The issues of hypertension paradox—more uncontrolled disease despite improved therapy—have received increased attention in the era of strict blood pressure (BP) control after SPRINT (Systolic Blood Pressure Intervention Trial) in 2015. The new direction in the management of hypertension is to pursue earlier and lower BP control throughout 24 hours. The new 2017 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines propose that all the BPs measured during the awake period (clinic BP and home BP measured in the morning and evening) and daytime ambulatory BPs should be controlled to <130/80 mm Hg as a universal BP goal. Even if the clinic BP is well-controlled, masked morning and daytime hypertension (uncontrolled daytime and morning or evening home BPs) pose an increased risk of cardiovascular diseases. The strict BP control of all these awake BPs would be effective for the reduction of cardiovascular events.

However, even after controlling these daytime BPs, there is still a residual risk in the management of hypertension. This is masked uncontrolled nocturnal hypertension. Here, I summarize the clinical implications of the control of night-time BP based on the pathophysiology and recent evidence and present up-to-date information on the research and development of night-time home BP monitoring (HBPM) systems.

**Clinical Implications**

The pattern of circadian rhythm of BP can be evaluated by ambulatory BP monitoring (ABPM). In healthy subjects, night-time BP decreases by 10% to 20% of daytime BP (normal dipper pattern). This circadian rhythm of BP is determined partly by the intrinsic rhythm of central and peripheral clock genes, which regulate the neurohumoral factor and cardiovascular systems, and partly by the sleep–wake behavioral pattern. Hypertensive patients without organ damage also exhibit the dipper pattern; however, those with organ damage tend to exhibit nondipper patterns with diminished night-time BP fall. Night-time BP dipping patterns are classified into 4 groups: dipper, nondipper, riser, and extreme dipper patterns. The definitions of these groups are based on night-time BP dipping. In addition, short-term BP variability—such as morning BP surge, physical or psychological stress-induced daytime BP, and night-time BP surges triggered by obstructive sleep apnea (OSA) episodes, arousal, rapid-eye-movement sleep, and nocturnal behavior, such as nocturia—modulates this circadian rhythm of BP, leading to the different individual circadian variation of 24-hour ambulatory BPs (Figure 1).

**Evidence**

It has been well-established that night-time BP during sleep is closely associated with cardiovascular events and organ damage in both community-dwelling subjects and hypertensive patients. The cutoff value of nocturnal hypertension has been 120/70 mm Hg for night-time BPs, and in the 2017 AHA/ACC guidelines, it was lowered to 110/65 mm Hg. The impact of controlling night-time BP would be greater in medicated hypertensive patients than in nonmedicated hypertensive patients because the BP-lowering effect of once daily use of an antihypertensive drug may not persist for 24 hours even in the hypertensive patients with well-controlled clinic and daytime BP. In fact, a study using a large ABPM database demonstrated that night-time ambulatory BP is more closely associated with fatal and nonfatal cardiovascular events (stroke, myocardial infarction, and cardiovascular death) than daytime ambulatory BP, especially in medicated patients. A riser pattern (higher night-time BP than daytime BP) has been associated with cardiovascular events. In patients with heart failure with a preserved ejection fraction, a nondipper (less night-time BP dipping)/riser pattern was an independent risk factor for future cardiovascular events, including recurrence of hospitalized heart failure, and cognitive dysfunction. In addition, a recent study using an international database demonstrated that an increase in night-time BP variability confers a risk of cardiovascular events independently of the average of night-time ambulatory BPs.

Nocturnal hypertension is also associated with subclinical organ damages. Silent cerebrovascular diseases detected by brain magnetic resonance imaging, such as silent cerebral infarcts, microbleeds, and white matter disease, are frequently found in patients with nocturnal hypertension and nondipper/riser patterns of night-time BP. The nocturnal hypertension and nondipper/riser patterns of night-time BP are predisposing conditions for psychocognitive dysfunction (cognitive dysfunction, apathy, falls and sedentary lifestyle, and stroke). Hypertensive heart disease (left ventricular hypertrophy, reduced diastolic function), vascular damage (increase in carotid intima–media thickness, pulse wave...
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velocity, and cardio ankle vascular index), and chronic kidney disease (CKD; reduced glomerular filtration ratio and urinary albumin/creatinine excretion ratio).19,23–28

Definition

The definition of nocturnal hypertension is night-time BP \( \geq 120/70 \text{ mm Hg} >110/65 \text{ mm Hg} \) by the new 2017ACC/AHA guidelines; Table 1). Clinic and morning home BP of \(<130/80 \text{ mm Hg} \) is defined as masked nocturnal hypertension and as masked uncontrolled nocturnal hypertension under a medicated condition. The night-time BP is calculated as the average of night-time BPs (from going to bed to arising) measured by ABPM or by the recently developed HBPM system with an automated measurement function for night-time BP (night-time HBPM). The number of night-time BP measurements required may be \( \geq 6 \). The night-time systolic BP dipping (\( \% \)) is calculated as \( (1−\text{average night-time systolic BP/average daytime systolic BP})\times100 \), and based on this percentage, the following 4 night-time BP dipping patterns are defined: extreme doper, >20%; doper: \( \leq 20%, >10% \); nondoper: \( \leq 10%, >0% \); riser: \( \leq 0% \).4,6–8 This classification is usually based on the ABPM data.

Associated Conditions

There are many conditions associated with nocturnal hypertension (Table 1). Advancing age, sedentary lifestyle, sleep and hot temperature, and risk factors all affect night-time BPs.6–8 Diabetes mellitus, CKD, and OSA are the 3 diseases most frequently associated with nocturnal hypertension. Age-related diseases frequently found in the elderly and poststroke patients, such as insomnia, cognitive dysfunction, frailty, slow walking speed, heart failure, and various diseases of secondary hypertension, are also closely associated with nocturnal uncontrolled hypertension. Asians are likely to have nocturnal hypertension because of their higher salt intake and higher salt sensitivity.29,30

Pathophysiology

Morning is generally considered a higher-risk period because the rupture of atherosclerotic plaques or arteriosclerotic bleeding can be triggered by a morning BP surge that is synergistically augmented by trigger conditions, such as cold, exercise, smoking, or work-site stress, resulting in morning onset of cardiovascular events (Figure 1).31,32

In addition, a blunted morning BP surge is also reported to confer a risk of cardiovascular events.33 The high prevalence of the riser pattern in patients with blunted morning BP surges may account for the cardiovascular risk previously reported in such patients. Blunted or inverse BP reactivity in the morning is also partly associated with orthostatic hypotension, as well as the riser pattern of night-time BP, and it seems to be related to autonomic nervous dysfunction. Considering that exaggerated morning surge is associated with an extreme doper pattern and orthostatic hypertension, both inverse and exaggerated extremes of disrupted BP variability would be pathological.

There are several pathogeneses of nocturnal hypertension (Figures 1 and 2). Advanced structural vascular disease (increased vascular resistance and arterial stiffness) and increase in salt sensitivity and high-salt diet are the main causes of nocturnal hypertension, especially in patients with an increase in basal night-time BP (Figure 2). Based on the pressure-natriuresis, in patients with increased circulating volume, not only daytime but also night-time BP are elevated over 24 hours to excrete sodium from the kidneys.35,36 Salt sensitivity is increased by the renal dysfunction, the sympathetic hyperactivity, and the activation of the renin–angiotensin–aldosterone system. These processes are advanced in turn by aging, stress, obesity, diabetest mellitus, and sleep disorders (OSA and insomnia).

There are several heterogeneous pathophysiological mechanisms that account for the specific risk of nocturnal hypertension (Figure 2). First, sympathetic drive-induced night-time BP surges may trigger night-time onset of cardiovascular events (stroke, acute heart failure, coronary artery disease, etc; Figure 2) and may advance age-related organ damages (cognitive dysfunction, CKD). Night-time BP surge is triggered by specific triggers (OSA episode, arousal, rapid-eye-movement sleep, and nocturia) and is augmented by the impaired baroreflex by increased sympathetic tonus and vascular stiffness (Figure 1). The mechanism by which night-time BP surge

![Figure 1. Components of nocturnal hypertension and determinants — night-time dipping status and surge in blood pressure. BP indicates blood pressure; CHF, chronic heart failure; CKD, chronic kidney disease; OSA, obstructive sleep apnea; and REM, rapid-eye-movement.](image-url)
higher sympathetic activity in the morning (which makes it easy to increase BP) while the rise in night-time BP comes last because of the lower sympathetic tonus in the night-time (which makes it more difficult to increase BP). Thus, when the night-time BP increases, it may express advanced structural changes of the large and small arteries (increase in arterial stiffness and vascular resistance) and increased circulating volume because of reduced ability of the kidneys to excrete sodium.

Third, during sleep, the supine position increases venous return from the lower body to the heart, resulting in increased LV preload (Figure 2). The LV wall stress by the afterload of nocturnal hypertension is augmented by the night-time increase in LV preload (Law of Laplace). This night-time increase in LV wall stress would constitute a risk for night-time onset of heart failure. In addition, the increased circulating volume by the shift of interstitial fluid from the soft tissue of the lower body to the circulating volume also increases the LV preload. In addition, the simultaneous increase in night-time circulating volume and BP would synergistically worsen the renal function by increasing the intraglomerular pressure and hyperfiltration (Figure 2).

Finally, the night-time is a blind-spot in terms of monitoring the current hypertensive drug, and thus the residual night-time risk may persist for a long time without the patient’s doctor noticing.

Table 1. Definition and Associated Conditions of Nocturnal Hypertension

| Definition | Associated Conditions |
|------------|-----------------------|
| Nocturnal hypertension | Average of night-time BPs ≥110/65 mm Hg |
| Clinic BP-masked nocturnal hypertension | Nocturnal hypertension with clinic BP <130/80 mm Hg |
| Morning BP-masked nocturnal hypertension | Nocturnal hypertension with morning home BP <130/80 mm Hg |
| Isolated masked nocturnal hypertension | Nocturnal hypertension with both clinic and morning home BPs <130/80 mm Hg |
| Determinants | Environmental condition |
| | Behavioral factors |
| | Salt sensitivity |
| | Autonomic nervous dysfunction |
| | Secondary hypertension |
| | Obstructive sleep apnea |
| | Endocrine disease (primary aldosteronism, renovascular hypertension, Cushing syndrome, pheochromocytoma) |
| | Chronic kidney disease |
| | Disease |
| | Heart failure |
| | CNS disease (stroke, cognitive dysfunction, depression) |
| | Restress leg syndrome |

BP indicates blood pressure; and CNS, central nervous system.

“Night-time BPs measured from bedtime to rising (at least 3 readings/night and 2 days).”

Research and Development of Night-Time HBPM and Relevant Findings

ABPM has historically been the gold standard for measuring night-time BP. However, self-measured HBPM was introduced to measure night-time BP during sleep. We recently developed an HBPM device that automatically measures night-time home BP (HBP) 20× with data memory (Medinote; Omron Healthcare Co, Ltd, Kyoto, Japan). The Jichi Medical University and Omron Healthcare Co, Ltd (Kyoto, Japan) have been conducting cutting-edge collaboration program projects in the SURGE (SUper cRculation monitorinG with high TEnchnology) R&D Center to develop a new HBPM system and a new index of clinically relevant BP profiles (Tables 2 and 3).

Night-Time HBPM

We developed the Medinote, a semiautomatic HBPM device that performs automatic, fixed-interval BP measurement during sleep and stores the data in memory. Using the Medinote, we initiated the J-HOP (Japan Morning Surge Home Blood Pressure) study, the first large nationwide night-time home BP cohort, and successfully measured night-time home BP 3× during sleep (at 2:00 AM, 3:00 AM, and 4:00 AM) for 14 days in 2562 participants. The baseline data of this study demonstrated that the self-measurement of night-time BP at home is feasible and that there was no difference between the night-time home systolic BP levels at 2:00 AM and 3:00 AM while that at 4:00 AM was slightly higher by 1.5 mm Hg (P<0.0001). The night-time HBP was almost comparable to night-time BP measured by ABPM and was significantly correlated with the urinary albumin/creatinine ratio, LV mass index, brachial-ankle pulse wave velocity, maximum carotid intima–media thickness, and plasma NT-proBNP (N-terminal pro-B-type natriuretic peptide) and high-sensitive cardiac troponin T levels, independently of clinic, morning, and evening home BPs. Even in those with well-controlled
morning home systolic BP <135/85 mm Hg, 27% exhibited masked home nocturnal hypertension with night-time home systolic BP >120 mm Hg, and these patients had higher urinary albumin/creatinine ratio and NT-proBNP, indicating that a significant number of cases of masked home nocturnal hypertension remained as a hidden risk unrecognized by conventional HBPM. In addition, in our J-TOP (Japan Target Organ Protection) trial, we used night-time HBPM to assess the night-time BP in a clinical intervention trial for the first time. The reduction of night-time home BP was more closely associated with the regression of LV hypertrophy evaluated by cardiac echography than clinic BP, indicating that night-time home BP is a better indicator of good BP control during antihypertensive treatment. Thus, night-time HBPM could be a valuable method for assessing night-time BP, with accuracy comparable to ABPM in clinical practice.

**Night-Time Home BP Telemonitoring**

The Medinote device has now advanced to a new information and communication technology (ICT)–based night-time home BP telemonitoring device, HEM-7252G-HP. This night-time home BP telemonitoring system directly sends night-time home BPs during the last sleep period at the time of the morning BP measurement from the patient’s home. Using this

**Table 2. Research and Development of Night-Time Home Blood Pressure Monitoring Devices and Evidence (Jichi Medical University School of Medicine)**

| Year | Source            | Device                      | Major Device Function                                                                 | ICT-Based | Validation | Competing Device |
|------|-------------------|-----------------------------|--------------------------------------------------------------------------------------|-----------|------------|------------------|
| 2010 | Kario et al⁵⁶     | Medinote (HEM-5041; Omron Healthcare) | Automatic BP monitoring during sleep with fixed intervals function                    | Not available | Coleman et al⁵³ | Watch BP Home N (microlife) |
| 2012 | Ishikawa et al⁵⁷  | Watch BP Home N (microlife) | Automatic BP monitoring during sleep with fixed intervals function                  | Available | Takahashi et al⁵⁴ | Watch BP Home N (microlife) |
| 2014 | Ishikawa et al⁵⁹  |                               | Automatic BP monitoring during sleep with fixed intervals function and timer function | Available | None        | None              |
| 2015 | Kario et al⁵⁸     | HEM-7252G-HP (Omron Healthcare) | Automatic BP monitoring during sleep with fixed intervals function and timer function | Available | None        | None              |
| 2017 | Kario et al⁵¹     | ICT-based TNP (ITNP)         | TNP with built-in third-generation mobile communication facility                    | Available | None        | None              |
| 2018 | Fujiwara et al⁵⁴  | Wearable beat-by-beat surge BP monitoring (WSP) | Wrist-type continuous BP monitoring based on the tonometry method                  | Not available | None        | None              |

BP indicates blood pressure; and ICT, information and communication technology.
device, we have successfully conducted 2 clinical trials and confirmed that this night-time HBPM system could be made available for clinical practice.

Trigger Night-Time HBPM (TNP)
The second advance was the development of a TNP, which was based on the automated fixed interval measurement technique of Medinote with an added trigger function of hypoxia and heart rate monitored by pulse oximetry. There is currently no night-time BP monitoring device to evaluate the quality of nocturnal hypertension with different pathogenic pressor mechanisms. This double TNP thus adopts a brand new approach: it evaluates the pathogenic pressor mechanism of night-time BP by measuring BP only under specific conditions.

Hypoxia-Trigger Function
In the patients with OSA, repetitive OSA episodes produce hypoxia. When the desaturation falls below a set oxygen level as determined by continuous oxygen monitoring using pulse oximetry, the TNP automatically sends the signal to measure BP (hypoxia-trigger function). Thus, the TNP can detect the specific night-time BP surges triggered by hypoxic episodes and evaluate the effect of medication and device treatment on night-time BP profiles in patients with OSA.

Heart Rate-Trigger Function
We also added a lowest heart rate-trigger function to TNP to detect the basal night-time BP when the sympathetic tonus and BP level and BP variability are at a minimum during slow wave sleep. The low heart rate-trigger function is an algorithm that sends the command to measure BP when the lowest heart rate persists for a significant time period.

Definition of Trigger Night-Time BP Parameters
The hypoxia-peak night-time BP is defined as the maximum systolic BP measured by the hypoxia-trigger function, and OSA-induced night-time BP surge is defined as the hypoxia-peak systolic BP minus the average of the 2 BPs measured by fixed interval measurement before and after the peak systolic BP measured by hypoxia-trigger function (Figure 3A). The basal BP is defined as the lowest BP measured by low heart rate-trigger function. Nocturnal hypertension exhibits similar average night-time BPs although possibly by a different mechanism: peak night-time BPs measured by a hypoxia trigger might be attributed to sympathetic overdrive while the basal night-time BP would be determined by the circulating volume and structural vascular disease with the least sympathetic tonus.

Reproducibility of Night-Time BP Parameters
We evaluated the distribution and reproducibility of night-time BP parameters obtained from TNP compared with those of fixed-interval night-time BP parameters for 2 consecutive nights in 147 patients with OSA. The mean and distribution (SD) of the hypoxia-peak systolic BP were much greater than those of the mean night-time systolic BP, by 25.4 mm Hg (mean ± SD: 148.8 ± 20.5 versus 123.4 ± 14.2 mm Hg; P < 0.001). The repeatability coefficient (expressed as %MV; the percentage of 4 times the SD of the average of the repeat measurements) of hypoxia-peak systolic BP between night 1 and night 2 was comparable to that of mean night-time systolic BP (43% versus 32%), indicating that hypoxia-peak night-time BP was much higher than mean night-time BP, and as reproducible as mean night-time BP. Among the patients with nocturnal hypertension (mean night-time systolic BP ≥120 mm Hg), 50% have reached hypoxia peak systolic BP ≥160 mm Hg. Among polysomnography-derived sleep parameters (apnea-hypopnea index, arousal index, percentage of hypoxia [SpO2 < 90%] of the total sleep), the most potent determinant of this hypoxia-peak and surge in night-time BP was the lowest oxygen saturation (lowest SpO2).

SPREAD Study
Using the TNP, we are now conducting a prospective study of SPREAD (Sleep Pressure and Disordered Breathing in Resistant Hypertension and Cardiovascular Disease); this study will provide the first TNP registry and will use this data to evaluate the clinical implications of night-time BP and night-time BP surges in high-risk patients with resistant hypertension and cardiovascular disease. This ongoing SPREAD study includes the case of a 36-year-old man in whom TNP-detected exaggerated hypoxia-triggered night-time BP surges. He actually developed the sleep-onset of ischemic and hemorrhagic stroke 3x. Moreover, in a 74-year-old woman with OSA, even when the mean night-time BP measured by ABPM with fixed 30-minute intervals was normotensive <120/70 mm Hg, TNP determined that the repetitive exaggerated hypoxia peak systolic BP reached ≥160 mm Hg for systolic BP.

ICT-Based TNP (ITNP) System for Night-by-Night Evaluation
Finally, we have recently developed the ITNP system, a cloud-computing–based composite management and analysis system for the data sent from the BP device in the patient’s home. The most important benefit of the ITNP is the repeated assessments at home. One-day polysomnography under alcohol-prohibited conditions in hospitals may underestimate the severity of OSA and related risk. The evaluation of OSA using ITNP in a real-life setting increases the sensitivity to detect OSA-related night-time BP surge. The repeated assessments enable the detection of day-by-day variabilities in night-time BP profiles, which can be affected by the daily OSA severity and sleep quality during sleep, as well as by daily behavioral changes (salt and alcohol intake at dinner, bedtime, sleep time, awakening time, nocturia, etc) and environmental factors (temperature, illumination, atmospheric pressure in the bedroom, etc).

Evaluation of CPAP Therapy
Continuous positive airway pressure (CPAP) treatment nearly eliminates TNP-detected night-time BP surge in patients with OSA. However, the cardiovascular protection and BP-lowering effect of CPAP are not perfect, and a significant number of OSA patients on CPAP develop cardiovascular events. The 2017 AHA/ACC guidelines described that in adults with hypertension and OSA, the effectiveness of CPAP to reduce BP has not been well established, and thus CPAP was classified only as a class IIb recommendation. Another
ITNP can evaluate the adherence and efficacy of CPAP on a day-by-day basis. Even in patients with OSA on nightly CPAP therapy, the CPAP mask may not be properly positioned on the face, or the pressure of CPAP may be insufficient because of poor conditions, such as upper tract infection and allergic rhinitis. Nonetheless, effective CPAP was shown to reduce the mean night-time systolic BP by 8 mm Hg in a patient on CPAP. This reduction was markedly greater by 42 mm Hg when evaluated by hypoxia-peak night-time systolic BP.

Wearable Beat-by-Beat Continuous Surge BP Monitoring (WSP)
Wearable noninvasive beat-by-beat BP monitoring has long been a dream of doctors who manage hypertension. Omron Healthcare Co, Ltd, recently publicized a prototype of a wearable wrist-type of tonometry BP monitor that capitalizes on advances in automatically controlled technology. This prototype has 2 tonometry sensor plates, and the angle of the arrayed sensor plate to cover the radial artery is automatically adjusted to obtain effective applanation. We are currently testing the clinical utility of this device and improving it in collaboration with Omron with the goal of developing a more accurate, WSP device, which could measure the absolute values of the maximum peaks of beat-by-beat pressure.

Using our current prototype of the WSP device, we successfully monitored beat-by-beat BP continuously during sleep while simultaneously performing polysomnography. In our recent study, this device demonstrated that the night-time BP level and variability were significantly lower in stage 2 and stage 3 sleep, and higher during stage 1 sleep, rapid-eye-movement sleep, and the waking (by nocturnal behaviors, such as nocturia, drinking water, etc) period. This device successfully detected the 3 night-time BP surges triggered by rapid-eye-movement sleep, arousal (unconscious microarousals), and OSA episodes (Figure 3B). Nonetheless, WSP has limitations because of weaknesses of the tonometry BP monitoring device: (1) the position of the sensor to cover the artery is strict, and (2) artifacts because of movement of the wrist, which disturb effective applanation, are frequent.

Figure 3. Night-time blood pressure (BP) profile detected by trigger night-time home BP monitoring (TNP) and wearable beat-by-beat surge blood pressure monitoring (WSP). A, Detection and definition of night-time BP profile by TNP. B, Sleep apnea-induced night-time BP surges detected by WSP (top), and effect of bedtime dosing of a β-blocker on the night-time surge BP. Middle, BPs detected by TNP; Bottom, BPs monitored by WSP. In a 50-y-old normotensive women with obstructive sleep apnea, the WSP-Tigger successfully detected the highest peak of night-time BP surge 1 d before (day 1: baseline) and on the day of night-time dosing of carvedilol 20 mg (day 2: carvedilol-added). Carvedilol therapy decreased the Surge Index (BP surges/h) from 17.2/h to 7.4/h. The peak of surge was also decreased from 178 to 133 mm Hg by the oscillometric method triggered by hypoxia (middle), and from184 to 137 mm Hg by the continuous beat-by-beat method (bottom). SBP indicates systolic BP.
Finally, we developed an approach using the WSP combined with the trigger function technique to measure the accurate absolute BP value (WSP-Trigger). The peak of systolic BP surge detected by the WSP-Trigger was always higher than the hypoxia-triggered BP surge detected by trigger TNP using the oscillometric method (Figure 3B). These peaks of hypoxia-triggered night-time BP detected by WSP-Trigger and by TNP were diminished by sympatholytics (Figure 3B).

We developed the WSP-Trigger because earlier detection of mild OSA and associated night-time BP surge is critically important because OSA is mostly diagnosed in a rather advanced stage of the disease and therapy may incompletely reverse organ damage (remodeling, lung function, and so on). However, it is not certain that the initiation of additional drug therapy and use of novel technologies, such as WSP-Trigger, will finally lead to zero cardiovascular events. TNP may underestimate the risk of OSA because in treated patients with OSA, there might be remaining hypopnea and apnea episodes without a clear trigger of hypoxia. Even by the combination therapy of CPAP and medication, the risk of OSA might remain significant. Extensive research will be needed to validate the quantity and quality of the night-time BP-lowering effects of CPAP and antihypertensive drugs of different classes.

Management of Nocturnal Hypertension

The 2017 AHA/ACC guidelines for the management of hypertension recommend a goal of <110/65 mm Hg for night-time BP control. In clinical practice, the morning home BP-guided titration of antihypertensive drugs is the first step to achieve perfect 24-hour BP control, which consists of 3 components: lowering 24-hour BP; maintaining a normal circadian rhythm (dipper-type); and suppressing exaggerated BP variability, especially for morning and night-time surges. Based on the recent results of the HONEST study (Home BP Measurement With Olmesartan Naive Patients to Establish Standard Target Blood Pressure), we practically recommend a 3-step strategy guided by morning home BP for the control of morning hypertension: the first step is to achieve a home systolic BP <145 mm Hg to reduce the relatively short-term risk, the second step is to realize morning home BPs <135/85 mm Hg, and the third step is to achieve the ideal target of morning home systolic BP <125 mm Hg. In consideration of the 2017 AHA/ACC guidelines, after morning home systolic BP is controlled to <130 mm Hg, masked uncontrolled nocturnal hypertension with night-time BP ≥110/85 mm Hg should be the next target (Figure 4).

Pressor Mechanism–Based Treatment Strategy

An increase in the basal BP depends on the increased circulating volume or advanced vascular disease (increased vascular stiffness and increased vascular resistance because of small artery remodeling; Figure 4). Salt restriction, diuretics, mineralocorticoid receptor antagonist (aldosterone blocker), sacubitril/valsartan, and sodium-glucose cotransporter 2 inhibitors for patients with increased circulating volume, and calcium channel blocker monotherapy or calcium channel blocker therapy combined with a renin–angiotensin system inhibitor for patients with advanced vascular disease are theoretically preferable. Recently, clinical outcome trials clearly demonstrated that sacubitril/valsartan improved cardiovascular prognosis and that sodium-glucose cotransporter 2 inhibitors reduced cardiovascular events, especially for patients with heart failure, and prevented the reduction of renal function. Sympatholytic treatment using β-α-blockers and renal denervation are effective for reducing the average and the peak of night-time BPs, especially in patients with OSA. Hypnotics, such as melatonin, melatonin receptor agonists, and orexin receptor antagonists, might be preferable for patients with sleep disorders.

Recent Evidence of Clinical Trials Using Night-Time HBPM

There have been only 3 clinical randomized control trials (RCTs) using night-time HBPM and 1 RCT using trigger night-time HBPM to compare the night-time BP-lowering effect of 2 arms of different antihypertensive drugs. All 4 of these studies concluded that the night-time BP-lowering effect of antihypertensive drugs was successfully monitored by night-time HBPM and clarified that these drugs exhibited different efficacies for improving the night-time BP profiles. The WSP-Trigger could detect the different BP-lowering profile of the short-term BP variability on a beat-by-beat basis.
Table 3. Research and Development of Night-Time Home Blood Pressure Monitoring and Evidence: Clinical Evidence Using Night-Time Home Blood Pressure Monitoring

| Year   | Source         | Study Name | Study Subjects | Device                        | Device Function                              | BP Measurement | Main Findings                                                                                                                                                       |
|--------|----------------|------------|----------------|-------------------------------|---------------------------------------------|----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cross-sectional study                                                                                             |
| 2001   | Chonan et al37  | …          | 49 hypertensive patients | HEM-747IC-N (Omron Healthcare) | Automated measurement at a fixed time       | 2 AM (10 d)   | Night-time BP at 2:00 AM was increased in proportion to the degree of 3-graded sleep disturbance.                                                            |
| 2006   | Shirasaki et al45 | …          | 16 patients with OSA | TNP                           | Hypoxia-triggered BP measurement            | At the time of heavy hypoxia episodes (1 d) | Night-time BP obtained by TNP was significantly associated with severity of OSA.                                                                            |
| 2011   | Shirasaki et al46 | …          | 23 patients with OSA (mean: 58 y) | TNP                           | Hypoxia-triggered BP measurement            | At the time of heavy hypoxia episodes (1 d) | Hypoxia-triggered BP monitoring with variable threshold was able to detect severe apnea episode-related BP surges.                                      |
| 2012   | Ishikawa et al27 | J-HOP      | 854 GP-based patients with CV risk factors (mean: 63 y) | Medinote (HEM-5041; Omron Healthcare) | Automated measurement at a fixed time       | 2 AM, 3 AM, 4 AM (14 d) | Night-time home BP was comparable to night-time BP measured by ABPM and was significantly correlated with target organ damage. |
| 2012   | Stergiou et al42 | …          | 81 hypertensive patients (mean: 58 y) | Watch BP Home N (microlife)   | Automated measurement with timer function   | 2, 3, 4 h after going to bed (3 d) | A strong association was found between night-time BP measured by ABPM and night-time home BP.                                                              |
| 2013   | Kario et al38   | J-HOP      | 2562 GP-based patients with CV risk factors (mean: 63 y) | Medinote (HEM-5041; Omron Healthcare) | Automated measurement at a fixed time       | 2 AM, 3 AM, 4 AM (14 d) | Night-time home BP was significantly correlated with measures of organ damage independently of clinic BP, morning home BP, and evening home BP. |
| 2017   | Kuwabara et al48 | …          | 147 patients with OSA (mean: 59 y) | TNP                           | Hypoxia-triggered BP measurement            | At the time of heavy hypoxia episodes (2 d) | The hypoxia-peak systolic BP measured by TNP was much higher than the mean night-time systolic BP measured at 30-min intervals, and it was reproducible as mean night-time systolic BP. |
| 2017   | Kollias et al42 | …          | 94 hypertensive patients (mean: 52 y) | Watch BP Home N (microlife)   | Automated measurement with timer function   | 2, 3, 4 h after going to bed (3 d) | Two nights of home BP monitoring seems to be the minimum requirement for reliable assessment of night-time home BP and provides reasonable agreement with ambulatory BP and association with preclinical organ damage. |
| 2018   | Kuwabara et al48 | …          | 116 patients with OSA (mean: 58 y) | TNP                           | Hypoxia-triggered BP measurement            | At the time of heavy hypoxia episodes (2 d) | In polysomnography-derived parameters, lowest SpO2, defined as the minimum SpO2 value during sleep, is the strongest independent determinant of hypoxia-peak systolic BP and OSA-related night-time systolic BP surge measured by TNP. |
| Clinical trials                                                                                                      |
| 2010   | Kario et al38   | J-TOP (RCT) | 161 hypertensive patients (mean: 59 y) | Medinote (HEM-5041; Omron Healthcare) | Automated measurement at a fixed time       | 2 AM, 3 AM, 4 AM (7 d) | The UACR was more markedly reduced in the bedtime-dosing group than in the awakening-dosing group, whereas there were no differences in the reduction of any of the home BPs, including the night-time BP, between the 2 groups. |
### Table 3. Continued

| Year | Source                         | Study Name/Method | Study Subjects | Device | Device Function | BP Measurement | Main Findings                                                                                                                                                                                                 |
|------|--------------------------------|-------------------|----------------|--------|----------------|----------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 2014 | Ishikawa et al<sup>39</sup>    | J-TOP (RCT)       | 50 hypertensive patients (mean: 67 y) | Medinote (HEM-5041; Omron Healthcare) | Automated measurement at a fixed time | 2 AM, 3 AM, 4 AM (7 d) | The reduction in night-time home BP was more closely correlated with the reduction in left ventricular hypertrophy, and UACR.                                                                                     |
| 2014 | Kario et al<sup>40</sup>       | VASSPS (crossover) | 11 patients with OSA (mean: 65 y) | TNP    | Hypoxia-triggered BP measurement | At the time of heavy hypoxia episodes (2 d) | The night-time dosing of both vasodilating and sympathetic antihypertensive drugs is effective to reduce night-time BP including night-time BP surges induced by OSA.                                                   |
| 2017 | Kario et al<sup>41</sup>       | NOCTURN (first RCT of nocturnal HBPM telemonitoring) | 411 patients with uncontrolled nocturnal hypertension (mean: 63 y) | HEM-7252G-HP (Omron Healthcare) | Automated measurement at a fixed time | 2 AM, 3 AM, 4 AM (5 d) | The irbesartan/amiodipine combination achieved a greater reduction in night-time home BP than the irbesartan / trichlormethiazide combination, independently of urinary sodium excretion and night-time BP dipping status. |
| 2018 | Fujiwara et al<sup>44</sup>    | SUNLIGHT (RCT)    | 129 patients with uncontrolled morning hypertension (mean: 68 y) | HEM-7252G-HP (Omron Healthcare) | Automated measurement at a fixed time | 2 AM, 3 AM, 4 AM (3 d) | Morning home BP surge, which is a new index defined as the morning systolic BP minus the night-time systolic BP, was significantly decreased from baseline in both groups, but there was no significant difference between the 2 groups. |
| 2018 | Kario et al.                   | SHIFT-J (RCT)     | 84 patients with uncontrolled nocturnal hypertension and type 2 diabetes mellitus (mean: 69 y) | HEM-7080-IC (Omron Healthcare) | Automated measurement at a fixed time | 2 AM, 3 AM, 4 AM (5 days) | In preparation for publication. (To investigate the effects of canagliflozin add-on versus intensified antihyperglycemic therapy on nocturnal home BP.)                                                                   |

ABPM indicates ambulatory blood pressure monitoring; BP, blood pressure; CV, cardiovascular; GP, general practitioner; HBPM, home BP monitoring; J-HOP, Japan Morning Surge Home Blood Pressure; J-TOP, Japan Target Organ Protection; NOCTURNE, Comparative Effects of ARB/Diuretic vs ARB/CCB Combination on Uncontrolled Nocturnal Hypertension Evaluated by ICT-based Nocturnal Home Blood Pressure Monitoring; OSA, obstructive sleep apnea; RCT, randomized controlled trial; Sp<sub>0,2</sub>, oxygen saturation; SUNLIGHT, Study on Uncontrolled Morning Surge for N-type CCB and Low Dose of HCTZ, Using the Internet Through Blood Pressure Data Transmission System; TNP, triggered nocturnal blood pressure monitoring; VASSPS, Effects of Vasodilating vs Sympatholytic Antihypertensives on Sleep Blood Pressure in Hypertensive Patients with Sleep Apnea Syndrome; and UACR, urinary albumin/creatinine ratio.

(Figure 3B),<sup>2</sup> but this device is currently at research and development stage and not ready for clinical use.

### Night-Time HBPM Study

The first night-time HBPM study was reported in 2014. This study, the J-TOP study,<sup>38,39</sup> was a multicenter open-label RCT in 450 hypertensives with self-measured home systolic BP ≥135 mm Hg and demonstrated that a bedtime dosing of can-desartan titrated by self-measured morning home BP was more effective for reducing albuminuria than an awakening dosing even though the night-time home BP-lowering effect was similar between the bedtime-dosing and awakening-dosing groups.

#### ICT-Based Night-Time Home BP Telemonitoring Study

The second clinical trial using night-time HBPM was the NOCTURNE study (Comparative Effects of Angiotensin II Receptor Blocker [ARB]/Diuretic vs ARB/Calcium-Channel Blocker [CCB] Combination on Uncontrolled Nocturnal Hypertension Evaluated by ICT-based Nocturnal Home Blood Pressure Monitoring).<sup>41</sup> This is the first multicenter RCT using the new ICT-based nocturnal home BP telemonitoring device (HEM-7252G-HP) and a cloud computing system in an independent study control center. It was conducted to compare the night-time home BP-lowering effects of differential ARB-based combination therapies in 411 Japanese patients with nocturnal hypertension. The NOCTURNE study was the first to demonstrate the feasibility of clinical assessment of night-time BP by ICT-night-time HBPM. Patients with nocturnal uncontrolled hypertension (night-time BP ≥120/70 mmHg) at baseline even under ARB therapy (100 mg irbesarta- tan daily) were enrolled. The ARB/CCB combination therapy (irbesartan 100 mg+amiodipine 5 mg) achieved a significantly greater reduction in night-time home systolic BP (primary end
point) than the ARB/diuretic combination (daily irbesartan 100 mg + trichlormethiazide 1 mg; −14.4 versus −10.5 mmHg; P < 0.0001), independently of urinary sodium excretion and night-time BP dipping status. However, the change in night-time home systolic BP was comparable among the post hoc subgroups with higher salt sensitivity (diabetes mellitus, CKD, and elderly patients). Both combinations significantly reduced urinary albumin/creatinine ratio and NT-proBNP levels while the reduction of NT-proBNP was greater in the ARB/CCB arm. The ARB/CCB combination was shown to be superior to ARB/diuretic in patients with uncontrolled nocturnal hypertension independently of sodium intake despite the similar impact of the 2 combinations in patients with higher salt sensitivity.

The third clinical trial using nocturnal HBPM was the SUNLIGHT (Study on Uncontrolled Morning Surge for N-type CCB and Low Dose of HCTZ, Using the Internet Through Blood Pressure Data Transmission System) study, an 8-week, multicenter, RCT using an ICT-based night-time home BP telemonitoring system in 129 patients with morning hypertension (≥135/85 mmHg) by the self-measuring ICT-based HBPM device, HEM-7252G-HP). In this study, we tested our hypothesis that a valsartan/cilnidipine combination would suppress the morning home BP surge more effectively than a valsartan/hydrochlorothiazide combination. At the end of the treatment period, the changes in night-time and morning home systolic BPs from baseline were significant in both the valsartan/cilnidipine and valsartan/hydrochlorothiazide groups (P < 0.001). The reduction of night-time systolic BP was significantly greater in the valsartan/hydrochlorothiazide group than the valsartan/cilnidipine group (−10.0 versus −5.0 mmHg; P = 0.035) while there was no significant difference in the reduction of morning systolic BP between the 2 groups (−13.6 versus −10.7 mmHg; P = 0.142). Morning home BP surge, which is a new index defined as the mean morning systolic BP minus the mean night-time systolic BP, was significantly decreased from baseline in both groups (P < 0.001), but there was no significant difference between the 2 groups.

**Trigger Night-Time HBPM Study**

The VASSPS (Effects of Vasodilating vs Sympatholytic Antihypertensives on Sleep Blood Pressure in Hypertensive Patients with Sleep Apnea Syndrome) trial is the first clinical trial using the trigger night-time HBPM (TNP). This study, which had a prospective, randomized, parallel-group crossover design, compared the effects of bedtime single-dose administration of a vasodilating antihypertensive agent (controlled-release nifedipine 40 mg) versus a sympatholytic antihypertensive agent (carvedilol 20 mg) on night-time BP in 11 hypertensive patients with OSA. The BP-lowering effects of nifedipine on the mean (P < 0.05) and minimum night-time systolic BPs (P < 0.01) as well as morning systolic BP (P < 0.001) were stronger than those of carvedilol. The night-time systolic BP surge (difference between the hypoxia-peak systolic BP measured by oxygen-triggered function and systolic BPs within 30 minutes before and after the peak systolic BP) was significantly reduced by carvedilol (P < 0.05) but not by nifedipine. The bedtime dosing of both the vasodilating and sympatholytic antihypertensive drugs was effective to reduce night-time BP but with different BP-lowering profiles.

In our cross-sectional study using TNP in 116 patients with OSA, antihypertensive medication lowered the slope of the regression line (absolute value) between hypoxia-peak systolic BP and lowest Sp2. These trends were also found in the association between lowest Sp2 and OSA-related night-time systolic BP surge. These facts might indicate that hypertensive medication could reduce hypoxia-peak systolic BP, especially in the patients with low lowest Sp2. Specifically, in our study, a calcium channel blocker significantly reduced the regression line (absolute value) between hypoxia-peak systolic BP and lowest Sp2, and α-adrenergic or β-adrenergic blockers significantly reduced that between night-time systolic BP surge and lowest Sp2. These results were the same as those in the above crossover study (VASSPS).

**Conclusion and Perspectives**

The current direction in the management of hypertension is toward earlier and lower BP control for 24 hours, including the nocturnal and morning periods. The night-time BP management is especially important to prevent cardiovascular events, especially heart failure, as well as age-related organ damages, such as CKD and cognitive dysfunction. Night-time home BP telemonitoring is expected to be introduced in clinical practice. In the near future, ICT-based antipredication medicine that predicts future BP levels will contribute to the target of zero cardiovascular events. For the precise anticipation of risk, the repeated measurement of individual time-series big data will be essential. Research and development into new HBPM devices with less consciousness of BP measurement and evidence of the efficacy of home BP telemedicine and telecare in consideration of night-time BP are also needed.

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