CHAPTER 1

First, focusing on "morning hypertension"

The morning is the most important period for cardiovascular diseases [1, 2]. Cardiovascular events occur most frequently in the morning just after awakening, at the time of the peak ambulatory blood pressure (BP) (Figure 1.1) [2]. Exaggerated morning BP surge (MBPS) and morning hypertension are a risk for cardiovascular events (Figure 1.2), and are associated with advanced organ damage (Figure 1.3) [3–7]. Morning BP level is more closely associated with organ damage to brain, heart, and kidney, and the risk of cardiovascular and cerebrovascular events (Figure 1.4) and disability in the elderly than clinic BP both in hypertensive patients and community-based normotensive populations [8, 9]. Finally, recent evidence demonstrates that uncontrolled morning hypertension on medication is a strong predictor of cardiovascular events [10].

What is the "perfect 24-hour blood pressure control"?

The management of "morning hypertension" is the most effective first step to achieve "perfect 24-hour BP control" [1]. The majority of the benefit of antihypertensive treatment is derived from BP control per se. There is robust evidence that indicates BP control throughout 24 hours is essentially important for lowering the risk of organ damage and cardiovascular events. However, not only strict reduction of the 24-hour BP level (amount of 24-hour BP lowering), but also restoring disrupted circadian BP rhythms, and reducing exaggerated BP variability (quality of 24-hour BP lowering), are required to achieve "perfect 24-hour BP control" (Figure 1.5) [11].

Recent guidelines such as the Japanese Society of Hypertension (JSH2014) Guidelines [12], European Society of Hypertension/European Society of Cardiology (ESH/ESC2013) Guidelines [13], and NICE 2011 Guidelines (UK) [14] recommend the practical use of the out-of-office BP for the diagnosis and management of hypertension. Clinically, two methods are available to measure our BP in clinical practice. One is ambulatory BP monitoring (ABPM), and the other is home BP monitoring (HBPM) (Figure 1.6). Figure 1.7 demonstrates the different thresholds of clinic, home, and ambulatory BPs for the definition of hypertension [11–13].

Essential Manual of 24 Hour Blood Pressure Management, First Edition. By Kazuomi Kario.

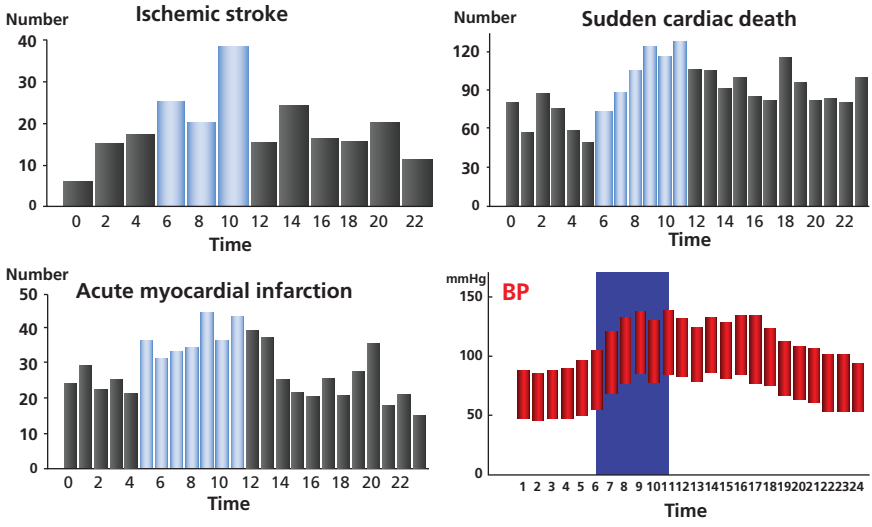


Figure 1.1 Onset time of cardiovascular events. *Source:* Muller et al. 1989 [2].

Masked hypertension is defined as normotension for office BP and hypertension for out-of-office BP, while white-coat hypertension is defined as normotension for out-of-office BP and hypertension for office BP [15]. There are three subtypes of masked hypertension, namely morning hypertension, daytime (stress-induced) hypertension, and nocturnal hypertension (Figure 1.8). Among these masked hypertension subtypes, only morning hypertension could be definitively detected by the conventional measurement of HBPM.

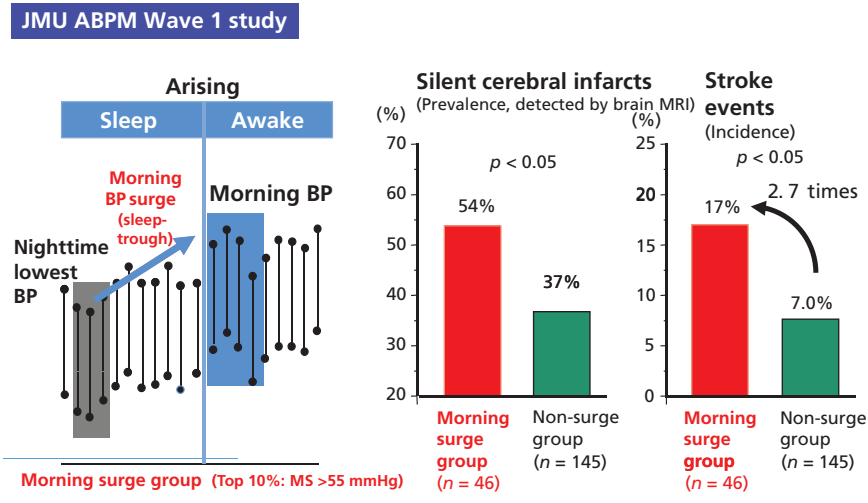
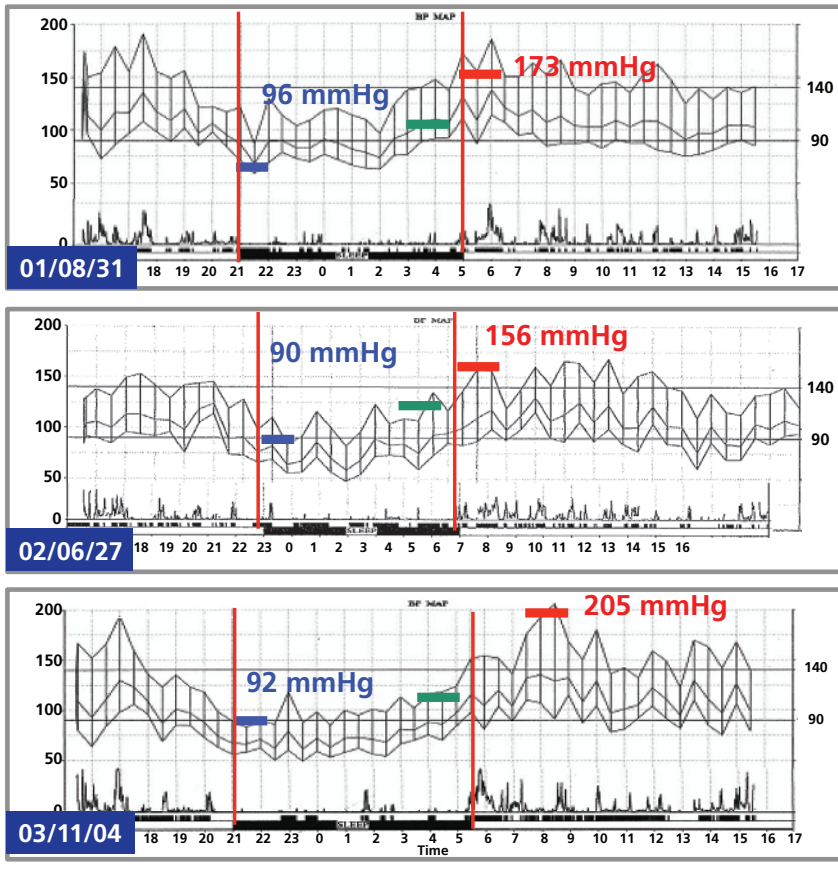


Figure 1.2 Morning BP surge and stroke risk in hypertension (matching for age and 24-hour systolic BP). *Source:* Kario et al. 2003 [3].



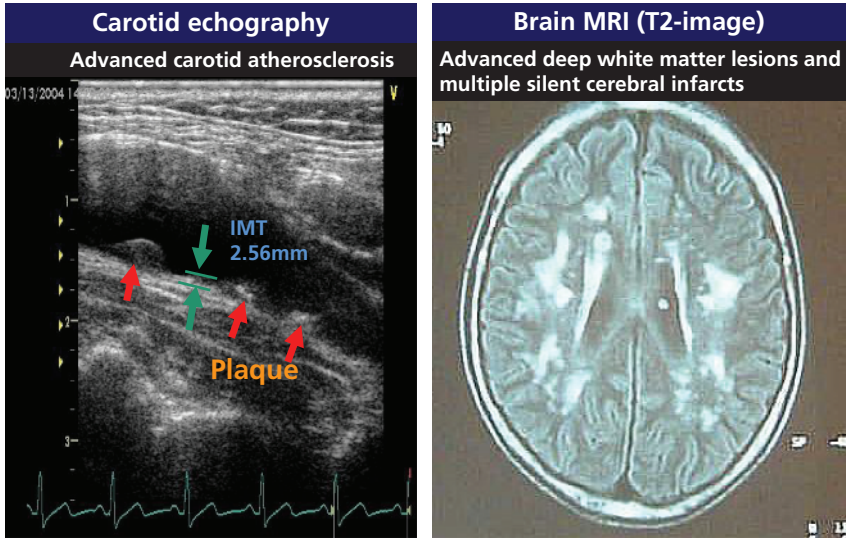


Figure 1.3 A 69-year-old man with morning hypertension exhibiting advanced organ damage. Cardiac echography demonstrated that concentric hypertrophy (left ventricular mass index = 144.2 g/m^2; relative wall thickness = 0.30) with reduced systolic function (ejection fraction = 46%). IMT, intima media thickness.

JMS ABPM prospective study wave 1
Cox regression analysis for clinical stroke events

Covariates	Relative risk (95%CI)	*p*-Value
Clinic SBP (10 mmHg)	NS	
24h SBP (10 mmHg)	NS	
Awake SBP (10 mmHg)	NS	
Evening SBP (10 mmHg)	NS	
Sleep SBP (10 mmHg)	NS	
Pre-awake SBP (10 mmHg)	NS	
Morning SBP (10 mmHg)	1.44 (1.25-1.67)	<0.0001

Morning SBP is the 2-hour average of ABPM-measured SBPs after arising.
After controlling for age, gender, body mass index, smoking status, diabetes, hyperlipidemia, silent cerebral infarct, and antihypertensive medication status at the final follow-up, all SBP variables (clinic, 24 hours, awake, evening, sleep, pre-awake, and morning) were added in the model, and were analyzed by stepwise Cox regression analysis. CI, confidence interval; SBP, systolic blood pressure; NS, not selected.

Figure 1.4 Morning BP is the strongest independent predictor of stroke events. *Source:* Kario et al. 2006 [5].

Definition of "morning hypertension"

Wide definition of "morning hypertension" is having the average of morning BPs ≥135 mmHg for systolic BP (SBP), or ≥85 mmHg for diastolic BP (DBP), regardless of clinic BPs (Figure 1.9) [1]. In addition, strict definition of "morning hypertension" is those with morning–evening difference (ME-dif) (morning

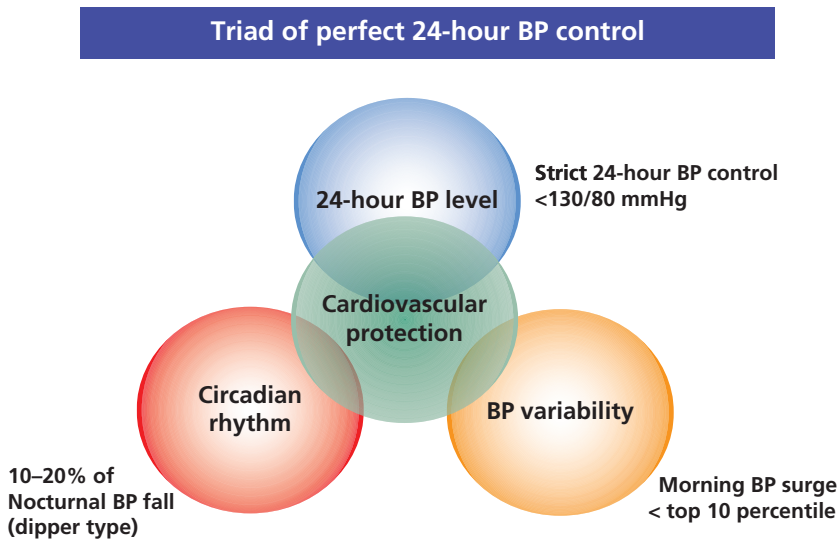


Figure 1.5 Triad of perfect 24-hour BP control. *Source:* Kario 2012 [11].

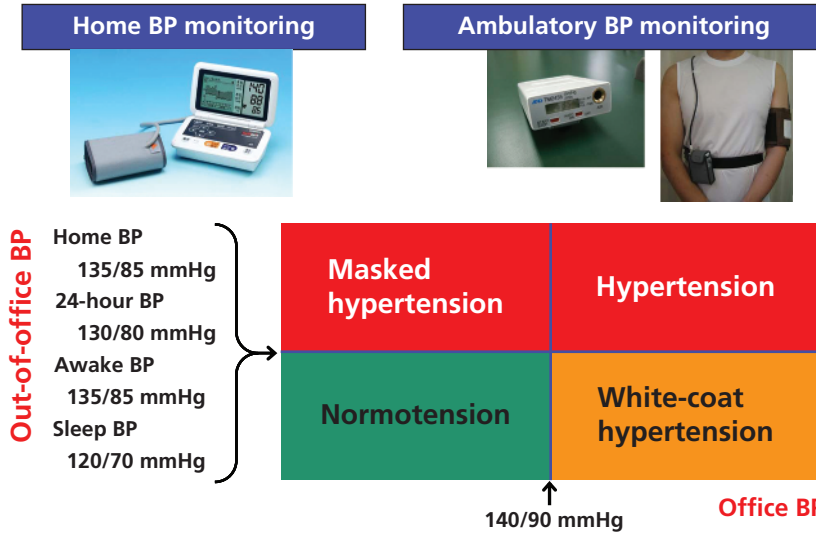


Figure 1.6 Out-of-clinic BP monitoring.

SBP – evening SBP) in home BP ≥15 mmHg [1,5]. Morning hypertension (ambulatory morning hypertension) can also be diagnosed using ABPM [5]. Masked morning hypertension is defined as morning hypertension with clinic BP <140/90 mmHg.

How to assess "morning hypertension"

Morning BP can be measured by HBPM and by ABPM. HBPM is the BP self-measured in sitting conditions at home, while ABPM measures ambulatory BP

Blood pressure (mmHg)	Systolic	Diastolic
Clinic	140	90
Home		
Morning	135	85
Daytime	135	85
Evening	135	85
Sleep	120	70
Ambulatory		
24 hours	130	80
Daytime (awake)	135	85
Nighttime (sleep)	120	70

Figure 1.7 Different thresholds of BP level for diagnosis of hypertension.

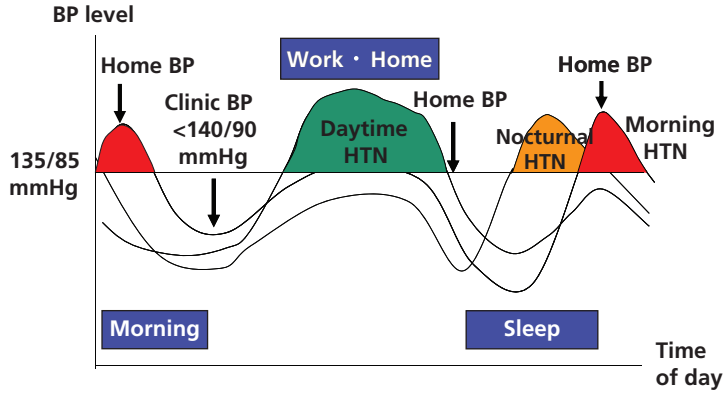


Figure 1.8 Three types of masked hypertension. *Source:* Kario K. Masked hypertension—pathogenesis and treatment. *Nihon Naika Gakkai Zasshi.* 2007;96:79–85.

with 15–30 minutes intervals throughout 24-hour periods. Clinical use of HBPM is superior to ABPM, because it is convenient without discomfort. However, the BP profiles evaluated by these two methods are different. HBPM only measures BPs in a specific time (morning and/or evening) and in a specific condition (resting while sitting), while ABPM measures dynamic ambulatory BP changes during daytime as well as MBPS, and nocturnal BPs during sleep period detecting dynamic nocturnal BP changes as well as detecting masked nocturnal hypertension. Recent advances in the HBPM device could practically measure nocturnal BP during sleep. In clinical practice, these HBPM and ABPM devices should be used not alternatively but complimentarily [12].

The clinical use of HBPM and ABPM increases quality of the management of hypertension. Ideally, HBPM and antihypertensive treatment based on HBPM are recommended for all hypertensive patients, while ABPM is recommended for high-risk hypertensive patients with home BP ≥125/75 mmHg, especially for

Morning hypertension (home BP monitoring)	
Wide definition	Average of self-measured home BPs in the morning ≥135 mmHg systolic and/or ≥85 mmHg diastolic
Specific definition	Above definition pulse ME difference (morning BP minus evening BP) ≥15 mmHg systolic
Ambulatory morning hypertension (ABPM)	
	Average of ambulatory BPs during 2 hours after arising ≥135 mmHg systolic and/or ≥85 mmHg diastolic
Masked morning hypertension	
	Morning hypertension with clinic BP <140/90 mmHg

Figure 1.9 Definition of morning hypertension. *Source:* Kario 2004 [1].

Monitoring	Subjects
Home BP monitoring	All the hypertensive subjects Age ≥30 years with cardiovascular risk factor
Ambulatory BP monitoring	High-risk hypertensive patients with • Home BP ≥125/75 mmHg • History of cardiovascular events • Organ damage (ECG-LVH, albuminuria, etc.) • Nocturnal hypertension-suspected comorbidities (sleep apnea syndrome, diabetes, chronic kidney disease)

Figure 1.10 Subjects for recommendation of home and ambulatory BP monitoring. LVH, left ventricular hypertrophy. *Source:* Kario K, *Essential Manual of 24-hour Blood Pressure Management from Morning to Nocturnal Hypertension*, Wiley-Blackwell, 2015.

those with a history of cardiovascular events, evidence of organ damage (ECG-LVH, etc.), and nocturnal hypertension-suspected comorbidities such as sleep apnea syndrome, diabetes, and chronic kidney disease (CKD) (Figure 1.10).

Home BP monitoring

Figure 1.11 shows the standard method of self-measured HBPM in the morning. In both medicated and non-medicated hypertensives, the ME difference of self-measured home BP was associated with left ventricular mass index (LVMI) and the risk of concentric hypertrophy, as well as with increased PWV [16–18]. In our previous study, ME-dif was significantly associated with left ventricular hypertrophy (LVH), and increased brachial-ankle pulse wave velocity (baPWV) (Figure 1.12) [16], and morning hypertension defined by the ME-dif and the average of morning and evening BPs (ME-ave) is a determinant of concentric LVH (Figure 1.13) [17]. Even among the home normotensives (white-coat

Morning BP measurement is performed as follows:

twice
after 1–2 minutes resting in a sitting position
within 1 hour after waking up
after urination
before breakfast
before taking pills

Calculation:
Average of two BPs at least 3 days
≥6 measures

Figure 1.11 Home BP measurement in the morning.

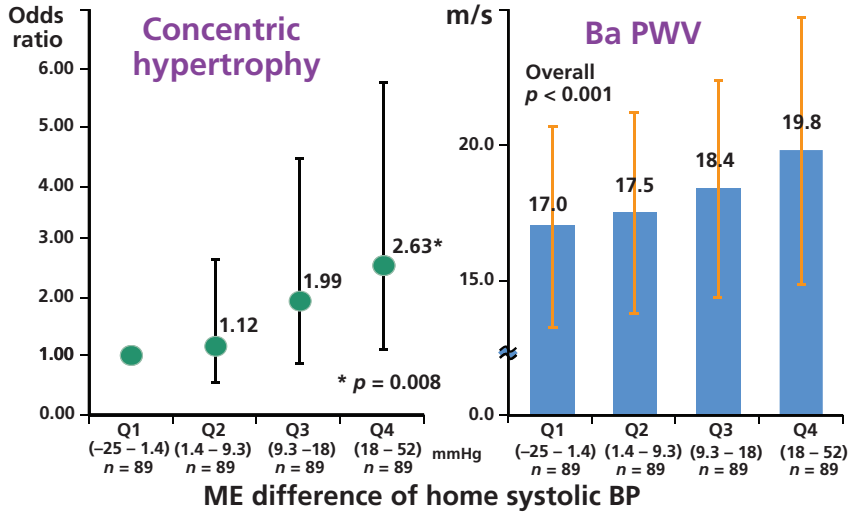


Figure 1.12 Morning–evening difference (ME-dif) of home BP and cardiovascular disease in unmedicated hypertensive patients ($N = 356$). baPWV, brachial-ankle pulse wave velocity. *Source:* Matsui et al. 2009 [16].

hypertensives), patients with ME-dif ≥15 mmHg had a higher percentage of concentric remodeling than those with ME-dif <15 mmHg (32.5% vs. 14.7%, $p = 0.017$). Recently, ME-dif assessed both by ABPM or by HBPM are reported to be associated with cardiovascular risk independently of the ME-ave [5, 19]. The ME-dif of ABPM is an independent predictor of future stroke events in elderly hypertensives [5].

If clinic BP is normotensive <140/90 mmHg, those with morning BP ≥135/85 mmHg are defined as having "masked" morning hypertension [1]. In addition,

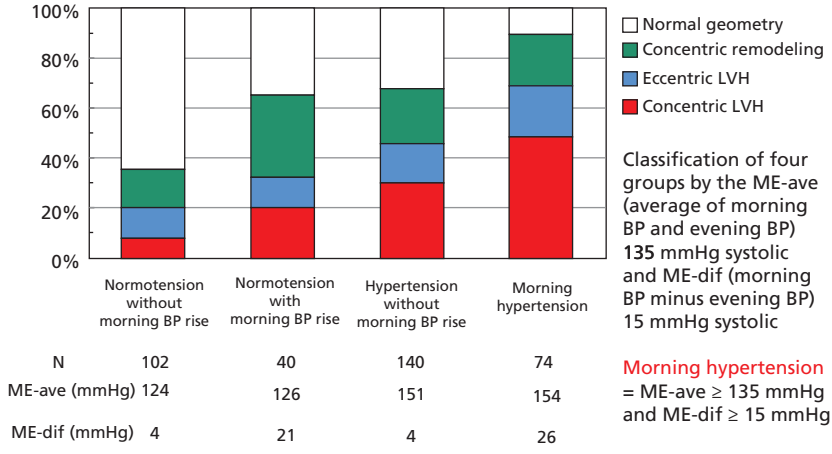


Figure 1.13 Morning hypertension and left ventricular hypertrophy in unmedicated hypertensive patients ($N = 356$). LVH, left ventricular hypertrophy. *Source:* Matsui et al. 2010 [17].

"isolated" morning hypertension, i.e. hypertension only in the morning (≥135/85 mmHg), but normotension in the evening or other BPs measured at different times of the day (<135/85 mmHg) or those with increased ME-dif ≥15 mmHg, could be considered as the predisposing condition (prehypertension) before development of clinic hypertension and/or 24-hour ambulatory hypertension [1, 20].

Evening BP measurement in addition to morning measurement is recommended especially for diabetic hypertensive patients, because the reduction of evening BP as well as morning BP is closely correlated with the reduction of urinary albumin/creatinine ratio (UACR) [21].

Ambulatory BP monitoring

Ambulatory BP monitoring (ABPM) could more extensively assess the 24-hour ambulatory BP profile including BP variability of individual patients. Figures 1.14, 1.15, 1.16, 1.17, and 1.18 show the ambulatory BP and BP variability parameters calculated from the ambulatory BPs obtained from one ABPM.

24-hour BP is the average of BPs during 24 hr and is the most important BP parameter as the cardiovascular risk factor [22].

Daytime BP and nocturnal BP are separately calculated from the average of daytime BPs and nocturnal BPs. The time periods to define daytime, nocturnal, and morning ambulatory BPs are based on the diary of the individual patient's behavior, or based on 24-hour clock time (Figures 1.14, 1.15, 1.16, 1.17, and 1.18). The diary-based definition of daytime and nocturnal BPs is superior to the 24-hour clock time definition, because the majority of

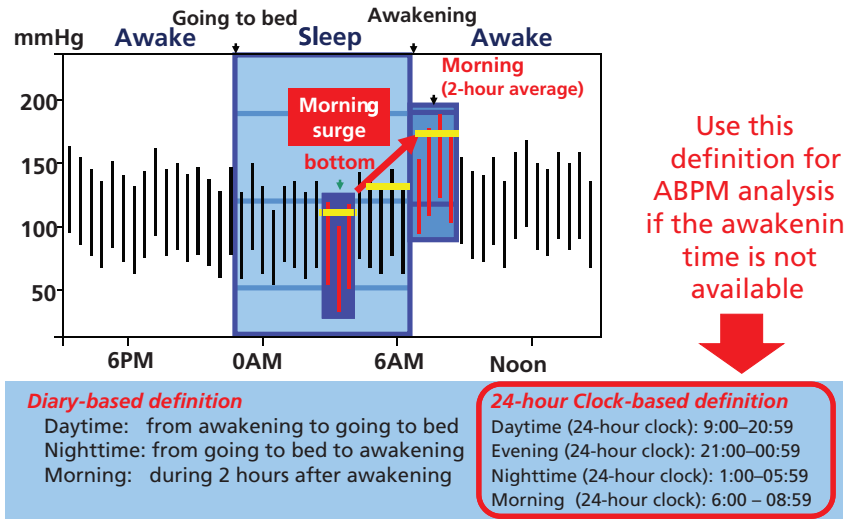


Figure 1.14 Definition of time period for calculating ABPM parameters. *Source:* Kario et al. 2003 [3].

Morning BP parameters	
Average morning SBP	= 2-hour average of morning SBPs during 2 hours after arising
Moving peak morning SBP	= Highest 1-hour moving average of consecutive SBPs during 2 hours after arising
Maximum morning SBP	= Maximum morning SBP (one SBP) during 2 hours after arising
Nighttime BP parameters	
Average nighttime SBP	= Average of nighttime SBPs from going to bed to arising
Average peak nighttime SBP	= Average of highest three different nighttime SBPs from going to bed to arising
Maximum nighttime SBP	= Maximum nighttime SBP (one SBP) from going to bed to arising
Minimum nighttime SBP	= Minimum nighttime SBP (one SBP) from going to bed to arising
Moving lowest nighttime SBP	= Lowest 1-hour moving average of consecutive SBPs from going to bed to arising
Prewakening nighttime SBP	= 2-hour average of nighttime SBPs during 2 hours before arising
Daytime BP parameters	
Average daytime SBP	= Average of daytime SBPs from arising to going to bed

Figure 1.15 Diary-based definition of morning and nocturnal BP parameters. *Source:* Kario K, *Essential Manual of 24-hour Blood Pressure Management from Morning to Nocturnal Hypertension*, Wiley-Blackwell, 2015.

ambulatory BPs is determined by the patient's behavior of arising and going to bed.

Morning BP parameters are defined as follows: average morning SBP (2-hour average of morning SBPs during 2 hours after arising or between 7 AM and 9 PM), moving peak morning SBP (highest 1-hour moving average of consecutive

Morning BP surge parameters	
Sleep-trough morning surge	= Average morning SBP minus moving lowest nighttime SBP
Dynamic morning surge	= Moving peak morning SBP minus moving lowest nighttime SBP
Maximum dynamic morning surge	= Maximum morning SBP minus minimum nighttime SBP
Prewakening morning surge	= Average morning SBP minus prewakening morning SBP
Nighttime BP surge parameters	
Average nighttime surge	= Average peak nighttime SBP minus average nighttime SBP
Dynamic nighttime surge	= Average peak nighttime SBP minus moving lowest nighttime SBP
Maximum dynamic nighttime surge	= Maximum nighttime SBP minus minimum nighttime SBP
Nighttime BP dipping parameters	
Nighttime dipping (%)	= (1 minus average nighttime SBP / average daytime SBP) X 100
Subgroup classification based on nighttime SBP dipping (%)	= Extreme-dipper: >20%; Dipper: ≤20%, >10%; Non-dipper: ≤10%, >0%; Riser: ≤0%

Figure 1.16 Diary-based definition of morning and nocturnal BP surge parameters. *Source:* Kario K, *Essential Manual of 24-hour Blood Pressure Management from Morning to Nocturnal Hypertension*, Wiley-Blackwell, 2015.

Morning BP parameters	
Average morning SBP	= 2-hour average of morning SBPs between 7 AM and 9 AM
Moving peak morning SBP	= Highest 1-hour moving average of consecutive SBPs between 6 AM and 10 AM
Maximum morning SBP	= Maximum morning SBP (one SBP) between 6 AM and 10 AM
Minimum morning SBP	= Minimum morning SBP (one SBP) between 5 AM and 9 AM before maximum morning SBP
Moving lowest prewakening morning SBP	= Lowest 1-hour moving average of consecutive SBPs between 5 AM and 9 AM before moving peak morning SBP
Nighttime BP parameters	
Average nighttime SBP	= Average of nighttime SBPs between 1 AM and 6 AM
Average peak nighttime SBP	= Average of highest 3 different nighttime SBPs between 1 AM and 6 AM
Maximum nighttime SBP	= Maximum nighttime SBP (one SBP) between 1 AM and 6 AM
Minimum nighttime SBP	= Minimum nighttime SBP (one SBP) between 1 AM and 6 AM
Moving lowest nighttime SBP	= Lowest 1-hour moving average of consecutive SBPs between 1 AM and 6 AM

Figure 1.17 24-hour-clock-based definition of morning and nocturnal BP parameters. *Source:* Kario K, *Essential Manual of 24-hour Blood Pressure Management from Morning to Nocturnal Hypertension*, Wiley-Blackwell, 2015.

Morning BP surge parameters	
Average morning surge	= Average morning SBP minus average nighttime SBP
Dynamic morning surge	= Moving peak morning SBP minus moving lowest nighttime SBP
Dynamic prewakening morning surge	= Moving peak morning SBP minus moving lowest prewakening morning SBP
Maximum dynamic morning surge	= Maximum morning SBP minus minimum nighttime SBP
Maximum prewakening morning surge	= Maximum morning SBP minus minimum morning SBP
Nighttime BP surge parameters	
Average nighttime surge	= Average peak nighttime SBP minus average nighttime SBP
Dynamic nighttime surge	= Average peak nighttime SBP minus moving lowest nighttime SBP
Maximum dynamic nighttime surge	= Maximum nighttime SBP minus minimum nighttime SBP
Daytime BP parameters	
Average daytime SBP	= Average of daytime SBPs between 9 AM and 9 PM

Figure 1.18 24-hour-clock-based definition of morning and nighttime BP surge parameters. *Source:* Kario K, *Essential Manual of 24-hour Blood Pressure Management from Morning to Nocturnal Hypertension*, Wiley-Blackwell, 2015.

SBPs during 2 hours after arising, or between 7 AM and 10 PM), and maximum morning SBP (maximum morning SBP (one SBP) during 3 hours after arising or between 7 AM and 10 PM). The prewakening nocturnal SBP or minimal (or moving prewakening) morning SBP between 5 AM and 9 PM is used to calculate the prewakening morning SBP surge.

Nocturnal BP parameters are defined as follows: average nocturnal SBP (average of nocturnal SBPs), average peak nocturnal SBP (average of three highest different nocturnal SBPs), maximum nocturnal SBP (one SBP), minimum nocturnal SBP (one SBP), moving lowest nocturnal SBP (lowest 1-hour moving average of consecutive nocturnal SBPs), and prewakening nocturnal SBP (2-hour average of nocturnal SBPs during 2 hours before arising).

MBPS parameters: Sleep-trough morning surge is calculated as the average morning SBP minus moving lowest nocturnal SBP, and prewakening morning surge is calculated as the average morning SBP minus prewakening morning SBP. Dynamic morning surge is calculated as the moving peak morning SBP minus moving lowest nocturnal SBP, and maximum dynamic morning surge is calculated as the maximum morning SBP minus minimum nocturnal SBP. As per the 24-hour clock-based analysis, instead of prewakening surge, peri-morning surge may be alternatively calculated as the maximum morning SBP minus minimum morning SBP.

Nocturnal BP surge parameters: Average nocturnal surge is calculated as the average peak nocturnal SBP minus the average nocturnal SBP, dynamic nocturnal surge as the average peak nocturnal SBP minus moving lowest nocturnal SBP, maximum dynamic nocturnal surge as the maximum nocturnal SBP minus minimum nocturnal SBP. In addition to increase in nocturnal BP, increased BP variability during sleep (standard deviation, SD, of sleep SBP) is an independent and synergistic risk factor of cardiovascular events.

Nocturnal BP dipping parameters: Nocturnal SBP dipping (%) is calculated as (1 minus average nocturnal SBP/average daytime SBP) × 100 for the following subgroup classification: extreme dipper: >20%; dipper: ≤20%, >10%; non-dipper: ≤10%, >0%; riser: ≤0% [23, 24].

Feasibility of controlling morning hypertension

BP-lowering effect of once-daily morning use of antihypertensive drugs is at a minimum the next morning just before taking pills. Thus, prevalence of "masked morning hypertension," defined as normotension in clinic BP and hypertension in morning BP, increases after conventional clinic-BP-guided treatment of hypertension. During the past 10 years, JSH has persistently recommended home morning-BP-guided antihypertensive treatment for hypertensive patients. We have compared the prevalence of uncontrolled masked hypertension in two different studies performed with a 10-year interval (Figures 1.19 and 1.20). The previous Jichi Morning Hypertension Research (J-MORE) study performed 10 years ago demonstrated the prevalence of uncontrolled masked morning hypertension as 52% in the well-controlled clinic BP <140 mmHg (Figure 1.19) [25]. However,

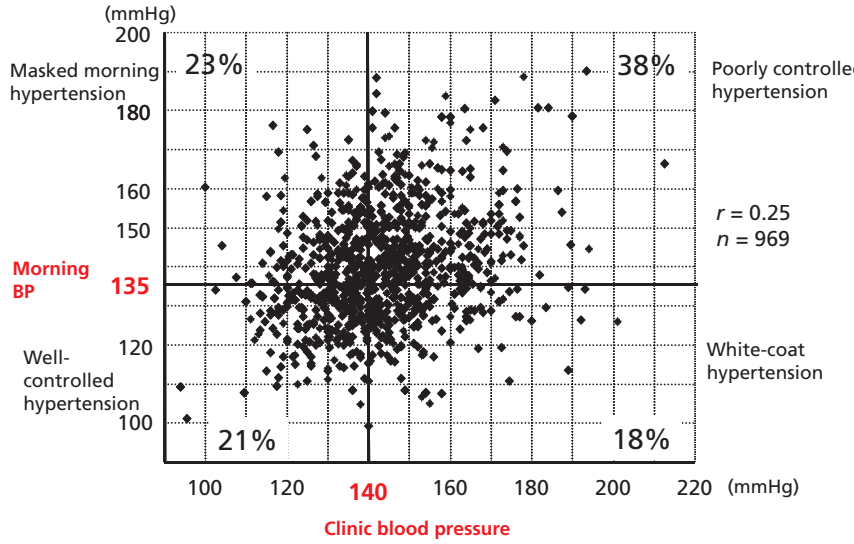


Figure 1.19 Jichi Morning Hypertension Research (J-MORE) study. 969 medicated hypertensives (mean age 66.5 years, men 42%) recruited from 45 doctors, 33 clinics. *Source:* Kario et al. 2003 [25].

in a recent J-HOP study [26], its prevalence was diminished by around 38% (Figure 1.20). Thus, the prevalence of masked uncontrolled morning hypertension among well-controlled clinic BPs <140/90 mmHg has been reduced by 14%. This trend suggests that it is feasible to achieve effective control rate in the morning BP by targeting the morning BP.

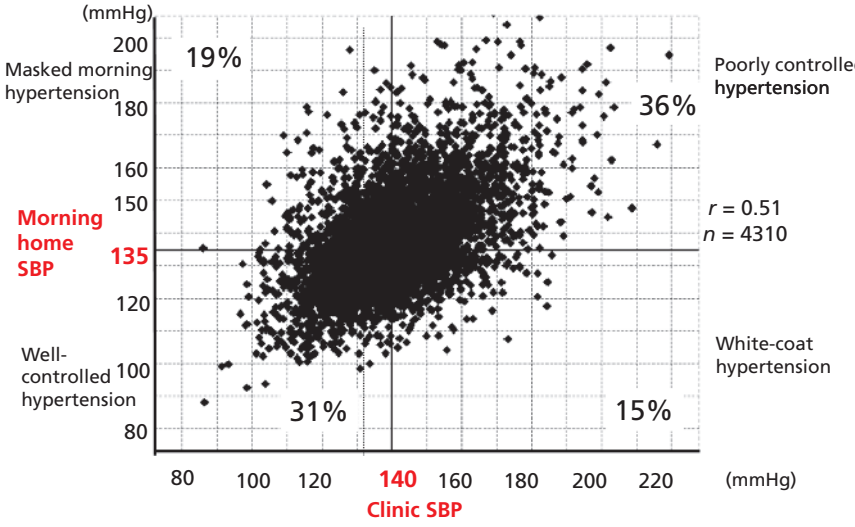


Figure 1.20 Japan Morning Surge-Home Blood Pressure (J-HOP) study. 4310 medicated hypertensives (mean age 64.9 years, men 47%). *Source:* Kario K, *Essential Manual of 24-hour Blood Pressure Management from Morning to Nocturnal Hypertension*, Wiley-Blackwell, 2015.

Subtypes of morning hypertension

There are two types of morning hypertension detected by HBPM [1, 4]. One is the "morning surge" type exhibiting exaggerated MBPS (morning BP minus the least nocturnal BP >35–55 mmHg SBP), and the other is "sustained nocturnal hypertension" type with continuous hypertension from nocturnal hypertension (non-dipper/riser type, nocturnal BP ≥120/70 mmHg) (Figure 1.21). Both types have different associated conditions, and both are at risk for cardiovascular and renal diseases through different pathogenic mechanisms. To differentiate these two types, ME-dif calculated by home BPs conventionally measured in the morning and in the evening is not useful. Only direct measurement of nocturnal BP during sleep, traditionally by ABPM, and by recently developed home nocturnal BP monitoring with timer, could differentiate the two subtypes.

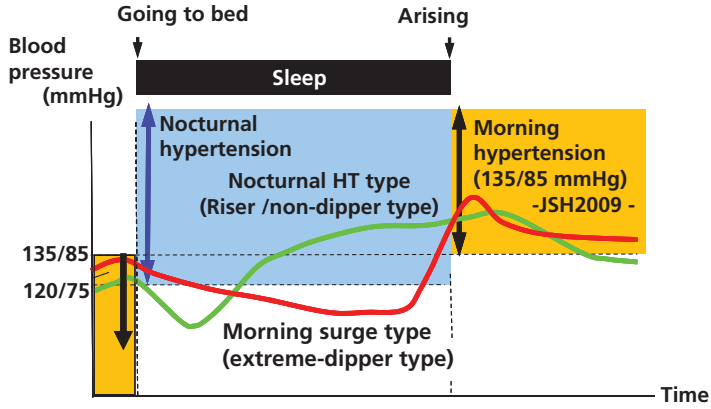


Figure 1.21 Two types of morning hypertension. *Source:* Kario 2005 [4].