%) were randomly assigned to the treatment with a fixed-dose combination of zofenopril 30 mg plus hydrochlorothiazide 12.5 mg (231 patients) or irbesartan 150 mg plus hydrochlorothiazide 12.5 mg (235 patients) once daily for 24 weeks. After 8 and 16 weeks, drug dosages were doubled if office BP was uncontrolled. In 20% of patients, an ambulatory BP monitoring was performed. There was no significant difference in the office and 24-hour ambulatory BP reduction (mean systolic/diastolic BP difference, 0.1/-0.9 mmHg, p ≥ .54) between the two groups, as well as the incidence of adverse events (both ~ 5%). In the MEtabolic parameters, DIabetes mellitus, and NephropAthy (MEDINA) study,[44] a total of 439 hypertensive patients with MetS and/or diabetes mellitus were randomized to 2 groups: group 1 receiving ramipril or perindopril (217 patients) or group 2 losartan (222 patients). Hydrochlorothiazide or amlodipine, and then a statin were added if BP was uncontrolled. Office BP decreased by 24.1/13.3 mmHg in the ACEIs group and 25.9/13.5 mmHg in the losartan group. There was also no significant difference in changes of the MetS components between the two arms.[44]

To improve BP control at night and in the morning, some researchers proposed to prescribe at least one antihypertensive drug at bedtime. However, for long-acting antihypertensive drugs with long half-life, such as amlodipine,[45] or for ACEIs or ARBs in high-dose or full-dose,[46] the 24-hour BP reduction was comparable between different strategies of dosing time. For patients on therapy of ≥1 antihypertensive agent, a

recent trial by Poulter et al also demonstrated that the 24-hour systolic and diastolic BPs, daytime, nighttime, and clinic BPs did not differ between the daytime (6 AM to 11 AM) and evening (6 PM to 11 PM) dosing.[47] The Hygia Chronotherapy Trial online-published in 2020 reported that bedtime dosing of antihypertensive drugs significantly reduced the incidence of cardiovascular events and mortality by ~40% to 50% along with a greater reduction in ambulatory nighttime systolic/diastolic BP by 3/2 mmHg. However, it is rather difficult to explain the observed huge benefit by the small BP difference between the groups. Therefore, whether chronotherapy of antihypertensive medication will be beneficial for hypertensive patients, especially for those having MetS, still needs to be explored in future trials.[48]

3 | CONCLUSION

Asian countries are facing an increasing prevalence of MetS, which may aggravate the burden of cardiovascular diseases in this region. MetS was closely associated with ambulatory BP. High-risk masked hypertension and blunted nighttime BP dipping were common in patients with MetS. A perfect 24-hour BP control by using long-acting antihypertensive drugs and early initiation of combination therapy might be especially important for patients with MetS.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Yan Li conceptualized the topic of this manuscript. Jian-Feng Huang and Yan Li performed literature search, independently reviewed and extracted data from the articles, and wrote the first draft of manuscript. All other authors read, edited, and approved the manuscript.

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