REVIEW ARTICLE

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Morning hypertension for stroke and cardiovascular: clinical pearls for primary care

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ABSTRACT

Hypertension is the world's leading cause of mortality and morbidity. One of the phenomena that commonly occur in hypertensive as well as normotensive patients, is morning hypertension. Blood pressure (BP) follows a diurnal rhythm, reaching its highest level during the morning hours and dropping to the lowest level at midnight. Transient increases in BP in morning hypertension plus persistent stressors within 24 hours are thought to increase target organ damage and trigger cardiovascular events. Therefore, ambulatory BP monitoring or morning home BP monitoring is recommended as a strong predictor of cardiovascular events. There are two types of morning hypertension according to its underlying mechanisms; the first one is called nocturnal hypertensive morning hypertension, and the other one is morning-surge hypertension. Numerous studies have proved that this phenomenon often leads to several acute cardiovascular events, such as stroke, coronary artery disease, and peripheral artery disease. To prevent these complications, cost-effective management is needed, especially for identifying accurate diagnostic tools, as well as creating specific regimens. Therefore, to achieve appropriate management of hypertension, including morning hypertension, long-acting antihypertensive drugs should be used, at full doses and in the form of combination therapy. The clinical usefulness of antihypertensive drugs with specific mechanisms for morning BP or split or timed dosing of long-acting drugs in controlling morning BP remains under investigation. More studies are needed, especially looking for other clinical evidence of the benefits of lowering BP in the morning. Home BP monitoring is recommended as a good choice for BP measurements, especially in the primary care setting.

Keywords: Morning hypertension, cardiovascular events, primary care, awareness, prevention

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INTRODUCTION

Hypertension remains the leading cause of cardiovascular morbidity and mortality, including stroke, coronary heart disease, heart failure, chronic kidney failure, and central and peripheral vascular disease.[1-3] Blood pressure (BP) values for diagnosis and therapy are taken from the average of two measurements, although there are diurnal variation factors that influence it.[4] Blood pressure tends to decrease during sleep and rise again in the morning.[5] This is evidenced by the results of 24-hour ambulatory BP monitoring (ABPM).[6,7] Based on various epidemiological studies, it was found that the prevalence of acute cardiovascular manifestations that have the potential to cause death, such as myocardial infarction, stroke, or sudden cardiac death, peaks in the morning, usually within 4-6 hours after awakening.[8,9] Transient increases in BP, known as morning BP surge (MBPS), in morning hypertension plus persistent stressors within 24 hours are thought to increase target organ damage and trigger these cardiovascular events.[10-12] Therefore, BP monitoring using out-of-clinic ABPM or morning home BP monitoring (HBPM), is recommended as a strong predictor of cardiovascular events.[13-15] Through these methods, the phenomenon of the white-coat effect and masked hypertension can be eliminated, and the measurements are more reproducible than in clinical examinations. This review will discuss more about morning hypertension and the things you need to know in primary care. Morning hypertension is a problem that is often taken for granted, but this condition can be potentially fatal, especially if not diagnosed early. The primary care physician as the front line in health services has an important role in diagnosing morning hypertension.

Morning hypertension and morning blood pressure surge

Available studies use several different definitions of MBPS as seen in Figure 1.[10] Assessment of MBPS is generally carried out with 24-hour ABPM. According to Kario [10] there are two definitions in use, namely *sleep-trough-surge* which is the value of BP in the morning (2 hours after waking) minus the lowest BP value during sleep, and *pre awakening surge* which is the value of BP in the morning minus the value of BP 2 hours before waking up. In other studies, MBPS is referred to as a *rising surge*, which is the difference in the value of BP that increases in the morning minus BP in the supine position as measured <30 minutes earlier.[17] In another study, the difference in BP between the morning and evening values is called the morning and evening (ME) difference.[2] In the Jichi Medical School-Ambulatory Blood Pressure Monitoring study and the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes, pathological morning BP increases were in the 10th percentile class of these BP values.[10] However, there is no official consensus on a definition of this phenomenon or a threshold for pathological elevation.

In contrast to MBPS, morning hypertension is a BP value of 135/85 mmHg in the morning, either through ABPM or HBPM. In the Japanese Society of Hypertension 2014 guidelines for the management of hypertension, the term masked morning hypertension was introduced, which refers to a home morning BP of ≥135/85 mmHg, but with normal clinic BP (<140/90 mm Hg).[17] Regardless of the mechanism, either pathophysiological or as a result of inadequate antihypertensive therapy, morning hypertension is associated with more frequently occurring significant cardiovascular events in the post-wake period.[14] The prevalence of this phenomenon is quite high in the population of patients who have been diagnosed with hypertension, namely 15.9–43.6%.[18] Cases of masked morning hypertension are still found at a high rate in the controlled hypertension population, which is 23.1 – 60.7%.[19]

Morning hypertension is classified into 2 types, namely *nocturnal hypertensive morning hypertension* and *morning-surge hypertension*.[20,21] The first type includes non-dippers (i.e. BP that does not decrease at night)

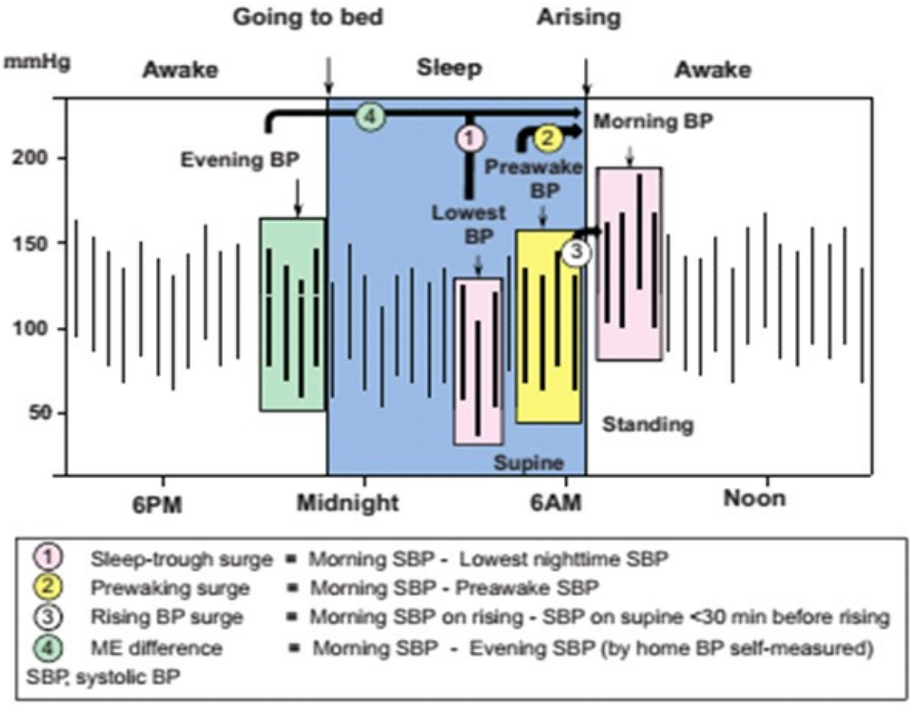

Figure 1. Definition of morning surge in BP [10]

and risers (i.e. BP at night that is higher than during the day).[22] Meanwhile, the second type is related to the phenomenon of morning surge, namely an increase in BP that starts 2 hours before waking up and increases after waking up.[22]

From the explanation above, it can be concluded that morning hypertension and MBPS are two different entities. A morning BP surge can still occur even without morning hypertension, for example in cases of excessively decreased nocturnal BP. On the other hand, morning hypertension can occur even though there is no significant MBPS, for example in the case of BP that remains high from night to morning.

Mechanism of morning hypertension

Morning hypertension is influenced by the sympathetic nervous system, the renin-angiotensin system, and cortisol secretion.[23,24] In normal individuals, this occurs physiologically, causing increased blood flow and shear stress.[25,26] If there is vascular stenosis due to atherosclerosis, platelet aggregation and activation of plasminogen activator inhibitor 1 (PAI-1) occur.[27] This mechanism is illustrated in Figure 2.[28]

Figure 2 explains the mechanism of damage to cardiovascular organs in this phenomenon. There are two genes that play a role, namely the central and peripheral clock genes.[28] The central clock gene regulates variations in blood pressure in the morning, including sleep-wake cycles, body position, and physical activity.[28] These things affect the body's physiology which is regulated by peripheral clock genes, namely the sympathetic nervous system and the renin-angiotensin system.[29] Both of these factors contribute to an increase in MBPS in morning hypertension.[27,28] Furthermore, MBPS also causes endothelial dysfunction and spasm, and platelet activation.[28] Endothelial dysfunction further leads to plaque rupture in the blood vessels. When combined with increased activity of PAI-1 so that fibrinolytic activity decreases, it can put a person at high risk for these cardiovascular events.[27,28] Several other studies have hypothesized that cardiovascular events in morning hypertension are associated with structural damage to large arteries, which in turn can lead to tearing of elastic fibers, hypertrophy and structural abnormalities of smooth muscle, and plaque rupture.[30-33] This mechanism mainly occurs in atherosclerotic

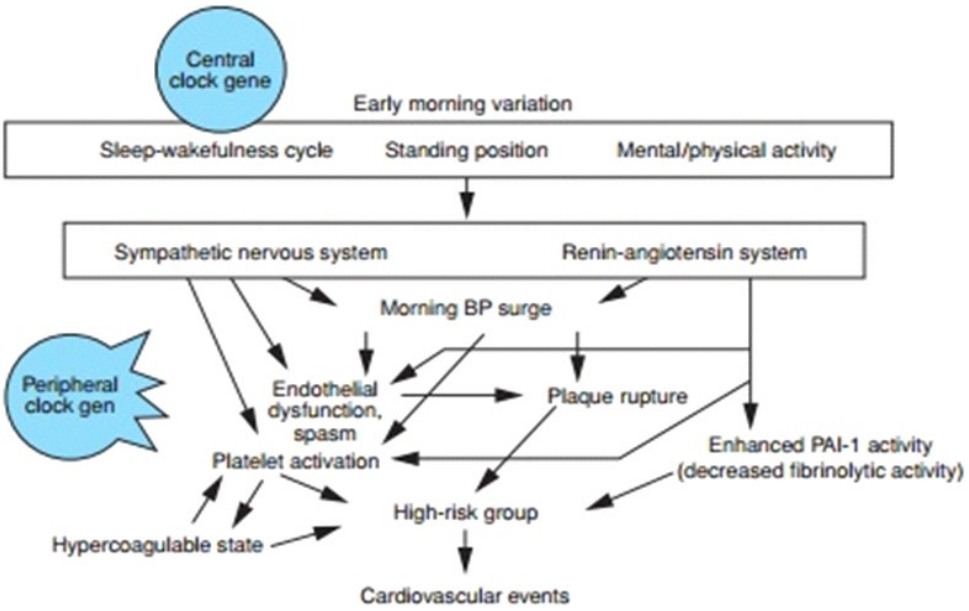

Figure 2. Organ damage mechanism in morning hypertension [28]

arteries, under conditions of high oxidative stress, and in the geriatric population with baroreflex dysfunction.[34]

Cardiovascular risk of morning hypertension

In previous studies, morning hypertension was considered a predictor of organ damage or cardiovascular outcome.[2] In a study in Japan on a population of hypertensive patients, it was found that the group with morning and night BP differences in the highest quartile had a higher risk of developing concentric left ventricular hypertrophy than the group in the lowest quartile.[35] In another study, the risk of stroke was found to be significantly higher in the morning hypertensive population than in the population with chronic hypertension.[36] The Japan Morning Surge-Home Blood Pressure (J-HOP) study showed that morning home systolic BP (SBP) itself should be evaluated to ensure best stroke prediction in clinical practice, at least in Japan.[37]

A recent study from the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome even shows that there is an increased risk of cardiovascular events by 30-40% in the population with MBPS.[38] The MBPS group in the highest decile class was associated with the prognosis of stroke or brain infarction twice as high in later life.[10] Sleep-trough MBPS was significantly associated with a 25% increased risk of stroke.[10] The study of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome concluded that the highest decile group in sleep trough (≥37 mmHg) and pre awakening (≥28 mmHg) MBPS had a significantly higher risk of all-cause mortality and total cardiovascular events.[39]

Recommendations for management of morning hypertension in primary care

Despite the important clinical implications, specific guidelines for the management of morning hypertension have not been published to date, although several guidelines on hypertension have general recommendations regarding the management of morning hypertension, such as the British NICE [40] and Canadian guidelines.[13] Both guidelines recommend out-of-office BP measurements, such as the ABPM or HBPM, for diagnostic and therapeutic purposes. However, specific recommendations regarding morning hypertension have not been listed in either. The importance of measuring BP regularly, especially in the morning, is also supported by guidelines from several other countries, such as China,[11]

Table 1. Commonly used oral antihypertensive drugs from Cooper et al.[48]

Class	Medication	Initial Dose	Dosing Interval	Maximal Dose
Peripheral antagonists	Prazosin	5 µg/kg	2 or 3 times per day	0.4 mg/kg (15 mg)
	Terazosin	1 mg	Daily	20 mg
	Doxazosin	1 mg	Daily	4 mg
Central antagonists	Clonidine[a]	5-10 µg/kg	2 or 3 times per day	0.9 mg
	Methyldopa[a,b]	10 mg/kg	2-4 times per day	3 g (65 mg/kg/d)
	Guanfacine[c]	1 mg	Nightly	2 mg
Nonselective β antagonists	Propranolol[a]	1-2 mg/kg	2 or 3 times per day	4 mg/kg
Selective β1 antagonists	Metoprolol [a,b]			
	Immediate release	1-2 mg/kg	2 times per day	6 mg/kg (200 mg/d)
	Extended release	1 mg/kg/d	Daily	2 mg/kg (200 mg/d)
	Atenolol[a]	0.5-1 mg/kg	Daily, 2 times per day	2 mg/kg (100 mg/d)
Mixed α/β antagonists	Labetalol[a]			
	Oral	4 mg/kg	2 times daily	40 mg/kg
	Intermittent bolus	0.2-1 mg/kg		20 mg
	Carvedilol[a]			
	Immediate release	6.25 mg	2 times daily	50 mg
	Extended release	20 mg	Daily	80 mg
Angiotensin-converting enzyme inhibitors	Captopril[a]	0.15-0.5 mg/kg	2-4 times per day	6 mg/kg
	Enalapril[a,b]	0.1-0.5 mg/kg	Daily, 2 times per day	0.5 mg/kg/ (40 mg))
	Fosinopril[b]	>50 kg, 5-10 mg	Daily	40 mg
	Lisinopril[a,b]	0.07 mg/kg	Daily	40 mg
	Benazepril[a,b]	0.1-0.6 mg/kg	Daily	40 mg
Angiotensin II receptor blockers	Candesartan[a,b]	0.2 mg/kg	Daily, 2 times per day	0.4 mg/kg (32 mg)
	Valsartan[a,b]	1.3 mg/kg	Daily	40 mg
	Losartan[a,b]	0.7 mg/kg	Daily	100 mg
	Olmesartan[a,d]			
	20-35 kg	10 mg	Daily	20 mg
	>35 kg	20 mg	Daily	40 mg
Calcium channel blockers	Amlodipine [a,b]	0.05-0.1 mg/kg	Daily, 2 times per day	10 mg
	Felodipine	2.5 mg	Daily	10 mg
	Nifedipine			
	Immediate release	0.2-0.5 mg/kg	Every 4-6 h	10 mg
	Extended release	0.2-0.5 mg/kg	Daily, 2 times per day	3 mg/kg (120 mg)
	Isradipine[a]			
	Immediate release	0.05-0.15 mg/kg	Every 4-6 h	0.8 mg/kg/d (20 mg)
	Extended release	0.05-0.15 mg/kg	Daily, 2 times per day	20 mg
Diuretics	Chlorothiazide[a,b]			
	Oral	20 mg/kg	2 times per day	1 g
	IV	40 mg/kg	Daily, 2 times per day	20 mg/kg
	Hydrochlorothiazide[b]	1 mg/kg	Daily	3 mg/kg (50 mg)
	Chlorthalidone[a]	0.3 mg/kg	Daily	2 mg/kg (50mg)
	Metolazone[a]	0.2-0.4 mg/kg	Daily, 2 times per day	6 mg/kg
	Furosemide[a]	1-2 mg/kg	Daily, 4 times per day	100 mg
	Spironolactone[b]	1-3 mg/kg	2-4 times per day	
Vasodilators	Hydralazine,[b]			
	Oral	0.7-1 mg/kg	2-4 times per day	25 mg (200 mg/d)

Note: [a]Extemporaneously prepared infusion; [b]Approved by the US Food and Drug Administration (FDA) for patients >6 years old; [c]FDA approved for patients >12 years old; [d]FDA approved for patients >1 year old

Korea [41] and Taiwan,[42] although they do not emphasize strict monitoring through ABPM and HBPM. The 2013 European Society of Hypertension guidelines,[43] the 2014 guideline of the US Eight Joint National Committee (JNC8) [44] and the 2020 guidelines of the International Society of Hypertension [45] have not discussed this phenomenon.

The selection of the right drug in the management of morning hypertension raises a question mark among clinicians. In one study, long-acting antihypertensive drugs have the advantage of controlling the blood pressure for 24 hours.[46] In another study, BP reductions were greater in the group receiving long-acting drugs, such as amlodipine and telmisartan.[47] In addition, morning BP control was also better when antihypertensive drugs were given at full/maximum doses compared to low doses, either in the form of monotherapy or combination therapy.[19] The commonly used oral antihypertensive drugs can be seen in Table 1 which is taken from Cooper et al.[48]

Several studies have also compared the effect of antihypertensives given alone (monotherapy) or in combination on 24-hour BP control. Combination therapy of an angiotensin-receptor blocker (ARB) or angiotensin-converting enzyme inhibitor (ACEI) with a calcium-channel blocker (CCB) or diuretic can improve BP control within 24 hours.[19] In a Japanese study, the combination of losartan and hydrochlorothiazide was able to significantly improve blood pressure control compared to high-dose losartan.[50] Another study using a combination of ARB-CCB and ARB-ACEI showed similar results.[50] In several other studies, the increase in morning blood pressure is associated with activation of the sympathetic nervous system and the renin-angiotensin system, therefore several hypotheses suggest the use of drugs that act specifically on this pathway.[51,52] However, there have been no studies comparing the potential of each of the antihypertensive drugs separately to lower blood pressure in the morning.

Although clinical evidence of the effect of morning hypertension is abundant, studies on the relationship of morning blood pressure control for preventing cardiovascular events have not been widely carried out. The Anglo-Scandinavian Cardiac Outcomes Trial compared hypertensive patients receiving amlodipine and atenolol. As predicted, the decrease in blood pressure in the amlodipine group was greater at the time of measurement in the clinic and in the subject's home at night.[53] After analysis, the hazard ratio for cardiovascular events in both groups was 0.74 (increased to 0.81 after adjusting for clinical systolic blood pressure measurements, and 0.85 after adjusting for night-time systolic blood pressure measurements).[53] These results suggest that the long-acting effects of amlodipine may be beneficial to cardiovascular outcomes.

CONCLUSION

Morning hypertension is one of the important factors for various cardiovascular events that often occur in post-wake times. This is important for clinicians to know for the management of hypertension and the prevention of cardiovascular complications. Uncontrolled BP in the morning is a sign that the antihypertensive regimen given is not appropriate, either due to inadequate duration of action, inadequate dosage, or not using combination therapy. Therefore, to achieve appropriate management of hypertension, including morning hypertension, long-acting antihypertensive drugs should be used, at full doses and in the form of combination therapy. More studies are needed, especially looking for other clinical evidence of the benefits of lowering BP in the morning, compared to other times, on cardiovascular outcomes. More research is also needed to find the most accurate blood pressure monitoring method in detecting the morning blood pressure surge, as well as its specific therapy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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CONTRIBUTORS

AR contributed to writing the manuscript. EW contributed to revising the manuscript. All authors have read and approved the final manuscript.

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