Review Article

Morning Hypertension: A Pitfall of Current Hypertensive Management

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Abstract

Morning hypertension has recently attracted more attention because of the close relation between blood pressure levels in the early morning and cardiovascular risk. Cases of morning hypertension, i.e., higher blood pressure in the early morning than in the evening, are classified into two types: the "morning-surge" type, characterized by a marked increase in blood pressure in the early morning, and the "nocturnal-hypertension" type, characterized by high blood pressure that persists from nighttime until early morning. Although these two types are caused by different pathologic mechanisms, both result in hypertensive organ damage and increase cardiovascular risk. Control of morning hypertension can be regarded as the gateway to strict 24-hour blood pressure control. Standard antihypertensive treatment in accord with current guidelines, when combined with chronobiologic antihypertensive treatment focused on morning hypertension and guided by home blood pressure monitoring, seems to provide more effective prevention of cardiovascular events.

Key words Morning hypertension, Morning surge, Nocturnal hypertension, Cardiovascular risk, Chronobiological antihypertensive medication

Introduction

Morning hypertension has attracted a great deal of attention in recent years. Morning blood pressure (BP) levels measured at home are more closely associated with risk of damage to the brain, heart, and kidney, as well as with the risk of all cardiovascular events, than are BP levels measured at clinics. In addition, an increase in BP that occurs from nighttime to early morning (i.e., morning-surge BP) is highly likely to be a cardiovascular risk factor, independent of 24-hour BP levels. However, in current clinical practice, no adequate control of hypertension has been achieved; morning BP levels before dosing are increased in more than half of hypertensive patients on antihypertensive therapy, even if they are under relatively good BP control at clinics (Fig. 1).[1] Thus, morning hypertension is a challenge to the current clinical practice of hypertension.

This paper describes the diagnosis and treatment of morning hypertension in daily clinical practice, providing the most up-to-date data obtained in studies from Jichi Medical School.

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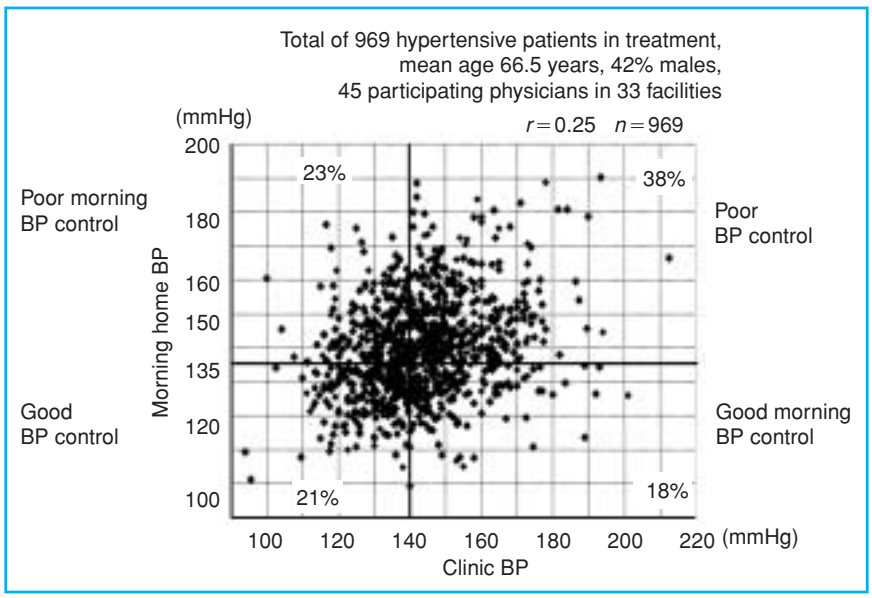

Fig. 1 Jichi morning hypertension research (J-MORE) study
(From Kario K, et al. Circulation. 2003;108:e72–e73)

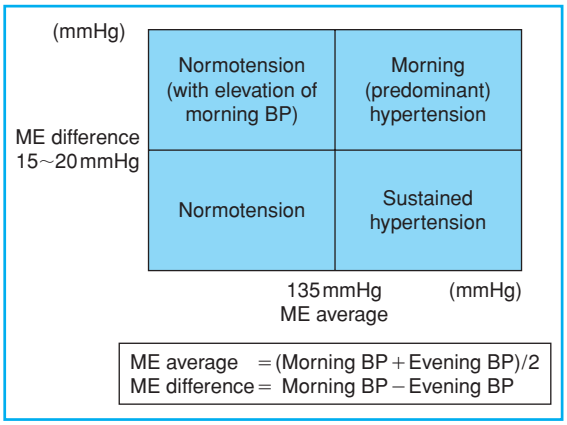

Fig. 2 Definition of morning hypertension using self-monitored home BP (Jichi Medical School)

Definition of Morning Hypertension

Recent clinical studies have shown that BP levels in the early morning are significantly associated with risk of damage to the brain, heart, and kidney as well as the risk of all cardiovascular events. The Ohasama Study, a longitudinal cohort study in which home BP was measured once every morning, showed that morning BP levels predicted cardiovascular death more accurately than randomly obtained BP levels in a general population of local residents in Japan.[2]

We use the definition of morning hypertension based on BP measurements in the early morning and at bedtime (Fig. 2).[3] There is a consensus that, when home BP is used to exclude white-coat hypertension, an average of multiple home BP measurements should be used. Therefore, we exclude cases of whitecoat hypertension using a cut-off value of 135 mmHg for averaged BP values in the morning and evening [morningness-eveningness (ME) average]. After that, patients are divided into sustained hypertension and morning (predominant) hypertension according to a difference (ME difference) in BP of 15–20 mmHg. That is, patients with morning (predominant) hypertension are those with high average values for morning and evening BP and prominent variations in morning and evening BP. In contrast, hypertensive patients who show only slight differences between morning and evening BP values are considered to have sustained hypertension.

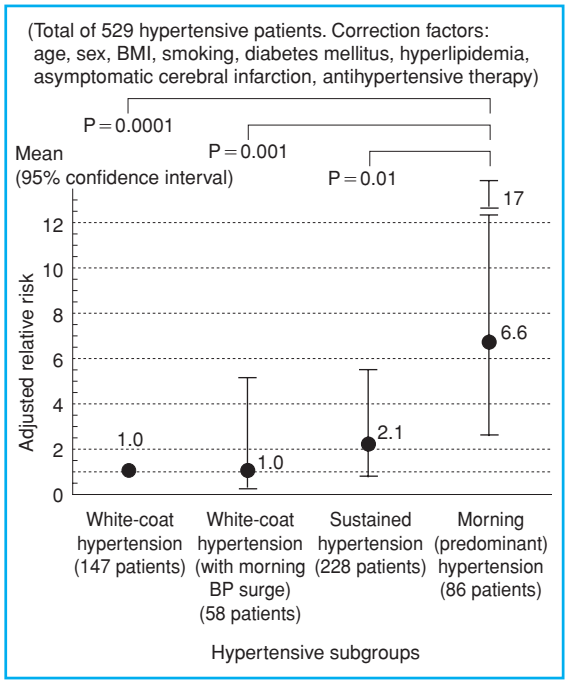

Fig. 3 Stroke risk of Japanese hypertensive patients (JMS ABPM study, Wave 1)

[Kario K, et al. Morning hypertension. (in preparation)]

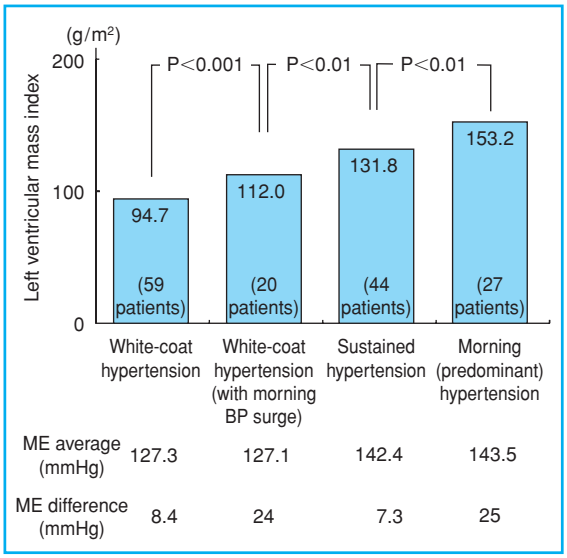

Fig. 4 Morning hypertension and left ventricular hypertrophy in hypertensive patients on antihypertensive treatment

(Kuroda T, Kario K, et al. Presented at the 26th Annual Scientific Meeting of the Japanese Society of Hypertension on Oct. 31, 2003)

Figure 3 shows the risk of stroke in Japanese hypertensive patients, based on our definition of morning (predominant) hypertension. In the Jichi Medical School Ambulatory Blood Pressure Monitoring (JMS ABPM) study (Wave 1) in elderly Japanese patients with hypertension, we followed 519 patients without a history of evident cardiovascular events (mean age, 72 years) for a mean of 41 months for possible onset of cardiovascular events. The patients underwent brain MRI and 24-hour ambulatory blood pressure monitoring (ABPM) at baseline.[4] In this study, the ME average and ME difference were independently associated with stroke risk.[5] Patients with white-coat hypertension who showed only slight variations in morning and evening BP were used as controls, with cut-off values of ME average (systolic pressure) and ME difference (systolic pressure) being 135 mmHg and 20 mmHg, respectively. As a result, stroke risk was about 2-fold for sustained hypertension and 6.6-fold for morning (predominant) hypertension.[3] Among patients with white-coat hypertension with a low ME average, there was no increase in stroke risk for those with morning BP surge.

We have also performed an echocardiographic study of hypertensive patients who are under treatment to evaluate hypertensive heart disease and determine its relationship with the state of home BP control. The results showed that the left ventricular mass index was greater in patients with morning (predominant) hypertension than in those with sustained hypertension, indicating advanced left ventricular hypertrophy (Fig. 4).

From the above results, we consider that our definitions of sustained hypertension and morning (predominant) hypertension based on home BP measurement are helpful for the management of hypertension in truly hypertensive patients, excluding cases of white-coat hypertension.

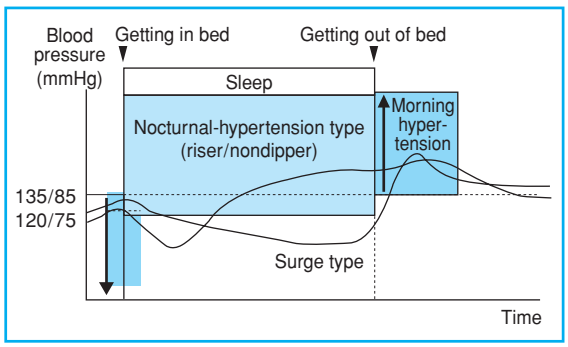

Fig. 5 Abnormal diurnal variation in blood pressure in two types of morning (predominant) hypertension

Two Types of Morning Hypertension

Prominent morning hypertension that is highly reproducible with a home BP monitor can be classified into two types according to BP levels at night determined by 24-h monitoring (Fig. 5), namely, nocturnal hypertensive morning hypertension and morning-surge hypertension. The former type presents a shift from nocturnal hypertension and includes non-dippers, with a diminished nocturnal fall in BP, and risers, with nocturnal levels higher than daytime levels. The latter group is characterized by BP elevation beginning about 2 hours before getting out of bed, followed by further elevation after rising from bed. Both riser-type hypertension and morning-surge hypertension serve as independent risk factors for stroke. Conditions presumed to be associated with these two types of morning hypertension are listed in Table 1.[6]

1. Morning hypertension of the nocturnal hypertensive type

The cardiovascular risk of risers is highest, involving fatal stroke—particularly cerebral hemorrhage—and cardiac events including sudden cardiac death.[7–9] Insufficient nocturnal depression by short-acting antihypertensive drug therapy in hypertensive patients induces morning hypertension of this nocturnal hypertensive type.[10] In addition, patients with diabetes mellitus, poststroke state, cardiac failure, and sleep apnea syndrome frequently have this type of morning hypertension. However, investigations of the time of onset of cardiovascular events in diabetic patients have found no diurnal variation in onset. In other words, the increased risk of morbidity due to morning hypertension occurs in the nighttime, and the increased risk in the early morning is an extension of nighttime risk.

Table 1 Conditions associated with morning hypertension

Nocturnal-hypertension (riser/nondipper) type
Increased intravascular volume (heart failure, renal failure, etc.)
Abnormal autonomic nervous system (diabetes, parkinsonism, Shy-Drager syndrome, cardiac transplantation, orthostatic hypotension, etc.)
Secondary hypertension (pheochromocytoma, primary aldosteronism, Cushing's syndrome, etc.)
Salt-sensitive hypertension
Sleep disorders (sleep apnea syndrome, etc.)
Metabolic syndrome (obesity)
Depressive state
Dementia
Elderly patients
Black male patients
Hypertensive target organ damage [cerebral infarction, asymptomatic cerebrovascular disorder (silent cerebral infarcts, deep white matter lesions), cardiac hypertrophy, proteinuria, microalbuminuria, etc.]
Surge type
Elderly patients
Orthostatic hypertension
Sleep disorders (sleep apnea syndrome, etc.)
Hypertensive target organ damage [cerebral infarction, asymptomatic cerebrovascular disorders (silent cerebral infarcts, deep white matter lesions), cardiac hypertrophy, proteinuria, microalbuminuria, etc.]
α-Sympathetic hyperactivity
Dehydration
Large artery stiffness
Baroreceptor dysfunction

2. Surge-type morning hypertension

Although it has been suggested that morning BP surge may be involved in the onset of cardiovascular events, whether or not it is an actual risk for cardiovascular events has not been clarified. Based on the results of the

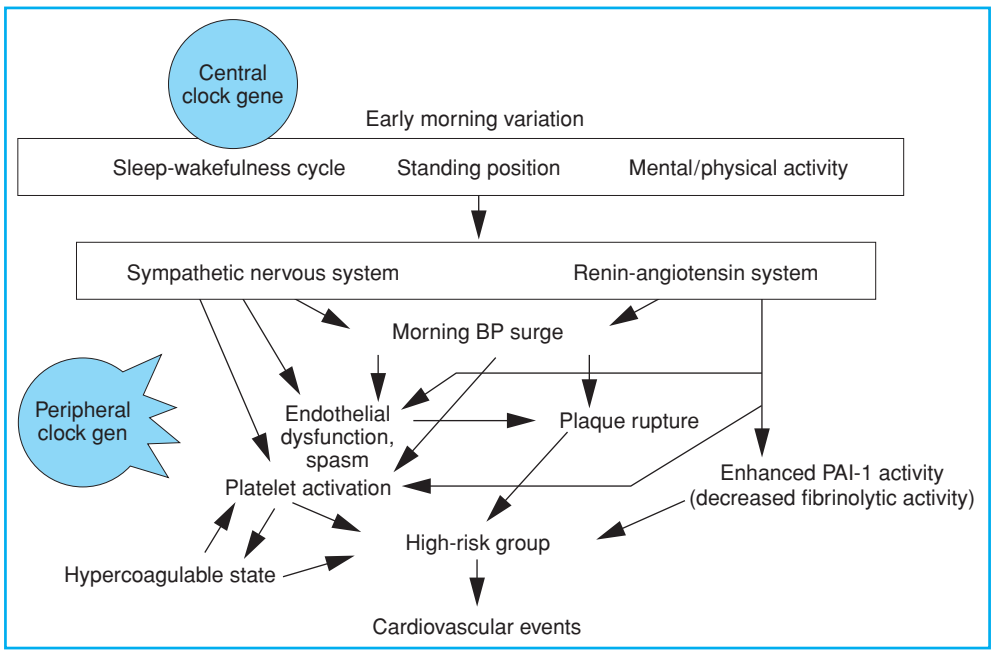

Fig. 6 Mechanism of the morning onset of cardiovascular events
[Kario K, et al. J Cardiovasc Pharmacol. 2003;42(Suppl 1):S87–S91]

JMS ABPM study, we reported that morning BP surge is associated with silent cerebral infarcts and represents a risk for cerebrovascular disorders.[4] In this study, both early morning BP levels and morning BP surge were important as risk factors for stroke.

In regard to the relationship with hypertensive heart disease, Kuwashima et al. first demonstrated in a study examining elderly patients with hypertension that morning BP surge measured at the time of rising from bed is correlated with the left ventricular weight coefficient obtained from echocardiogram.[11] In addition, hypertensive patients with morning surge are reported to show an increase in the ratio of the low- to high-frequency element of heart rate—an index of sympathetic activity level—as well as prolonged QTc interval and increased QTc dispersion.[12] These findings suggest that patients with morning surge have considerable variability in electric excitation at the myocardial level in response to sympathetic activity, and thus are prone to develop arrhythmia. A relationship between morning BP surge and early diabetic nephropathy has also been reported.[13]

Mechanism of Target Organ Damage

In the early morning, not only blood pressure but also other cardiovascular risk factors including cardiovascular response and thrombotic tendency are worsened, leading to the occurrence of cardiovascular events in the early morning (Fig. 6).[14] The morning surge in BP is influenced by the sympathetic nerve system and renin-angiotensin system. Healthy individuals also experience morning BP surge as a physiological phenomenon, but a prominent increase in BP leads to the risk of cardiovascular events. Morning BP surge itself places a direct load on the vascular wall and causes an increase in shear stress as a result of increased blood flow, leading to an increased likelihood of vascular wall spasm and rupture of plaque. At the site of vascular stenosis resulting from atherosclerosis, high shear stress is present, and platelets are activated. Because of this, increased platelet

aggregation may be triggered in the early morning as a result of morning BP surge. Further, tissue plasminogen activator inhibitor 1 (PAI-1), a fibrinolysis inhibitor, is elevated in the early morning, increasing the risk of symptomatic and asymptomatic cardiovascular disease.[15]

Recent years have seen remarkable progress in molecular biologic studies in the area of chronobiology. In 1997, the first mammalian clock gene was cloned from the mouse hypothalamus. It was reported that this gene forms a central biological clock. In addition, it became apparent that the clock gene is expressed not only in the central nervous system but also in peripheral tissue, where it is present in the cells. The central clock synchronizes each peripheral clock and thereby regulates the circadian rhythm of the body. It is presumed that the circadian rhythm of the cardiovascular system is under the influence of both the central clock and the peripheral clock present in cardiovascular tissue. Questions relating to the involvement of the clock gene in peripheral tissue to the increasing risk of cardiovascular events in the early morning, as well as the extent of this involvement, are important subjects of future investigation.

Treatment of Morning Hypertension

Since not only blood pressure but also various other cardiovascular risk factors are aggravated in the early morning, antihypertensive treatment for morning hypertension is likely to offer greater benefit in preventing cardiovascular events. Hypertensive patients on standard antihypertensive treatment often have morning hypertension of the nocturnal-hypertension type because the effect of most antihypertensive drugs does not last for 24 hours. Antihypertensive treatment targeting morning hypertension combined with standard treatment may enable more effective prevention of cardiovascular events.

The first step in the treatment of morning hypertension in clinical practice is for the patient to self-monitor early morning BP at home. In addition, in patients with prominent morning hypertension in whom the difference between morning and evening systolic BP is more than 15–20 mmHg, it is important to determine by ambulatory blood pressure monitoring whether the hypertension is of the nocturnal-hypertension type or the morning-surge type. Specifically, it is recommended to combine non-specific and specific antihypertensive treatments as shown in Fig. 7, to control morning BP levels to achieve an average of morning (before dosing) and evening (at bedtime) BP of under 135/85 mmHg and a morning-evening pressure difference of less than 15–20 mmHg.

In principle, a long-acting antihypertensive drug whose effect lasts for 24 hours initially is used as non-specific treatment. This therapy is aimed at reducing the ME average to less than 135 mmHg (systolic pressure). Typical drugs used in this therapy include long-acting calcium antagonists[16,17] and diuretics. However, even antihypertensive drugs designed for once-daily doses are rarely effective from the morning dosing

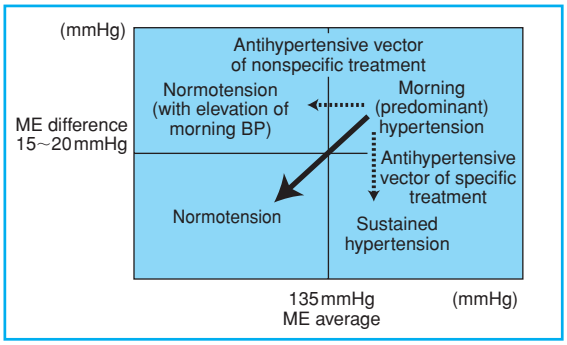

Fig. 7 Specific antihypertensive treatment for morning (predominant) hypertension using home BP monitoring

Nonspecific treatment: long-acting antihypertensive drugs (twice-daily, morning and evening, doses should also be considered), diuretics

Specific treatment: α-blockers used at bedtime

Renin-angiotensin-aldosterone system inhibitors (dosing at bedtime should also be considered)

Heart rate-controlling calcium antagonists (cilnidipine, azelnidipine, diltiazem)

until the following morning, with individual differences noted in the duration of the antihypertensive effect. When the ME difference exceeds 15–20 mmHg after actual prescription, dosing in both the morning and evening (or at bedtime) may be more useful.

Specific treatment includes inhibitors of the sympathetic nervous system and renin-angiotensin system, which show aggravation in the early morning. Administration of α-blockers at bedtime provides a relatively specific reduction in early morning BP.[18,19] β-Blocker monotherapy does not cause a specific decrease in early morning BP. Since the renin-angiotensin system is augmented in the early morning, treatment with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists can be considered specific treatment.[20,21] However, for some drugs, the antihypertensive effect of one morning dose may not last until the following morning. In such cases, two divided daily doses or one daily dose at bedtime may be useful.[21] Recently, calcium antagonists such as cilnidipine, azelnidipine, and diltiazem have been used as specific treatments because they have an inhibitory effect on increasing heart rate.

Conclusion

For more effective prevention of cardiovascular diseases, the use of a chronobiological approach that targets morning hypertension and employs home BP monitoring is recommended in addition to standard antihypertensive treatment according to current guidelines.

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