# Morning Surge in Blood Pressure and Cardiovascular Risk
## Evidence and Perspectives

Kazuomi Kario

Hypertension is the most powerful risk factor for the cardiovascular diseases, including stroke, coronary artery disease, heart failure, chronic kidney disease, and aortic and peripheral arterial diseases. There is a significant variability in BP level among hypertensives; however, the diagnosis of hypertension and the therapeutic target of BP are based on the average of each BP measured. There is marked diurnal variation in the onset time of cardiovascular events, with the peak being exhibited in early morning. Blood pressure (BP) also exhibits a similar diurnal variation, with a decrease during sleep and a surge in the morning.[1,2] In addition to the persistent pressor stress (averaged throughout a 24-hour period), dynamic diurnal variation in pressor stress from the nadir to the peak in the morning, that is, the morning surge in BP, would be expected to progress target organ damage and trigger cardiovascular events, particularly those occurring in the morning.[3,4] Because my group first demonstrated that exaggerated morning surge in BP constitutes a risk for stroke independent of 24-hour BP,[5] there has been a steady increase in cross-sectional and prospective evidence supporting the idea that morning BP surge is an independent risk factor for cardiovascular disease. Here I review the recent evidence and the remaining unresolved issues on this topic.

## Prospective Findings on Cardiovascular Events

Normal morning BP surge is a physiological phenomenon, but an exaggerated morning BP surge is a cardiovascular risk. Thus, the association between the degree of morning BP surge and cardiovascular risk is not linear but rather has a threshold. There have been 6 prospective studies demonstrating that the morning surge in BP is a risk for cardiovascular events (Table 1).[5–10] These studies have used 3 different definitions of the morning BP surge as follows (Figure 1): (1) a sleep-trough surge defined as the morning BP (2-hour average of four 30-minute BP readings just after wake-up) minus the lowest nocturnal BP (1-hour average of the 3 BP readings centered on the lowest nighttime reading)[5,7,9,10]; (2) a prewaking surge defined as the morning BP minus the prewaking BP (2-hour average of 4 BP readings just before wake-up)[5,7,8,10]; and (3) a rising BP surge defined as the morning BP measured on rising minus the BP in a supine position <30 minutes before rising.[6] All of the different morning BP surges were associated with cardiovascular events.

Among the above 6 studies, only 1 study, the Jichi Medical University School of Medicine Japan Morning Surge (JMS)-Ambulatory Blood Pressure Monitoring (ABPM) Study,[5] investigated the association between the time of onset of events and morning BP surge and demonstrated that the incidence of stroke events in the morning hours was higher in those with exaggerated morning BP surge than in those without exaggerated morning BP surge. This association should be investigated in a large database in the future.

## Cross-Sectional Evidence on Target Organ

There is compelling evidence suggesting a significant association between morning BP surge and various surrogate markers of target organ damage (Figure 2).

### *Hypertensive Heart Disease*

Many previous studies have demonstrated that an exaggerated morning BP surge is associated with echocardiographic measures of hypertensive heart disease. Morning BP surge increases cardiac afterload and arterial stiffness, contributing to the progression of left ventricular (LV) hypertrophy. In hypertensive patients, the rising surge has been significantly correlated with the LV mass index (LVMI)[6,11] and the A/E ratio, which represents the diastolic function.[11] In addition, hypertensive patients with an exaggerated morning BP surge have been shown to have a prolonged QTc duration and dispersion in the morning period (as detected by Holter ECG recording) compared with those without morning BP surge.[12] The prolonged QTc duration and dispersion are not only markers of hypertensive heart disease but also imply the contribution of autonomic dysfunction to morning BP surge. Another study demonstrated that ST depression as detected by Holter ECG was associated with significantly higher BP peaks in the early morning hours.[13]

The association between morning BP surge and LV hypertrophy is also found in normotensives and well-controlled hypertensives.[14–16] In a study on community-dwelling subjects, the sleep-trough surge adjusted for physical activity was significantly correlated with LVMI.[14] In well-controlled hypertensives with 24-hour BPs <130/80 mm Hg, sleep-trough

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From the Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Shimotsuke, Tochigi, Japan.
Correspondence to Kazuomi Kario, Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, 3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan. E-mail kkario@jichi.ac.jp
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**Table 1. Six Prospective Studies Demonstrating the Association Between Morning Surge in BP (Based on ABPM) and Cardiovascular Events**

| Year | Source | Definition of Morning Surge by ABPM | No. of Patients | Mean Follow-Up | Cardiovascular End Point | Main Findings |
|---|---|---|---|---|---|---|
| 2003 | Kario et al (JMS-ABPM Study)[5] | Sleep-trough surge, prewaking surge | 519 elderly Japanese nondedicated hypertensives (mean: 72 y) | 3.4 y | Stroke | Those with sleep-trough surge >55 mm Hg (the highest decile) had a higher stroke incidence than those with a surge <55 mm Hg (19.0% vs 7.3%; $P=0.004$). After matching for age and 24-h BP, the RR of the surge group vs the nonsurge group was 2.7 ($P=0.04$). |
| 2004 | Gosse et al (Bordeaux Cohort)[6] | Rising surge | 507 untreated hypertensives (mean: 49 y) | 7.7 y | Cardiovascular events | The rate of cardiovascular events increased in relation to the quartile (Q1 through Q4) of rising BP surge (Q1: 4.0%; Q2: 2.3%; Q3: 7.1%; Q4: 11.0%; $P=0.02$). In multivariate analysis, the association between rising BP surge and cardiovascular events remained significant independent of age and 24-h BP level ($P=0.009$). |
| 2006 | Metoki et al (Ohasama Study)[7] | Prewaking surge, sleep trough surge | 1430 community-dwelling subjects aged ≥40 y (mean: 61 y) | 10.4 y | Stroke | Those with a prewaking surge >25 mm Hg (the highest quintile: Q5) had a higher hemorrhagic stroke risk (hazard ratio: 4.0 vs the Q2 with 3.0 to 11.0 mm Hg of surge; $P=0.04$). Those with a sleep-trough surge >40 mm Hg (Q5) had a higher hemorrhagic stroke risk (hazard ratio: 8.9 vs the Q2 with 16.0 to 23.0 mm Hg of surge; $P<0.05$). |
| 2008 | Dolan et al (Dublin Outcome Study)[8] | Prewaking surge | 11 291 referred hypertensive patients off-medicated (mean: 55 y) | 5.3 y | Cardiovascular mortality, stroke mortality, and cardiac mortality | The hazard ratios for a 10-mm Hg increase in morning surge for total cardiovascular, stroke, and cardiac mortality were 1.38 (1.31 to 1.45), 1.37 (1.23 to 1.51), and 1.39 (1.30 to 1.49), respectively. After adjusting for covariates including age and 24-h BP, these remained significant. |
| 2009 | Amici et al[9] | Sleep-trough surge | 10 normotensive and 32 well-controlled hypertensive elderly outpatients <135/85 mm Hg of 24-hour BPs (mean: 66 y) | 5.0 y | Cardiovascular events | Those with a sleep-trough surge ≥34 mm Hg (the highest tertile: T3) had a higher cardiovascular risk than those with a surge <34 mm Hg (T1 and T2; 5 events vs 0 event; $P=0.001$). |
| 2010 | Li et al (IDACO)[10] | Sleep-trough surge, prewaking surge | 5645 subjects from 8 populations (mean: 53 y) | 11.4 y | Cardiovascular, cardiac, coronary, and cerebrovascular events | For all of the cardiovascular, cardiac, coronary, and cerebrovascular events, and all-cause mortality, the hazard ratios in the top decile of the systolic sleep-through surge (>37 mm Hg) were 1.30 ($P=0.01$), 1.52 ($P=0.004$), 1.45 ($P=0.03$), 0.95 ($P=0.74$), and 1.32 ($P=0.004$), respectively. |

RR indicates relative risk; SBP, systolic BP; IDACO, International Database on Ambulatory BP in Relation to Cardiovascular Outcome; sleep-through surge, 2-h morning SBP minus 1-hour lowest nighttime SBP; prewaking surge, 2-h morning SBP minus 2-h prewaking BP; rising surge, BP on rising minus the last ambulatory BP in a supine position <30 min before rising.

The corresponding reference numbers are shown as superscripts.

surge was significantly associated with increases in LVMI and carotid intima-media thickness.[15] The association found in both studies was not linear but rather nonlinear with a threshold of morning surge. In a recent study on normotensives with clinic BPs <140/90 mm Hg and 24-hour BPs <130/80 mm Hg, sleep-trough surge was significantly correlated with LVMI.[16]

### *Vascular Disease and Inflammation*

The morning surge in BP and increased time rate of BP variation in the morning have been reported to be associated with carotid atherosclerosis in untreated hypertensive patients.[15,17–19] This association may be accompanied by increased vascular inflammation that can induce plaque instability.

Hypertensive patients with morning BP surge had higher levels of carotid intima-media thickness and urinary catecholamine excretion, as well as higher levels of inflammatory markers, compared with those without morning BP surge.[18] In addition, a more direct histological study on carotid endoatherectomy specimens demonstrated that carotid

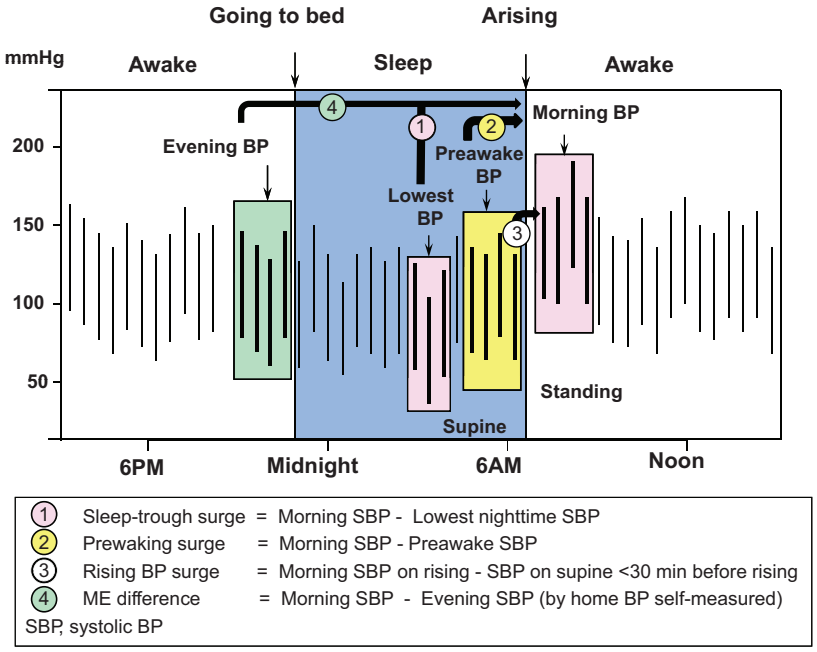
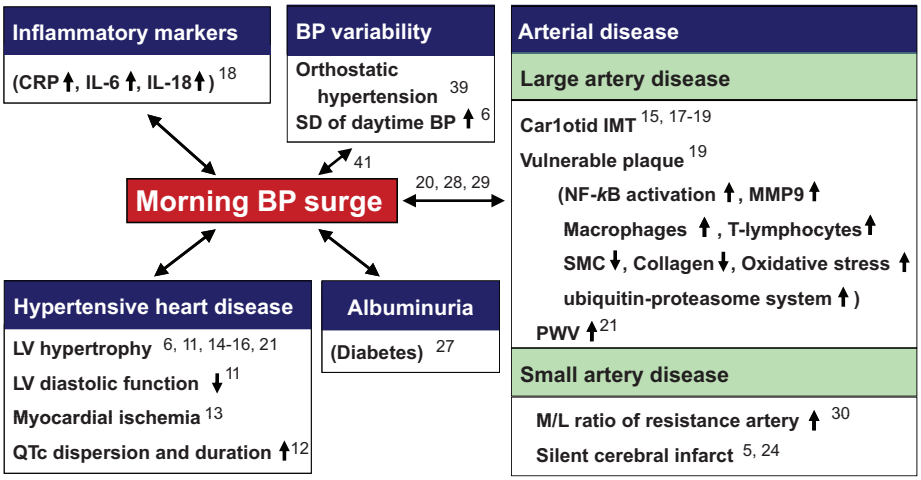



**Figure 1.** Definition of morning surge in BP.

plaques in those with exaggerated morning BP surge were associated with characteristics of vulnerable plaques, increased levels of markers of oxidative stress, and activation of the ubiquitin-proteasome system.[19] In that study, the finding that subjects with exaggerated morning BP surge had higher levels of activated subunits of nuclear factor-κB (a central transcription factor regulating inflammatory genes) and matrix metalloproteinase 9 (an important enzyme in plaque rupture) suggests that exaggerated morning BP surge is associated with vascular inflammation and plaque instability. Clinically, hypertensive patients with carotid plaques, which are likely to be vulnerable, may receive potential benefit from anti-inflammatory treatment using statins, renin-angiotensin system (RAS) inhibitors, and thiazolidinediones, as well as from treatment to suppress morning BP surge.[20] Finally, the sleep-trough rising surge has been significantly correlated with arterial stiffness pulse wave velocity.[21]

### *Silent Cerebrovascular Disease*

Silent cerebral infarcts (SCIs) are the strongest surrogate markers of clinical stroke, particularly in those with increased C-reactive protein levels.[22,23] In the JMS-ABPM Study, SCIs, particularly multiple SCIs, were more frequently detected by brain MRI in the morning surge group than in the nonsurge group.[5] SCIs usually consist of lacunar infarcts of the small cerebral arteries (small artery disease). Although it is well known that sympathetic activity, particularly α-adrenergic activity, is increased in the morning, SCI has been shown to be more closely associated with the exaggerated morning BP




BP, blood pressure; CRP, C-reactive protein; IL-6, interleukin 6, IL-18, interleukin 18; SD, standard deviation; LV, left ventricular; IMT, intima-media thickness; NF-kB, nuclear factor kappa B; MMP-9, matrix metalloproteinase-9; SMC, smooth muscle cell; PWV, pulse wave velocity, M/L ratio, media thickness to lumen diameter ratio

**Figure 2.** Risk factors and target organ damage associated with morning surge in BP. The corresponding reference numbers are shown as superscripts.

surge related to α-adrenergic activity defined as a reduction of morning BP surge by an α-adrenergic blocker (doxazosin) than with the overall morning BP surge.[24]

### *Microalbuminuria*

Despite the above-described associations between morning BP surge and cardiac and vascular complications, there have been few studies demonstrating positive associations between morning SB surge and renal disease. The chronic kidney disease is likely to exhibit a nondipping pattern of nocturnal BP falls,[25] and this nondipping pattern might precede microalbuminuria.[26] One cross-sectional study in newly diagnosed type 2 diabetic normotensives demonstrated that morning BP levels and morning BP surge were significantly higher in patients with microalbuminuria than in patients without microalbuminuria.[27] This indicates that a morning surge in systemic BP might directly induce a morning surge in intraglomerular pressure under the diabetic condition of disrupted autoregulation of the afferent arterioles of the glomerulus.

## Vascular Mechanism of Exaggerated Morning BP Surge

Vascular diseases of both the small and large arteries are considered to be not only consequences but also the leading cause of exaggeration of morning BP surge, a circumstance giving rise to a vicious cycle in the cardiovascular continuum.[28,29]

### *Small Artery Disease and Endothelial Dysfunction*

A recent study that directly assessed small artery remodeling by examining biopsy specimens demonstrated that the sleep-trough surge was significantly positively correlated with an increased media thickness:lumen diameter ratio (a measure of remodeling) of the subcutaneous small arteries in patients with essential hypertension.[30] The association between contraction of the resistance arteries and vascular resistance is not linear but rather curvilinear in keeping with Folkow's principal.[31] Compared with the sleep when the vascular tonus is decreased, the difference in vascular resistance between the small artery with remodeling and that without remodeling is more extensively augmented in the morning when the vascular tonus is increased.

The activation of various pressor neurohumoral factors, including the sympathetic nervous system and RAS, occurs early in the morning. Increased sympathetic activity, particularly of the α-adrenergic component,[32] increases the vascular tone in the small resistance arteries and may contribute to the morning BP surge. In addition, plasma renin activity, angiotensin II, and aldosterone levels are all increased before awakening and then further increased after awakening.[33] The mRNA levels of RAS components in the tissue levels of the cardiovascular system exhibit diurnal variation, particularly in the hypertensive model, with increases occurring during the awaking period.[34] The results of a recent report using a vaccine targeting angiotensin II indicated that both the RAS and the related pressor effect are highly activated in the morning.[35] In addition, in the morning, endothelial dysfunction is found even in healthy subjects and reduces the capacity for vasodilatation.[36] Thus, the threshold of augmentation of BP surge by pressor stimulation may be the lowest in the morning. Using BP surge, the morning may be the best time window to detect the early stage of vascular damages, such as small artery remodeling and endothelial dysfunction.[29]

**Table 2. Associations of Morning Surge in BP**

| Factor | Association |
|---|---|
| Risk factors | Aging |
| | Hypertension |
| | Glucose abnormality |
| | Metabolic syndrome |
| Behaviors | Alcohol drinking |
| | Smoking |
| | Psychological stress |
| | Excessive physical activity in the morning |
| Sleep conditions | Poor sleep quality |
| | Nocturnal hypoxia |
| Clocks | Monday |
| | Winter season |
| | Central and peripheral clock genes |

### *Large Artery Disease and Baroreflex Dysfunction*

In addition to being a consequence of morning surge, increased arterial stiffness in large artery diseases is itself important as a leading cause of exaggerated BP variability and morning BP surge. The pulse wave velocity, a measure of large artery stiffness, is correlated with sleep-trough surge, rising surge, and the SD of daytime BPs.[21] Baroreceptor sensitivity decreases with an increase in large arterial stiffness and exhibits diurnal variation with a decrease early in the morning.[37] Thus, the reduced baroreceptor sensitivity in patients with large artery disease may be insufficient to suppress the BP surge, particularly in the morning. In fact, the impaired dynamic Valsalva-baroreceptor sensitivity has been significantly correlated with an increase in morning BP.[38]

## Association With Orthostatic Hypertension

Orthostatic hypertension is associated with morning BP surge and increased neurohumoral activation.[39] Orthostatic hypertension has also been associated with developing hypertension and with the progression of target organ damages, such as SCI, carotid intima-media thickness, and microalbuminuria, independent of sitting BP.[40,41] Theoretically, rising BP surge, by definition, should be the most closely associated with orthostatic hypertension among the variously defined morning BP surges. However, the morning BP surge (morning BP−sleep BP) is also increased in hypertensives with orthostatic hypertension compared with hypertensives without orthostatic hypertension.[39] Finally, rising BP surge was reported to be associated with increased daytime BP variability (SD of daytime BPs) in unmedicated hypertensives of the Bordeaux cohort study.[6]

## Associations of Morning BP Surge

Morning BP surge is increased by various factors, including aging, hypertension, glucose abnormality, alcohol intake, smoking, psychological stress, and physical stress (Table 2).[5,14,42,43]

**Table 3. Unresolved Issues on Morning Surge in BP**

| |
|---|
| 1. Definition of morning BP surge |
| Which surge is the best in terms of CV risk: sleep-trough, prewaking, or rising surge? |
| What is the best way to exclude the effects of other BP variability, such as that attributed to nondipping of nocturnal hypertension, orthostatic hypertension, etc? |
| 2. Threshold of the pathological morning BP surge |
| The threshold of surge as CV risk may be different among different ages. |
| 3. Reproducibility of the morning BP surge |
| An irreproducible exaggerated surge may be a risk for triggering CV events. |
| Morning surge reactivity (the slope of the morning surge reactivity plotted against physical activity) may have potential as a new marker of CV risk. |
| 4. Intervention study to reduce the morning surge |
| Is there any benefit in reducing the morning BP surge independent of a reduction in 24-h BP? |
| Which class of antihypertensives is best for reducing the morning BP surge and its related CV risk? |

CV indicates cardiovascular.

As the underlying mechanism of these pressor factors, diurnal variation and activation of neurohumoral factors that regulate the vascular tonus and cardiac output, such as RAS and sympathetic nervous system, potentially in relation to central and peripheral clock genes, have been considered to be involved in diurnal BP variation and morning BP surge. These are weekly and seasonal variations in the morning BP surge. Morning BP surge is augmented on Mondays[44] and over the winter,[45] particularly in elderly subjects, accounting partly for the Monday peak and winter peak of cardiovascular events.[46] In addition, nocturnal hypoxia or poor sleep quality augments morning BP surge, probably through an increase in sympathetic nervous system activation and in endothelial dysfunction, even in children with sleep apnea without any early vascular damage.[47]

## Unresolved Issues on Morning BP Surge

The unresolved issues on morning BP surge are listed in Table 3.

### *Definition and Threshold of Morning BP Surge*

Morning BP surge is usually assessed using ABPM, and there are several definitions of morning BP surge (Figure 1); however, there is no consensus on a single definition or on the threshold of pathological morning BP surge. Sleep-trough surge is one of the dynamic diurnal surges during the specific period from sleep to early morning,[5] when the cardiovascular risk is exaggerated. Thus, to establish the clinical implications of sleep-trough surge, it is important to exclude the effects of circadian rhythm in BP. As expected, sleep-trough surge is likely to be associated with extreme dippers with marked nocturnal BP fall and is less likely to be associated with nondippers with less dipping of nocturnal BP or with risers with higher nocturnal BP than daytime BP. Even after controlling for these dipping statuses of nocturnal BP or the mean nocturnal BP level, the risk of sleep-trough surge remains significant.[5] Prewaking surge is the BP change occurring 4 hours before and after arising.[5] Although the sleep-trough and prewaking surges are defined based on the BP difference, theoretically the speed of the surge (the slope of the increase in morning BP against time) may be a better indicator of the risk of morning surge.[48] This is because the rising surge may detect the morning risk just after arising,[6] but it may underscore the BP surge subsequently augmented by physical activity in the morning.

In the JMS-ABPM Study, because we considered that the risk of morning BP surge is not linear, we first used the top 10th percentile as the threshold of pathological morning BP surge.[5] The recent International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes Study clearly confirmed that the risk of morning BP surge is only increased in the top 10th percentile both of sleep-trough surge and prewaking surge.[10] However, the absolute levels of morning BP surge of the top 10th percentile were different between the 2 studies (55 mm Hg for the JMS-ABPM Study and 37 mm Hg for the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes Study). This difference may be partly because of the difference in the age and BP level of the study subjects, because advancing age and hypertension are the 2 major determinants of morning BP surge. In the JMS-ABPM Study, the mean age was 72 years, and the 24-hour BP level was 136/78 mm Hg, whereas in the International Database on Ambulatory Blood Pressure Monitoring in Relation to Cardiovascular Outcomes Study, the mean age of the study subjects was 53 years, and the 24-hour BP level was 123/74 mm Hg. In a future study, the threshold of morning BP should be determined for clinical practice.

Clinically, the use of self-measured home BP (HBP) is now widely recommended for the management of hypertension.[49–51] Recently, the ME difference (morning systolic BP minus evening systolic BP; Figure 1) was reported to be associated with cardiovascular risk independent of the mean of morning and evening BPs. The ME difference of ABPM was shown to be an independent predictor of future stroke events in elderly hypertensives,[52] whereas the ME difference of HBP was associated with LVMI and the risk of concentric hypertrophy, as well as with increased pulse wave velocity.[53] Thus, the BP-related morning risk of cardiovascular disease may be partly detected by HBP. However, HBP self-measured in the morning in a seated position may underscore the risk of ambulatory morning BP surge, which is augmented by morning physical activity. The simple examination of orthostatic BP change using self-measured HBP monitoring can detect "home orthostatic hypertension" with high reproducibility without a white-coat effect.[41] The morning HBP self-measured in the standing position may be better to detect the risk of morning BP surge than sitting HBP.

### *Reproducibility and Morning BP Surge Reactivity*

The day-to-day reproducibility of ambulatory BP affected by physical activity is less than that of HBP self-measured in the sitting position. Using the conventional ABPM, there are limitations to the precision of the assessment of the risk of morning BP surge. First, the time of arising is not accurate, and, second, the degree of morning BP surge is significantly

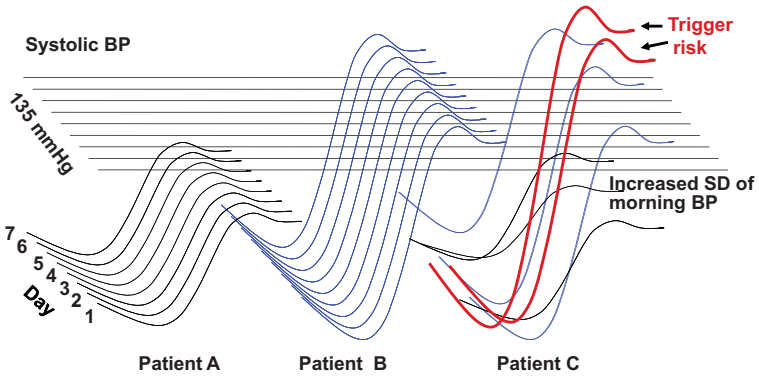



**Figure 3.** Reproducibility of morning surge in BP and cardiovascular risk. Patient A exhibits an appropriate morning surge; patient B exhibits a reproducible exaggerated surge; patient C exhibits an exaggerated variability of morning surge (irreproducible). The maximum morning BP surge occurring in patient C may be the most potent risk for triggering a cardiovascular event.

determined by the day-to-day variability of physical activity. The arising and ambulating from supine sleep is the major determinant of morning BP surge. The BP and pulse change little before and after awakening if the subjects remain supine.[54]

There have been 3 reports on the reproducibility of morning BP surge. The first study was performed on elderly patients with isolated systolic hypertension and found that the short-term and long-term reproducibility of morning BP surge were poor.[55] The second study assessed the short-term reproducibility of 2 sets of ABPM data obtained with a 2-week interval and found that the reproducibility depended on the definition of morning BP surge.[56] The morning BP surge defined as the morning BP (BP 2-hour after rising) minus the sleep BP (the average BP during sleep) provided the most reproducible results. The third study investigated in 4 sets of ABPM data conducted twice at the baseline and twice after antihypertensive medication and found that morning BP surge was moderate when defined by the precise actigraphically determined time of arising.[57]

Poor reproducibility does not simply mean that the morning BP surge is not a risk for cardiovascular events. The Ohasama study on a community-dwelling population demonstrated that an increase in the SD of HBP self-measured in the morning was an independent risk for future cardiovascular events.[58] Thus, in addition to the reproducible exaggerated morning surge (Figure 3, patient B), the exaggerated morning BP surged with poor reproducibility and increased SD of morning BPs, which may increase cardiovascular risk (Figure 3, patients C). In particular, the maximum morning BP surge may be a risk for triggering stroke events, because a recent study clearly demonstrated that the top 10th percentile of day-to-day clinic systolic BP variability (the SD of clinic BP) and that of maximum systolic BP were markedly associated with future stroke independent of the average of each BP.[59]

To exclude the effect of physical activity on morning BP surge, the morning BP surge reactivity could be used as a new measure of morning BP surge (Figure 4). Using the ABPM data with physical activity simultaneously assessed by actigraphy, we previously calculated the slope of daytime ABP against physical activity measured during the 6-minute period just before each ABP recording as an ambulatory BP reactivity index.[60] A previous study demonstrated that this index has diurnal variation with the morning peak, indicating that

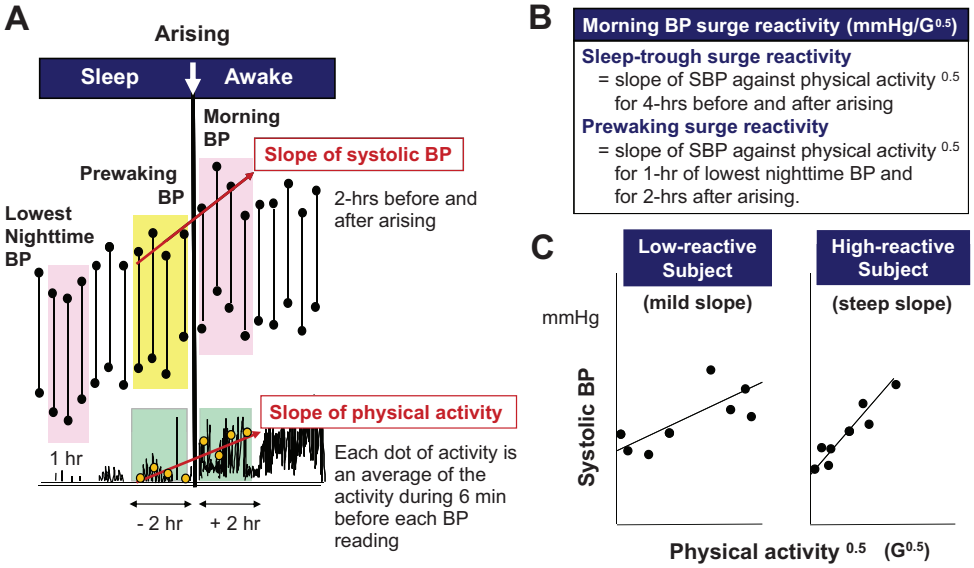



**Figure 4.** Definition of morning BP surge reactivity. The degree of morning BP surge is closely associated with the physical activity (A). Morning BP surge reactivity is defined as the slope of SBP against physical activity (B). Figure C demonstrates 2 typical patients with low- and high-morning BP surge. Even when their morning BP surge is similar to that of low-reactive patients, high-reactive patients tend to have greater risk than low-reactive patients when the physical activity is maximized.

the pressor effect of physical activity is augmented more extensively in the morning than at any other period of time.[61] In addition, the morning BP surge reactivity was independently associated with LV hypertrophy in a community-dwelling sample.[14] Even with similar exaggerated morning BP surge, the risk may be greater in high-reactive patients than in low-reactive patients. Because the exaggerated morning BP surge occurs in high-reactive patients even with less physical activity, high-reactive patients would exhibit poorly reproducible exaggerated morning BP surge with increased day-to-day variability of morning BP according to different physical activities (Figure 3, patient C) and would have the greatest risk for cardiovascular events when the physical activity is occasionally maximized.

### *Intervention on Morning Surge*

There has been no study that scientifically tested the hypothesis that selective suppression of exaggerated morning BP surge leads to the regression of target organ damage and the reduction of subsequent cardiovascular events. From a practical point of view, antihypertensive treatment targeting morning BP <135/85 mm Hg leads to strict 24-hour BP control, which would achieve more effective protection than conventional antihypertensive treatment based on clinic BP.[3]

Nonspecific medications for morning BP surge include long-acting calcium channel blockers, such as amlodipine. Because the BP-lowering effect of calcium channel blockers depends on the baseline BP level, the higher ambulatory BP levels decrease more extensively, the lowest nocturnal BP does not decrease as much, and, thus, the morning BP surge decreases significantly. In contrast, although diuretics also provide the longest duration of BP-lowering effect, when morning hypertension is treated using diuretics, nighttime BP levels are predominantly reduced compared with daytime BP, and nondippers shift toward dipper status.[25] A greater nocturnal fall of BP by diuretics may lead to a greater morning BP surge. These characteristics of calcium channel blockers and diuretics could be considered in the combination therapy with RAS inhibitors.[62]

More specific chronological treatment for morning BP surge may be achieved by bedtime dosing of antihypertensives that reduce the pressor effect of the RAS or sympathetic nervous system potentiated in the morning. The JMS-1 Study, an open-label multicenter trial that enrolled 611 medicated patients with morning hypertension with self-measured morning systolic HBP >135 mm Hg, demonstrated that the bedtime dosing of an $\alpha$-adrenergic blockade (doxazosin), on top of baseline antihypertensives, significantly reduced morning BP and albuminuria.[63] Another open-label multicenter trial, the Japan-Target Organ Protection study in 450 hypertensives with self-measured systolic HBP >135 mm Hg, demonstrated that a bedtime dosing of an angiotensin receptor blocker (candesartan) titrated by self-measured HBP was more effective for reducing albuminuria than an awakening dosing in patients with sufficiently well-controlled HBPs both in the morning and in the evening.[64] This beneficial effect of bedtime dosing was stronger in subjects with morning-dominant hypertension with an ME difference >15 mm Hg for systolic HBP than in those with an ME difference <15 mm Hg. In the Japan-Target Organ Protection Study, although the morning BP-lowering effect was similar between the bedtime-dosing and awakening-dosing groups, bedtime dosing of an angiotensin receptor blocker may be more effective for reducing albuminuria because it may more potently suppress RAS activated during the sleep-early morning period than awakening dosing. This possibility should be confirmed using a different class of antihypertensives in the future.

## Conclusion

Based on evidence gathered in the last several years, morning BP surge is one of the treatable ambulatory BP variabilities and is a potential risk for cardiovascular disease independent of the average of 24-hour BP. Before establishing a clinical practice for patients with morning BP surge, it will be necessary to reach a consensus on the definition and threshold of pathological morning surge. The development of BP monitoring, which more accurately detects the risk of morning BP surge, and a randomized clinical trial offering specific treatments for morning BP surge on cardiovascular events will be needed in the future.

## Disclosures

None.

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