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STATE-OF-THE-ART REVIEW

Research and Development of Information and Communication Technology-based Home Blood Pressure Monitoring from Morning to Nocturnal Hypertension

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Abstract

Asians have specific characteristics of hypertension (HTN) and its relationship with cardiovascular disease. The morning surge in blood pressure (BP) in Asians is more extended, and the association slope between higher BP and the risk for cardiovascular events is steeper in this population than in whites. Thus, 24-hour BP control including at night and in the morning is especially important for Asian patients with HTN. There are 3 components of "perfect 24-hour BP control": the 24-hour BP level, adequate dipping of nocturnal BP (dipper type), and adequate BP variability such as the morning BP surge. The morning BP-guided approach using home BP monitoring (HBPM) is the first step toward perfect 24-hour BP control. After controlling morning HTN, nocturnal HTN is the second target. We have been developing HBPM that can measure nocturnal BP. First, we developed a semiautomatic HBPM device with the function of automatic fixed-interval BP measurement during sleep. In the J-HOP (Japan Morning Surge Home Blood Pressure) study, the largest nationwide home BP cohort, we successfully measured nocturnal home BP using this device with data memory, 3 times during sleep (2, 3, and 4 AM), and found that nocturnal home BP is significantly correlated with organ damage independently of office and morning BP values. The second advance was the development of trigger nocturnal BP (TNP) monitoring with an added trigger function that initiates BP measurements when oxygen desaturation falls below a variable threshold continuously monitored by pulse oximetry. TNP can detect the specific nocturnal BP surges triggered by hypoxic episodes in patients with sleep apnea syndrome. We also added the lowest heart rate-trigger function to TNP to detect the "basal nocturnal BP," which is determined by the circulating volume and structural cardiovascular system without any increase in sympathetic tonus. This double TNP is a novel concept for evaluating the pathogenic pressor mechanism of nocturnal BP. These data are now collected using an information and communication technology (ICT)-based monitoring system. The BP variability includes different time-phase variability from the shortest beat-by-beat, positional, diurnal, day-by-day, visit-to-visit, seasonal, and the longest yearly changes. The synergistic resonance of each type of BP variability would produce great dynamic BP surges, which trigger cardiovascular events. Thus, in the future, the management of HTN based on the simultaneous assessment of the resonance of all of the BP variability phenotypes using a wearable "surge" BP monitoring device with an ICT-based data analysis system will contribute to the ultimate individualized medication for cardiovascular disease.

KEY WORDS home blood pressure, hypertension, Asians, 24-hour blood pressure, blood pressure variability

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INTRODUCTION

Hypertension (HTN) is one of the strongest risk factors for cardiovascular disease (CVD), worldwide. All of the international guidelines for the management of HTN were recently revised and stress the importance of blood pressure (BP) control in the prevention of cardiovascular events,[1-5] but much more knowledge about BP issues remains to be gained, including the need to address the racial and ethnic gaps in BP studies.[6] For example, there are significant differences in the demographics of CVD and its risk factors between Asians and Westerners (Fig. 1).[7] In Asians, the incidence of stroke is higher than that of myocardial infarction (MI), whereas this tendency is the opposite in Westerners.[8] Even in a 2014 prospective study of >20,000 medicated Japanese patients with HTN, the incidence of stroke was 3 times higher than that of MI.[9] Regarding stroke cases, the incidence of hemorrhagic stroke in particular is higher in Asians among both untreated individuals and patients treated with anticoagulants compared with Westerners.

The relationship between BP and cardiovascular events is stronger in Asia, and salt intake and salt sensitivity are greater in Asia.[10] Western lifestyle-induced increases in obesity, metabolic syndrome, and diabetes-increased salt sensitivity have been observed across Asia. As the phenotype of HTN, although there is no direct comparison study, morning HTN may be more common in Asians than Westerners, as the morning BP surge was shown to be greater in Japanese than in Italian and Spanish hypertensive patients.[11] Increased systolic HTN and chronic kidney disease (CKD) are important risk factors for cardiovascular events in aging Asian societies.[12] These characteristics indicate that strict 24-hour BP control for the effective prevention of cardiovascular events is even more important in Asia than it is in the West.[13]

The more recent version of the guidelines of the Japanese Society of Hypertension regarding the management of hypertension (JSH2014) were published in 2014.[5] For these guidelines, we collected evidence from both Asian and Western studies, taking Asian characteristics into special consideration. The JSH2014 guidelines use the BP value 130/80 mm Hg, a lower target clinic BP compared with Western guidelines (140/90 mm Hg), for hypertensive patients with diabetes or albuminuria. Additionally, the JSH2014 guidelines recommend that patients with HTN and diabetes achieve home BP values <125/75 mm Hg, as 2 studies demonstrated the benefit of achieving this level.[14,15] However, the existing data from Asian studies are more limited than the accumulated data from Western countries.

In this review, we discuss the current status of BP control and some perspectives regarding the management of HTN in Japan in the near future.

MEASUREMENT AND CLINICAL EVALUATION OF BLOOD PRESSURE

Home BP monitoring (HBPM) has been widely used in clinical practice, and several guidelines recommend the home BP-guided management of HTN.[2,5] The JSH2014 guidelines highly recommend the home BP-guided management of HTN: "When there is a discrepancy of diagnosis between clinic blood pressure and home blood pressure, a home blood pressure-based diagnosis should have priority."[5]

The JSH2014 guidelines essentially stress the importance of 24-hour BP control including sleep and morning periods,[5] as do several recently published Western and international guidelines[1,2] with the exception of 2 organizations' guidelines.[3,4] Based on the discrepancy of the office BP and out-of-office BP values, the diagnoses of white-coat hypertension (in which a patient's office BP indicates HTN but his or her out-of-office BP indicates normotension)[16] and masked HTN (in which a patient's office BP indicates normotension but his or her out-of-office BP indicates HTN)[17,18] can be made (Fig. 2). The diagnosis of these classifications is based on the average of BP values measured by HBPM or by ambulatory BP monitoring (ABPM).[19-21] The complementary use of both HBPM and ABPM is recommended for the diagnosis of hypertension (Fig. 3).[13] HBPM in particular is recommended for use in clinical practice as the first step, whereas ABPM is recommended for high-risk patients with HTN.

1. Stroke, especially hemorrhagic stroke, more common than coronary artery disease
2. Steeper association between BP and cardiovascular disease
3. High salt intake with high salt sensitivity
4. Obesity and metabolic syndrome epidemic
5. Morning hypertension more common

Figure 1. Characteristics of hypertension in Asia. Modified from Kario K. Proposal of a new strategy for ambulatory blood pressure profile-based management of resistant hypertension in the era of renal denervation. Hypertens Res 2013;36:478–84. Abbreviation: BP, blood pressure.

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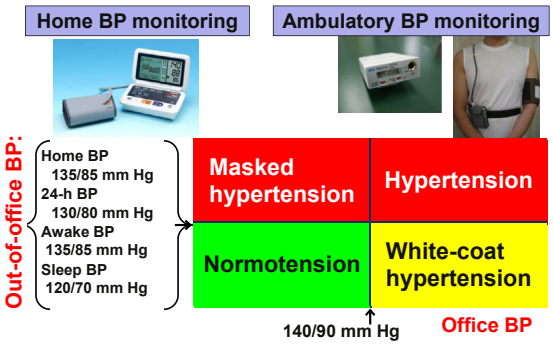

Figure 2. **Out-of-office BP monitoring. Abbreviation: BP, blood pressure.**

Several studies revealed that home and ambulatory BP values were more closely associated with organ damage and cardiovascular prognosis compared with office BP in both hypertensive patients and community-dwelling individuals, in both Western[19-21] and Asian[22-27] cohorts. Compared with normotension (ie, normotensive values for both office and out-of-office BP) and white-coat hypertension, masked hypertension and sustained hypertension (ie, hypertensive values for both office and out-of-office BP) are associated with the risk for organ damage and subsequent cardiovascular events.

Masked hypertension is classified into the following 3 types:

1. Morning hypertension (morning BP ≥135/85 mm Hg),
2. Nocturnal hypertension (night-time BP ≥120/70 mm Hg), and
3. Daytime hypertension (daytime BP ≥135/85 mm Hg) (Fig. 4).[5,13]

The greater part of the benefit of antihypertensive treatment is derived from BP control per se.

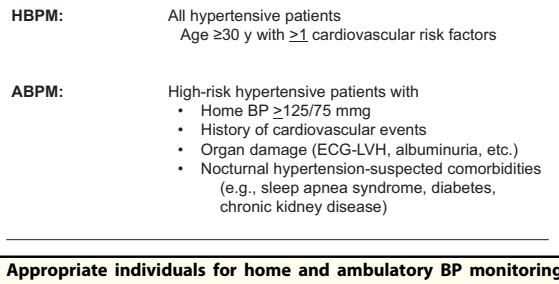

Figure 3. **Appropriate individuals for home and ambulatory BP monitoring. Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; ECG, electrocardiogram; LVH, left ventricular hypertrophy.**

There is robust evidence indicating that BP control throughout the 24-hour day is essential for lowering the risk for organ damage and cardiovascular events. However, not only strict reduction of the 24-hour BP level (ie, the amount of 24-hour BP lowering) is required; restoring disrupted circadian BP rhythms such as nondipper and riser rhythms and reducing exaggerated BP variability such as exaggerated morning BP surges (ie, the quality of 24-hour BP lowering) are also necessary to achieve perfect 24-hour BP control (Fig. 5). ABPM can be used to identify these 3 components of perfect 24-hour BP control.[13]

Morning Hypertension. It is well known that cardiovascular events occur more frequently in the morning, and that BP levels increase upon waking in the morning (the morning surge). We first defined the morning BP surge by ABPM, and our findings demonstrated that the morning BP surge in elderly hypertensive patients is associated with silent cerebral infarcts defined by brain magnetic resonance imaging (MRI) and future clinical stroke events, independently of age or average 24-hour BP level (Fig. 6).[28] Numerous studies have described the strong predictive ability of morning BP surge as a risk for CVD (stroke, coronary artery disease, total mortality) independently of the 24-hour BP level in both hypertensive outpatients and community-dwelling individuals, although some studies did not find that this ability was present independently of the 24-hour BP level, and a few studies have struck a discordant note.[29-34]

The morning BP surge is positively correlated with inflammatory biomarkers and other types of BP variability such as orthostatic HTN and increased daytime ambulatory BP variability.[30] The morning BP surge is associated with target organ damage such as left ventricular hypertrophy, albuminuria, and large- and small-artery diseases such as carotid atherosclerosis, arterial stiffness, albuminuria, and silent cerebrovascular disease, independent of the 24-hour BP level. In an international collaboration ABPM study, Asians had more extended morning BP surges than Westerners (Fig. 7).[11] The steeper association between office BP and CVD (particularly stroke) in Asian populations may be partly explained by their exaggerated morning BP surge.

Morning BP per se is a stronger risk factor for organ damage and cardiovascular events than the BPs during other times of the day.[35,36] We first defined morning HTN as having an average of morning BP values >135 mm Hg for systolic BP

(SBP), or >85 mm Hg for diastolic BP (DBP), regardless of office BP values, and we stressed the importance of controlling morning HTN in clinical practice (Fig. 8).[37] In addition to this broad definition, a more strict definition of morning HTN is the morning-evening difference (morning SBP minus evening SBP) in home BP (ME-dif) >15 to 20 mm Hg.[37,38] Morning HTN (ie, ambulatory morning HTN) can be diagnosed using ABPM. Masked morning HTN is defined as morning HTN with office BP <140/90 mm Hg.[13]

The BP-lowering effect of a once-daily morning use of antihypertensive drugs is minimal the next morning just before any other medication is taken. Thus, the prevalence of masked morning HTN, defined as normotension in office BP and HTN in morning BP, increases after a conventional office BP-guided treatment of HTN. During the past decade, we have persistently recommended home morning BP-guided antihypertensive treatment for patients with HTN. We compared the prevalence of uncontrolled masked HTN in 2 different studies performed at a 10-year interval. The first of the 2 studies, the J-MORE (Jichi Morning Hypertension Research) study performed 10 years ago, demonstrated that the prevalence of uncontrolled masked morning HTN was 52% in the individuals with well-controlled clinic BP (<140 mm Hg) (Fig. 9A).[39] However, in the recent J-HOP study,[40] this prevalence had fallen to approximately 38% (Fig. 9B). Thus, the prevalence of masked uncontrolled morning HTN among individuals with well-controlled office BP values of <140/90 mm Hg was reduced. This trend suggests that it is feasible to achieve an effective control rate of morning BP by targeting morning BP.

Latest Evidence About Controlling Morning Hypertension: The HONEST Study. We recently published the main results of the HONEST (Home Blood Pressure Measurement with Olmesartan-Naive Patients to Establish Standard Target Blood Pressure) study, the largest-scale prospective, real-world observational study of 21,591 outpatients with essential HTN in Japan. The results of the study demonstrated that on-treatment morning home BP is much more important than office BP during antihypertensive treatment. In the HONEST study, the patients received olmesartan-based treatment throughout the treatment period. Both office and home BP values were comparably reduced by olmesartan, in both the patients treated with monotherapy and in those on combination therapy with other classes of antihypertensive drugs. The primary endpoint was major cardiovascular events (stroke, MI, and angina pectoris with coronary intervention) and sudden death.

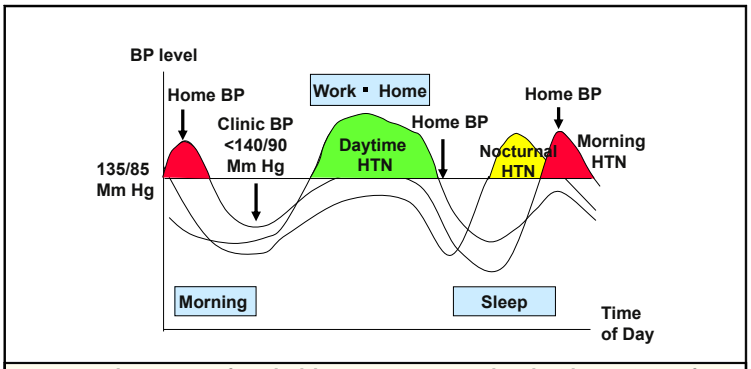

Figure 4. Three types of masked hypertension. Reproduced with permission from Kario K. Masked hypertension—pathogenesis and treatment. Int Med 2007;96:79–85. Abbreviations: BP, blood pressure; HTN, hypertension.

During the mean follow-up period of 2.02 years, cardiovascular events occurred in 280 patients (incidence, 6.46 of 1000 patient years). The risk for the primary endpoint was significantly higher in the patients with on-treatment morning home SBP values of >145 to 155 mm Hg (hazard ratio [HR], 1.83) and >155 mm Hg (HR, 5.03) compared with the patients with corresponding values of <125 mm Hg, and compared with those with on-treatment office BP of >150 to 160 mm Hg (HR, 1.69) and >160 mm Hg (HR, 4.38) than those with <130 mm Hg. The morning home BP value associated with the minimum risk was 124 mm Hg by a spline regression analysis, and the office SBP associated with the minimum risk was 131 mm Hg (Fig. 10A). There is no J-curve phenomenon in home BP until 100 mm Hg, whereas a slight increase in the cardiovascular risk around 100 mm Hg was found in office BP (Fig. 10B). When morning BP was controlled at <125 mm Hg, there

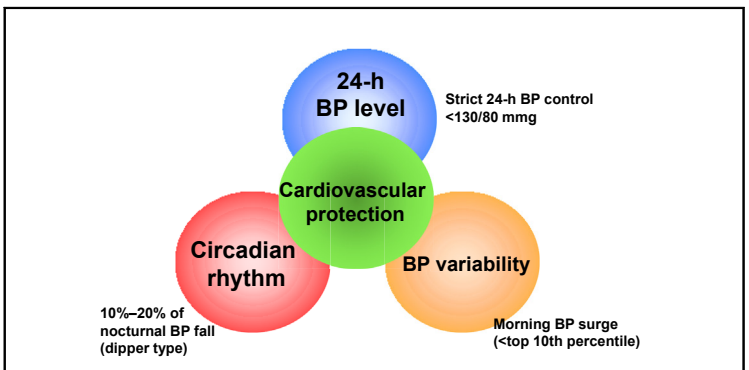

Figure 5. Triad of perfect 24-hour BP control. Reproduced with permission from Kario K. Morning surge in blood pressure in hypertension: clinical relevance, prognostic significance and therapeutic approach. In: Berbari AE, Mancia G (eds.). New York: Springer; 2012: 71–89. Abbreviation: BP, blood pressure.

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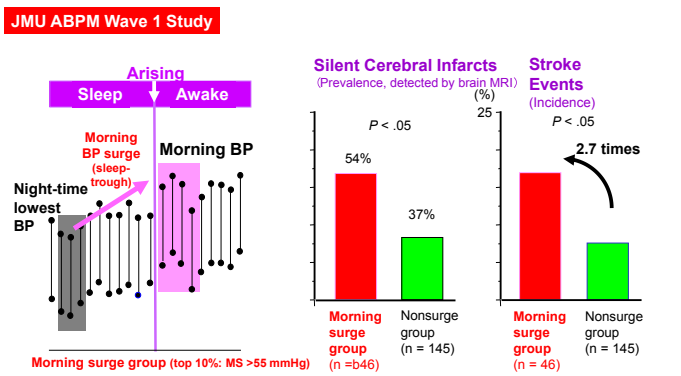

Figure 6. Morning BP surge and stroke risk in hypertension (matching for age and 24-hour systolic BP). Reproduced with permission from Kario K, Pickering TG, Umeda Y, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation 2003;107:1401-1406. Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; JMU, Jichi Medical University; MRI, magnetic resonance imaging.

was no increase in cardiovascular risk even when the office SBP was increased to >150 mm Hg. Instead, the cardiovascular risk was increased in the patients with morning home BP >145 mm Hg and office BP <130 mm Hg (HR, 2.47) compared with those who had morning home BP of <125 mm Hg and office BP of <130 mm Hg (Fig. 11). Thus, the risk for cardiovascular events was high in the patients with masked uncontrolled morning HTN, although their office BP was not increased.

These real-world findings emphasize the importance of HBPM in clinical practice. Based on this evidence, it is essential to control morning home SBP to <145 mm Hg as a first step, even in patients with controlled office BP. Then, achieving morning home SBP of <135 mm Hg, that is, the target home BP level of the JSH2014 and other international guidelines, is the second step, and around 125 mm Hg is the ultimate goal of the home BP-guided management of HTN (Fig. 12).

The White-Coat Effect-Excluded BP Measurement May Explain "the Lower, the Better" in SPRINT. The recent SPRINT study clearly demonstrated that strict office SBP control at <120 mm Hg was superior to the usual SBP control of <140 mm Hg for preventing cardiovascular events including heart failure and mortality in hypertensive patients aged ≥ 75 years and high-risk patients with CVD or CKD.[41] This beneficial effect may be due in part to the automated office BP (AOBP) measurements by a HBPM device in a quiet room without a doctor. Such BP measurements could exclude the white-coat pressor effect, and the AOBP level is lower by approximately 10 mm Hg than office BP levels measured by conventional BP methods.[42] The office BP in the SPRINT study thus seems to be more similar to home BP or ambulatory BP than to usual office BP.

Only 2 studies collected on-treatment home BP data throughout the follow-up period and examined the data's association with cardiovascular risk. The HOMED BP study, a randomized clinical investigation using self-measured HBPM, randomized hypertensive patients into a strict BP control group (target home BP <125/80 mm Hg) and a usual BP control group (125-134/80-84 mm Hg).[26] Unfortunately, BP control was insufficient in the strict BP control group, and the actual between-group difference in on-treatment home SBP levels during the follow-up period was only 1.4 mm Hg. That study could not validate the superiority of strict home BP control compared with usual home BP control, but the 5-year risk for cardiovascular events was minimal when the on-treatment home SBP was <132 mm Hg. The HONEST study showed that even among patients with well-controlled office SBP (<130 mm Hg), the masked uncontrolled HTN group with higher home SBP (≥145 mm Hg) was associated with a 2.5-fold higher risk for cardiovascular events compared with the patients with home SBP of <125 mm Hg. This masked HTN group was likely to have had characteristics of the SPRINT study group, such as a history of CVD and an increased number of antihypertensive drugs used. There was no J-curve until 100 mm Hg for home SBP, even when heart failure was included as a cardiovascular endpoint. On the contrary, when on-treatment home SBP was well-controlled at <125 mm Hg, higher on-treatment office SBP (even ≥150 mm Hg) was not associated with any increase in cardiovascular events compared with well-controlled office SBP <130 mm Hg.

Considering these results, we propose that strict BP control targeting white-coat effect-excluded BP measurements such as those obtained by AOBP or home BP conducted "on top of" conventional strict office BP control may achieve more effective prevention of cardiovascular events in high-risk hypertensive patients.

The Disaster Cardiovascular Prevention Network: A Model of the ICT-based Approach. The next stage in the management of HTN is the information and communication technology (ICT)-based approach using HBPM. We developed an ICT-based BP monitoring system at the time of the

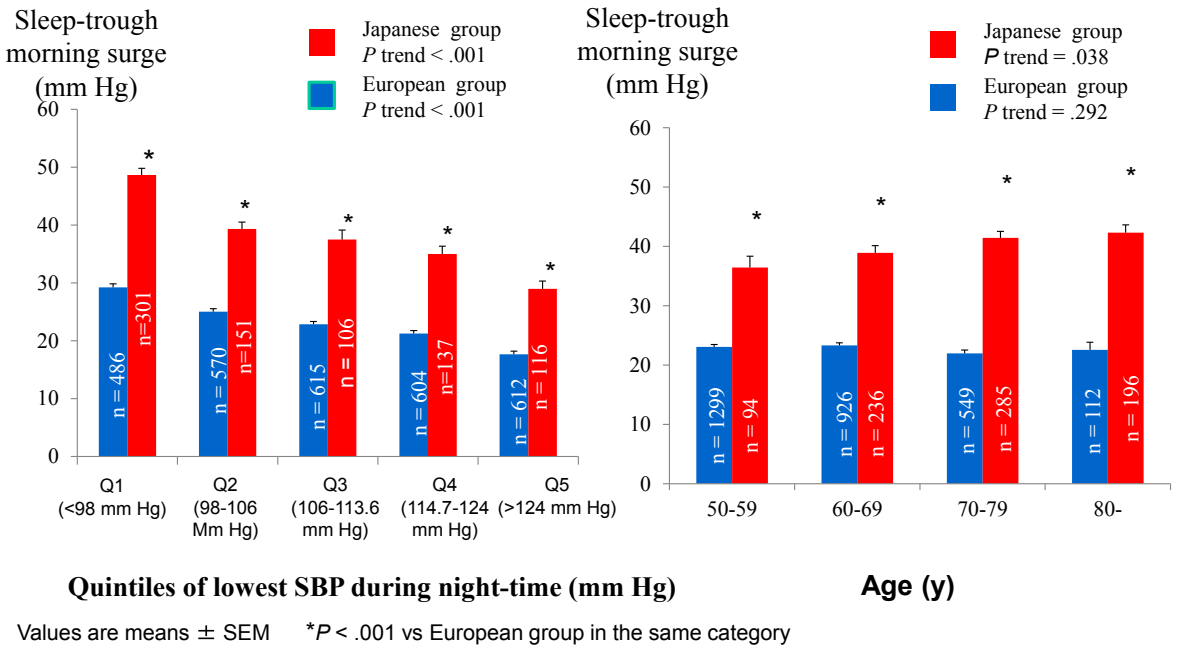

Figure 7. Ethnic differences in the degree of morning BP surge ARTEMIS study (811 Japanese and 2887 whites). *P < .001 vs. European group in the same category. Reproduced with permission from Hoshide S, Kario K, Parati G, et al. Ethnic differences in the degree of morning blood pressure surge and in its determinants between Japanese and European subjects: data from the ARTEMIS study. Hypertension 2015;66:750–6. Abbreviations: BP, blood pressure; SBP, systolic blood pressure.

Great East Japan earthquake (March 2011) to improve BP control in individuals who had been affected by this disaster.

A major disaster increases the thrombophilic tendency and BP, both of which trigger disaster-induced cardiovascular events such as stroke and cardiac events.[43-46] The high salt intake and the increased salt sensitivity caused by disrupted circadian rhythms are the 2 major leading causes of disaster hypertension through neurohumoral activation under stressful conditions.[46] At the time of the Great Hanshin-Awaji earthquake (January 1995), the Awaji-Hokudan public clinic in areas near the earthquake's epicenter reported a disaster-associated increase in BP.[44] Most of the hypertensive patients developed uncontrolled HTN, but their BP levels returned to the previous levels within 1 month after the earthquake. However, some patients (especially those with CKD) developed persistent uncontrolled disaster HTN.[44,47] After the time of the Great East Japan earthquake, marked uncontrolled disaster HTN was observed in people who were housed in the public shelters.

To better assess and reduce the risks for disaster-associated cardiovascular events, a web-based disaster cardiovascular prevention (DCAP) network (which provided a DCAP risk and prevention score assessment and self-measured BP monitoring that could be conducted at a public shelter or at home) was developed for survivors of the 2011 earthquake.[48,49] It had been shown that disaster-induced increases in BP are affected by the white-coat effect (office BP minus home BP), and thus the BP measurement by a disaster medical assistance team (DMAT) or unknown medical staff under stressful conditions in a shelter may tend to result in overestimation; self-measured BP could therefore be considered for

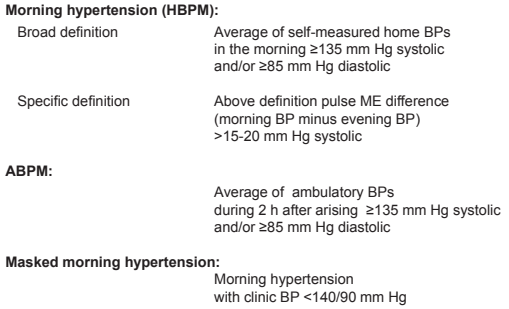

Figure 8. Definition of morning hypertension. Abbreviation: BP, blood pressure.

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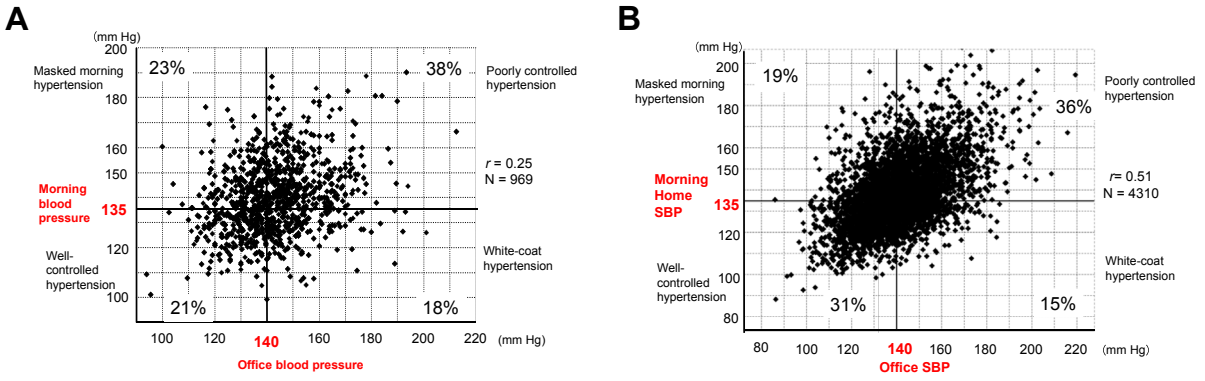

Figure 9. **(A) J-MORE (Jichi Morning Hypertension Research) study; 969 medicated hypertensives (mean age 66.5 y, 42% male) recruited from 45 doctors, 33 clinics. (B) J-HOP (Japan Morning Surge-Home Blood Pressure) study; 4310 medicated hypertensives (mean age 64.9 y, 47% male). Reproduced with permission from Kario K, Eguchi K, Umeda Y, et al. Response to: Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives. Circulation. 2003;108: e72-73. Abbreviation: SBP, systolic blood pressure.**

obtaining more accurate BP values under such conditions.[50] The DCAP network system was developed using cloud computing on the Internet to monitor the individual BP data self-measured at home or at a shelter; this system was introduced to a shelter in one of the most damaged areas (Minami Sanriku).[48,49] The results revealed marked differences between the volunteer-measured BP and the BP self-measured in conjunction with the DCAP system.[46]

In most patients affected by a disaster, the increases in clinic BP and self-measured BP are transient, and BP levels return to the predisaster baseline levels within 4 weeks.[44-46] This characteristic of a disaster-induced BP increase is important because persistent intense antihypertensive treatment for individuals with high BP at the time of a disaster could result in excessive BP reduction, as was observed in a patient who had been started on treatment with antihypertensive agents just after the Great Hanshin-Awaji Earthquake.[51] She was referred to a clinic when she developed dizziness 3 months after the earthquake. Her antihypertensive medication was discontinued and her ambulatory BP level was monitored. It was found to be normal and her symptoms disappeared. Thus, it is recommended that the BP levels of individuals who are affected by a disaster be monitored ideally by self-measured BP in the disaster shelter or at home, and the dose of antihypertensive medication should be reconsidered every 2 weeks during the disaster situation.

Additionally, compared with the Hanshin-Awaji Earthquake in 1995, the pressor effect of the East Japan Earthquake in 2011 lasted longer because of the greater and more complex damage caused by the combination of the tsunami and the accident at the Fukushima nuclear plant. In

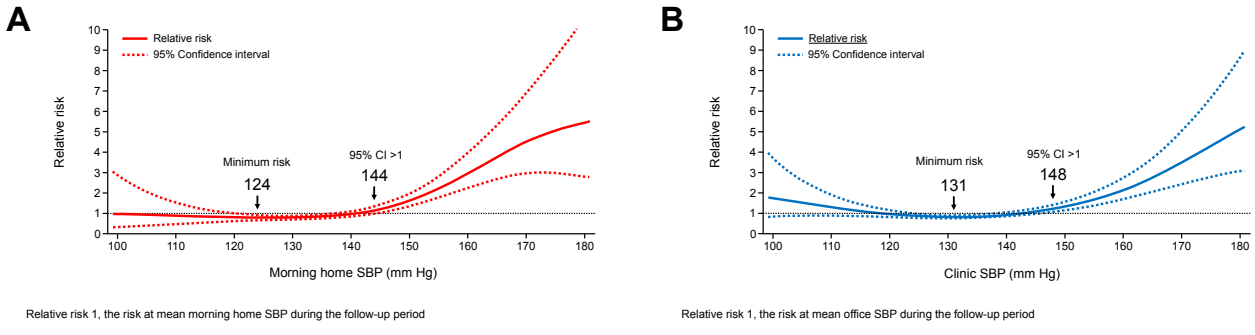

Figure 10. **(A) Minimum and statistically significant increase in cardiovascular risk for morning home blood pressure by spline regression analysis. Adjusted for sex, age, family history of cardiovascular disease, dyslipidemia, diabetes mellitus, chronic kidney disease, history of cardiovascular disease, and smoking status. (B) Minimum and statistically significant increase in cardiovascular risk of office blood pressure by spline regression analysis. Adjusted for sex, age, family history of cardiovascular disease, dyslipidemia, diabetes mellitus, chronic kidney disease, history of cardiovascular disease, and smoking status. Reproduced with permission from Kario K et al.[9] Abbreviation: SBP, systolic blood pressure.**

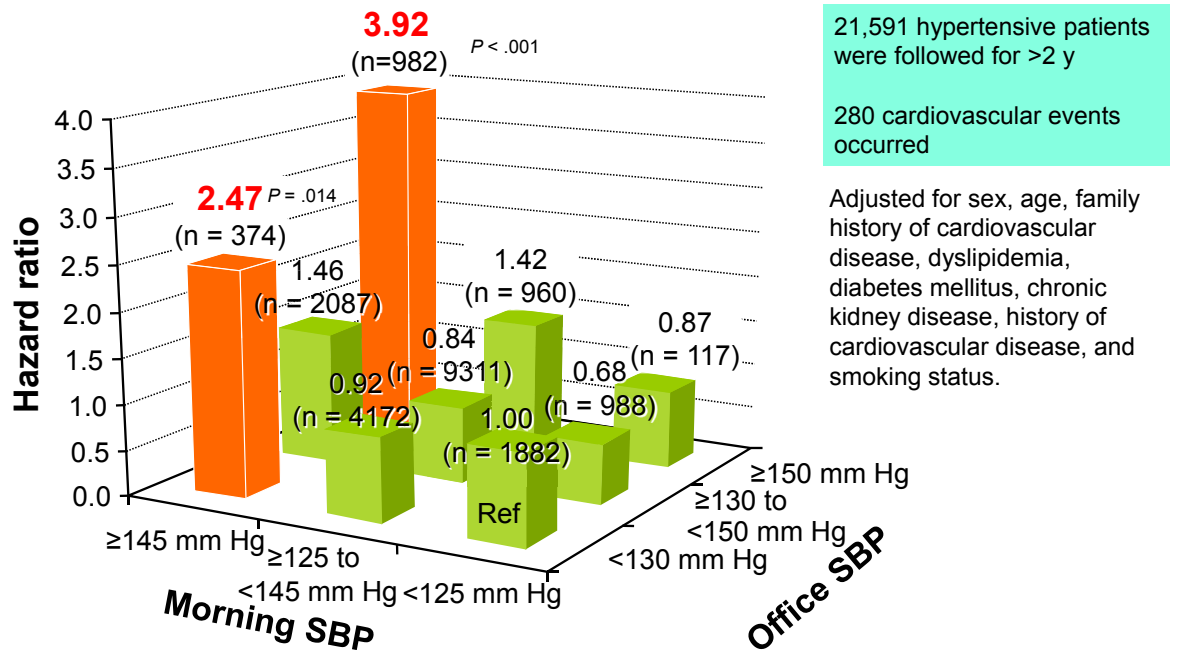

Figure 11. Impact of morning home SBP and clinic SBP on cardiovascular events (HONEST study). Reproduced with permission from Kario K et al.[9] Abbreviation: SBP, systolic blood pressure.

an ABPM study of 8 patients who lived in the disaster area, conducted on the day of the largest aftershock with the first tsunami warning (sirens) on December 7, 2012—21 months after the Great East Japan Earthquake—there was a pressor effect followed by increased nocturnal and morning BP levels.[52] The nocturnal and morning BP levels were significantly higher in those living in temporary housing at the time compared with those living in their own homes. The stress of the change in living conditions following the disaster might have contributed to an increased risk for cardiovascular events.

We continued to monitor home BP using the DCAP system in the outpatients of the Minami Sanriku clinic for at least 4 years. After the earthquake, the outpatients' home BP levels gradually decreased and reached about <125 mm Hg, resulting in an approximately 50% reduction of cardiovascular events in this geographic area. The successful use of the DCAP network in the Minami Sanriku area validates our introduction of an ICT-based home BP-guided approach for the management of HTN with the goal of reducing the incidence of cardiovascular events.

Nocturnal Hypertension. The pattern of circadian rhythms of BP can be evaluated by ABPM. In healthy individuals, nocturnal BP decreases by 10% to 20% of their daytime BP; this is the normal dipper pattern. The nocturnal BP fall tends to be diminished with advancing age. Hypertensive patients without organ damage also exhibit the dipper pattern, but those with organ damage tend to exhibit a nondipper pattern with a diminished nocturnal BP reduction. The recent guidelines for the management of HTN classify the dipping patterns of nocturnal BP into 4 groups: dipper, nondipper, riser, and extreme dippers (Fig. 13).[2,5,19,21] The definitions of these groups are based on the night-time BP dipping.

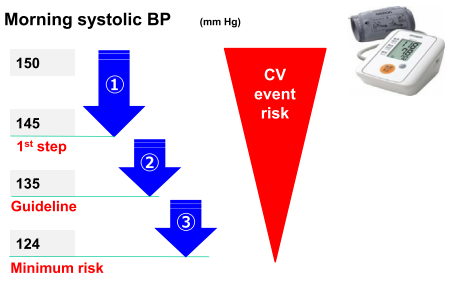

Figure 12. Home blood pressure-based antihypertensive strategy for morning hypertension. Reproduced with permission from Kario K.[13] Abbreviations: CV, cardiovascular; SBP, systolic blood pressure.

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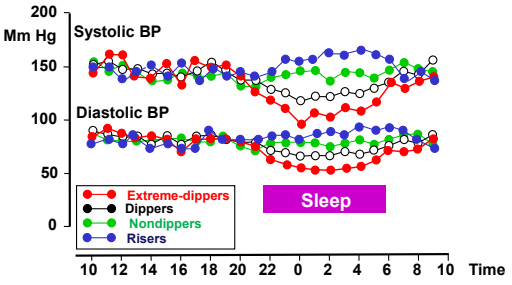

Figure 13. **Four different dipping statuses of nocturnal blood pressure in hypertensive patients. Reproduced with permission from Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. Hypertension 2001;38:852–7. Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.**

O'Brien et al. first documented the nondipping concept associated with advanced organ damage.[53] Shimada et al. were the first to demonstrate that in elderly hypertensive patients, the nondipper pattern of nocturnal BP fall is associated with both advanced silent cerebral diseases such as silent cerebral infarcts and deep white-matter lesions, both of which were detected by brain MRI.[54] We first used the term *risers* to describe the extremely disrupted circadian BP rhythm of higher night-time BP than daytime BP,[55] and the term *extreme dippers* to describe the disrupted circadian BP rhythm with an exaggerated nocturnal BP fall by 20% or more of daytime BP.[56] Some authors use the term *reverse dipper* or *inverted dipper* rather than riser. In our study, extreme dippers had advanced silent cerebral disease and an increased risk for future clinical stroke (Fig. 14).[56,57]

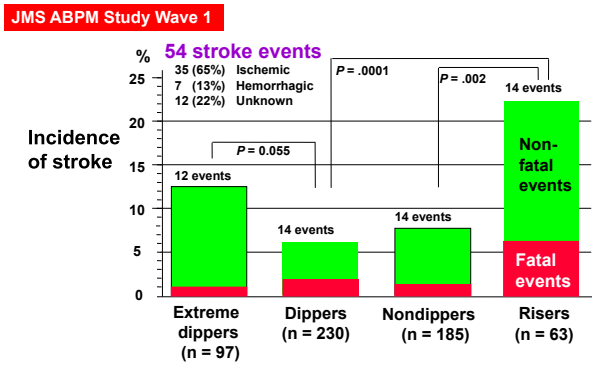

Figure 14. **Nocturnal blood pressure dipping status and stroke prognosis in older sustained hypertensives. Reproduced with permission from Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. Hypertension 2001;38:852–7. Abbreviations: ABPM, ambulatory blood pressure monitoring; JMS, Jichi Medical School.**

Nocturnal HTN could be partly overlapping with morning HTN when nocturnal HTN persists until the morning. Thus, there are 2 types of morning HTN detected by HBPM (Fig. 15).[58] One is the morning surge, which exhibits an exaggerated morning BP surge (morning BP minus the lowest nocturnal BP of >35–55 mm Hg systolic), and the other is the sustained nocturnal hypertension type with continuous HTN from nocturnal HTN (nondipper/riser type, nocturnal BP of ≥120/70 mm Hg). Both types have different associated conditions, and both are risks for CVD and renal disease, through different pathogenic mechanisms.

The definition of nocturnal HTN is shown in Figure 16. Nocturnal HTN is diagnosed by the average of nocturnal BP values of ≥120/70 mm Hg. Nondippers and risers are likely to exhibit nocturnal HTN. To differentiate these 2 types, the ME-dif calculated using home BP values conventionally measured in the morning and in the evening is not useful. Only the direct measurement of nocturnal BP during sleep traditionally by ABPM and that obtained by the recently developed home nocturnal BP monitoring with a timer can differentiate the 2 subtypes.

Population-based and clinical studies using ABPM demonstrated that night-time BP is a better predictor of CVD than daytime BP, especially in medicated hypertensive patients.[59,60] Patients with nocturnal HTN with higher night-time BP and a nondipper/riser pattern with higher nighttime BP than awake BP (even if their clinic and 24-hour BP values indicate normotension), are reported to be at risk for organ damage and subsequent cardiovascular events.[61-64]

Increased circulating volume, autonomic nervous dysfunction, and poor sleep quality are the 3 major mechanisms of nocturnal HTN exhibiting nondipper and riser patterns.[13] Increased circulating volume may compensatorily increase the nocturnal BP (in addition to daytime BP) to excrete sodium from the kidney, based on Guyton's theory of a pressure-natriuresis relationship, resulting in nocturnal HTN of the nondipper/riser type.[65] Thus the conditions with increased sympathetic nervous activity and renin-angiotensin-aldosterone system increase the circulating volume due to reduced sodium excretion, resulting in the nondipper/riser type of nocturnal HTN. The effect of the activation of neurohumoral factors due to orthostatic hypotension during the daytime may persist in the supine position during sleep. Causes of poor sleep quality such as sleep apnea, insomnia in the elderly, depression,[66] shift work, etc., contribute to nocturnal HTN.

DEVELOPMENT OF HOME NOCTURNAL BP MONITORING

Basic Nocturnal BP Monitoring at Home. Traditionally, ABPM has been the only method to measure nocturnal BP during sleep. We recently developed a semiautomatic nocturnal HBPM device with the function of automatic fixed-interval BP measurement during sleep (Medinote, Omron Healthcare Inc., Kyoto, Japan).[7] Patients are instructed to put the Medinote's cuff on their arm just before going to bed, and the Medinote then automatically measures the wearer's BP at fixed intervals during sleep. We first introduced this HBPM device in cohort studies.[67,68] The BP data are stored in the device's memory file. The development of the Medinote was the first step in obtaining basic nocturnal BP information using self-measured home BP monitoring in a method other than ABPM. The development of the Medinote has now advanced to another new IT-based nocturnal BP monitoring device, the HEM-7252G-HP.

The J-HOP study enrolled the largest nationwide home BP cohort to date and used the Medinote.[40,67,68] In that study, the nocturnal home BP of 2562 participants was monitored using this device 3 times during sleep (at 2, 3, and 4 AM) as well as 3 times each in the morning and evening for 14 days. The results indicated that the self-measurement of nocturnal BP at home is feasible (Fig. 17).[68] There was no significant difference between the nocturnal home SBP levels at 2 and 3 AM, whereas the 4 AM levels were slightly but significantly higher by 1.5 mm Hg ($P < .0001$). Thus, we defined nocturnal home BP as the average of 3 nocturnal BP values measured at 2, 3, and 4 AM.

In the J-HOP study, the participants' sleep home SBP was significantly correlated with the urinary albumin-to-creatinine ratio (UACR), the left ventricular mass index, the brachial-ankle pulse wave velocity, the maximum carotid intima-media thickness, and the plasma N-terminal pro-hormone brain natriuretic peptide (NTproBNP) and high-sensitive cardiac troponin T levels (Fig. 18).[68] Additionally, nocturnal home BP was significantly correlated with organ damage independently of clinic, morning, and evening BP values. Even among the participants with well-controlled morning home SBP of <135/85 mm Hg, 27% exhibited masked home nocturnal HTN with nocturnal home SBP of >120 mm Hg (Fig. 19),[68] and they had higher UACR and NTproBNP values.

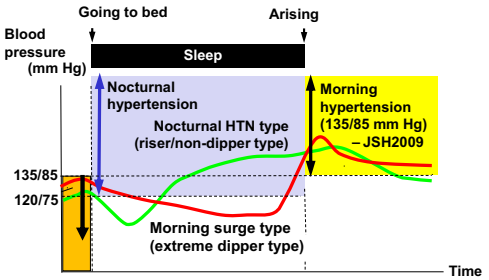

Figure 15. Two types of morning hypertension. Reproduced with permission from Kario K. Time for focus on morning hypertension. Am J Hypertens 2005;18:149–51. Abbreviation: HTN, hypertension.

In the J-HOP subanalysis, nocturnal home BP values obtained were almost the same as those of nocturnal BP values obtained by ABPM,[67] and the association with organ damage (left ventricular hypertrophy [LVH] and microalbuminuria) was greater for nocturnal home SBP than for nocturnal SBP detected by ABPM.[67] Nocturnal home BP was a better indicator of BP control during antihypertensive treatment. In the J-TOP (Japan Morning Surge-Target Organ Protection) trial, the reduction of nocturnal home BP was more closely associated with the regression of LVH evaluated by cardiac echography and electrocardiography.[50]

These study results indicate that even after morning BP is well controlled by a conventional home BP-guided approach, the remaining nocturnal uncontrolled HTN should be a target of future antihypertensive treatment.

A "Thermosensitive HTN"-detecting Home BP Device. The HEM-7252G-HP includes a thermosensor within the device. BP is partly associated with temperature. The morning BP level in particular is closely determined by cold temperatures,

Nocturnal hypertension:
Average of night-time BPs* ≥120 mm Hg systolic or ≥ 85 mm Hg diastolic

Masked nocturnal hypertension:
Nocturnal hypertension with clinic BP <140/90 mm Hg

Masked home nocturnal hypertension:
Nocturnal hypertension with home morning BP <135/85 mm Hg

Isolated nocturnal hypertension:
Nocturnal hypertension with clinic BP <140/90 mm Hg and home morning BP <135/85 mm Hg

Figure 16. Definition of nocturnal hypertension. *Night-time BP are BPs measured when going to bed to arising or between 1 and 6 AM by ABPM or HBPM (≥3 readings/1 night). Abbreviations: ABPM, ambulatory blood pressure monitoring; BP, blood pressure; HBPM, home blood pressure monitoring.

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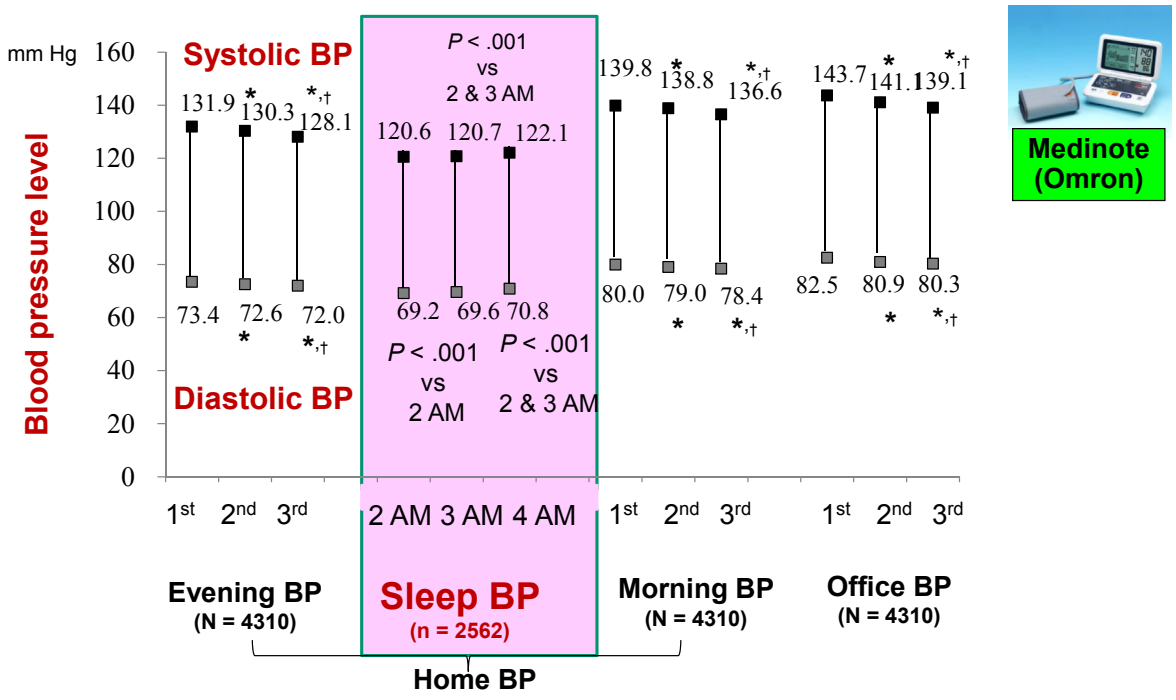

Figure 17. Home BP levels in the J-HOP study. Reproduced with permission from Kario K et al.[68] Abbreviation: BP, blood pressure.
***P<.001 vs first measurement.**
†P<.001 vs second measurement by paired t test. Home BPs were self-measured three times during sleep, three times in the morning, and three times in the evening, and the average for each time point is shown.

especially in the elderly. However, this characteristic varies among different hypertensive patients. The term *thermosensitive HTN*[13,34] is used here to define the HTN status in which home BP is closely determined by the seasonal change of temperature (eg, R^2 >0.3, change of morning SBP >10 mm Hg/10°C) (Fig. 20).[13] Patients with thermosensitive HTN may exhibit a winter morning surge in BP,[69] resulting in an increased rate of cardiovascular events in the winter.

ICT-based Triggering of Home Nocturnal BP Monitoring. The concept of "triggered BP measurement" in home BP monitoring was recently introduced.[7,13] Prior to this concept, no home BP device existed that could measure BP at a trigger signal of specific conditions. The concept of triggered BP measurement aims to repeatedly measure BP levels and BP variability related to risky situations. As one of the benefits of HBPM is repeated measurement, we hypothesized that repeated BP measurements could increase the ability to detect cardiovascular risk-related abnormal BP peaks.

We developed trigger home nocturnal BP monitoring (TNP), which was based on the automated fixed-interval measurement technique of the Medinote with an added trigger function that initiates BP measurement when the Medinote wearer's oxygen desaturation falls below a variable threshold that is continuously monitored by pulse oximetry.[7,13,70-73] TNP can detect the specific nocturnal BP surges triggered by hypoxic episodes in patients with obstructive sleep apnea syndrome (OSAS).

The nocturnal BP profile of ABPM in patients with OSAS is characterized by nocturnal HTN with the nondipper/riser pattern, increased sleep BP variability, and exaggerated morning BP surge.[72] However, neither the previous HBPM nor ABPM could detect augmented nocturnal BP or the nocturnal BP surge specific to each sleep apnea episode. In patients with OSAS, exaggerated nocturnal BP surges triggered by hypoxic episodes during sleep were successfully detected by the TNP method of monitoring (Fig. 21).[13] Exaggerated nocturnal BP surges may partly explain why sleep-onset cardiovascular events occur more frequently during sleep.

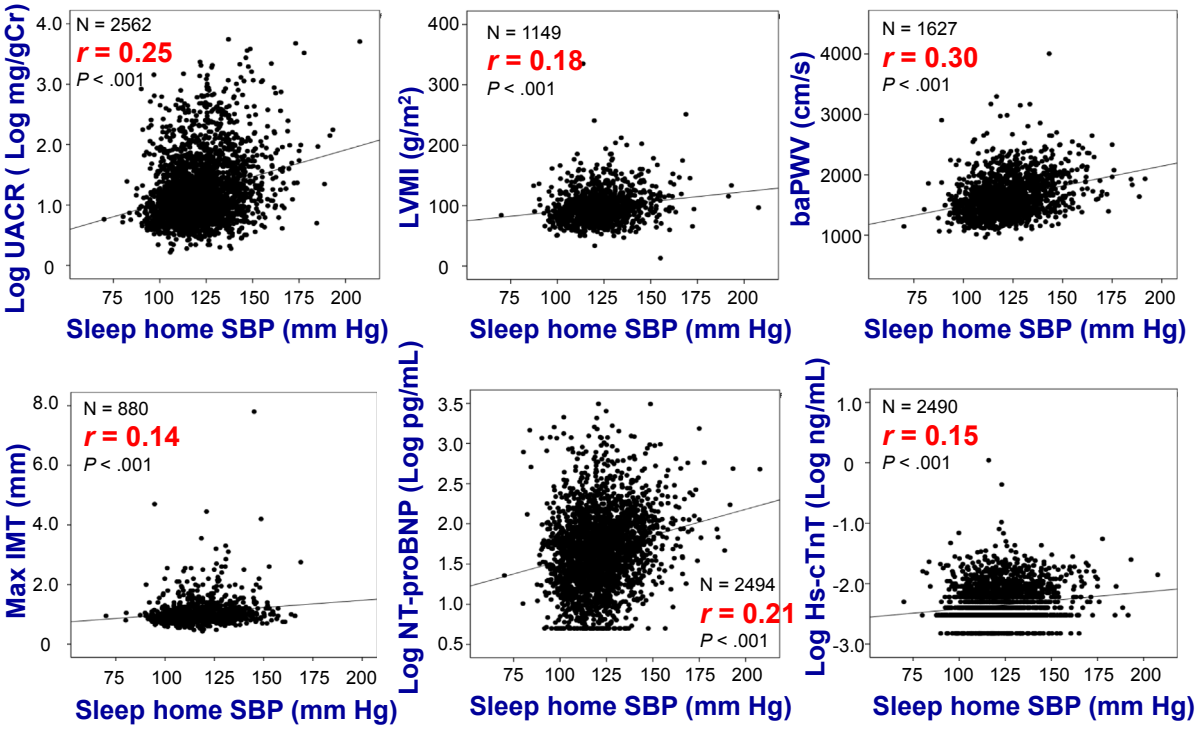

Figure 18. **Association of home nocturnal BP and organ damage. Abbreviations: baPWV, brachial-ankle pulse-wave velocity; BP, blood pressure; HS-cTnT, high-sensitivity cardiac troponin T; IMT, intima-media thickness; LVMI, left ventricular myocardial infarction; NT-ProBNP, N-terminal pro-hormone brain natriuretic peptide; SBP, systolic blood pressure; UACR, urinary albumin-to-creatinine ratio.**

We also added a trigger function based on the lowest heart rate to detect the basal BP (see Fig. 21).[13] The definition of the basal BP is the nocturnal BP values measured by the trigger signal based on the lowest heart rate during sleep. The basal BP is the sleep BP with the lowest sympathetic drive, and it is predominantly determined by the circulating blood volume and structure of the vasculature.

The pathophysiology of nocturnal HTN is heterogeneous. The TNP method measuring double-trigger signals (hypoxia and heart rate) was able to identify 2 selective nocturnal BPs with different clinical implications (ie, sympathetic activity-related BP and cardiovascular structure-determined basal BP). Thus, using TNP may help select the class of antihypertensive drugs for more effective control of nocturnal HTN with a different pressor mechanism. ABPM using fixed-interval measurements could not differentiate nocturnal BP values with these different pressor mechanisms.

In a 2014 study of TNP, the bedtime dosing of nifedipine and carvedilol significantly reduced all of the measures of nocturnal BP, although the nocturnal BP-lowering properties of these 2 drugs are different.[71] Compared with nifedipine, carvedilol comparably reduced the peak nocturnal BP, while it significantly but less extensively reduced basal BP, resulting in a significant suppression of hypoxia-induced nocturnal BP surges.[71]

An ICT-based nocturnal BP monitoring system (ITNP) with oxygen and heart rate triggers and a 3G web system was recently developed (Fig. 22).[73] The ITNP system is a cloud computing-based composite management and analysis system for the data sent from the BP device in the patient's home. This system can detect repeated and day-by-day variabilities in nocturnal BP as well as morning BP, basal nocturnal BP, and nocturnal BP surges associated with sleep apnea episodes, the degree of which can be affected by daily environmental changes. Using this ITNP, a prospective study, SPREAD (Sleep Pressure and Disordered Breathing in Resistant Hypertension and Cardiovascular Disease), was initiated to study the clinical implications of nocturnal BP and nocturnal BP surges in high-risk patients with resistant HTN and/or CVD.

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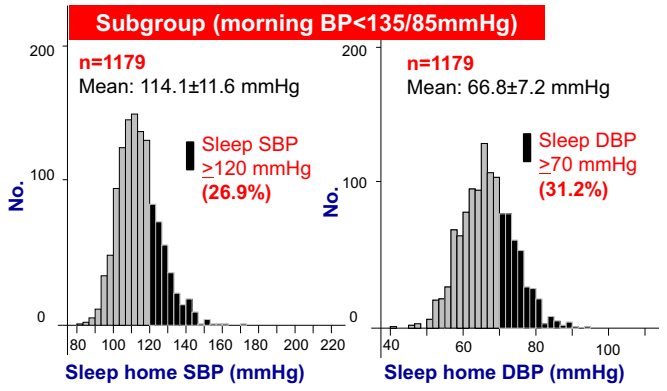

Figure 19. Distribution of home nocturnal BP levels. Reproduced with permission from Kario K et al.[68] Abbreviations: BP, blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

The repeated assessment of sleep apnea syndrome (SAS) using ITNP in a real-life setting increases the sensitivity of the diagnosis of SAS and the related nocturnal BP surge. One-day polysomnography in alcohol-prohibited conditions in hospitals may underestimate the severity of OSAS and may miss individuals with moderate SAS. The participants of the SPREAD study with mild to moderate SAS exhibited significant night-by-night variability of the degree of apnea/hypopnea episodes. These patients exhibited apnea/hypopnea more frequently, and their nocturnal BP values and nocturnal BP surges increased on their alcohol-intake days.[13]

The ITNP system also can evaluate the efficacy of continuous positive airway pressure (CPAP). Effective CPAP reduces the mean nocturnal SBP.

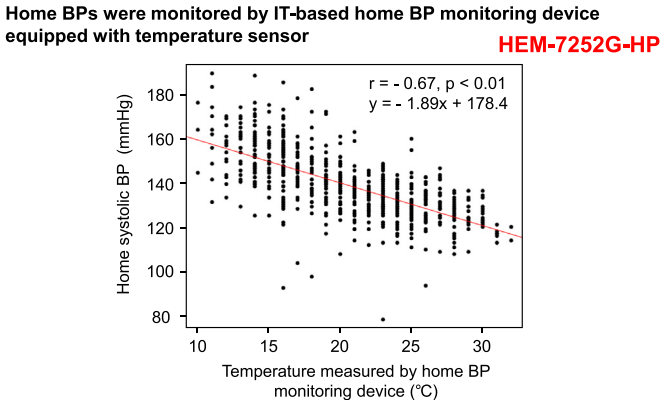

Figure 20. Correlation between room temperature and home BP in an 82-year-old woman. Abbreviations: BP, blood pressure; HBPM, home blood pressure monitoring; IT, information technology.

This reduction was markedly greater when evaluated by measuring the hypoxia-peak nocturnal SBP.[13] Even in an OSAS patient with well-controlled mean nocturnal SBP, approximately 50% of the hypoxia-triggered peak nocturnal SBP values were >140 mm Hg. After bedtime, the dosing of nifedipine reduced both the mean and hypoxia-peak SBP values.

The ITNP system will contribute to the detection of high-risk SAS patients with nocturnal HTN and/or a nocturnal BP surge, and to assessments of the quality of BP control during the use of CPAP and/or antihypertensive treatment in SAS patients. Strict BP control throughout the 24-hour day including the nocturnal BP and hypoxia-induced peak would effectively suppress the development of organ damage and cardiovascular events in OSAS patients. An ITNP system would contribute to achieving this goal.

SHATS AND THE SYNERGISTIC RESONANCE OF BP VARIABILITY

In recent guidelines, the diagnosis and management of HTN are based on the average of BP values, even those measured by different BP measurements (eg, office, home, and ambulatory BP measurements). However, there are various types of BP variability with different time intervals from short- to long-term forms (Fig. 23).[34] These include beat-by-beat, orthostatic, physical, or psychological stress-induced, diurnal, day-by-day, visit-to-visit, seasonal and yearly BP variability, and clinically these are detected by different office, home, and ABPM methods.[34,74]

Evidence that increased BP variability presents a risk for organ damage and cardiovascular events—independently of the average of BP levels—is accumulating.[34,74-76] BP variability is considered the master biomarker of human health care because it is not only a modifiable risk factor of organ damage and CVD but also a sensor of cardiovascular dysregulation that is affected by individualized characteristics and stressors of daily behavioral factors and environmental conditions. Almost all of the phenotypes of BP variability are partly correlated with each other and are reported to be cardiovascular risk factors.[13,34,77-79]

A novel disease entity, systemic hemodynamic atherothrombotic syndrome (SHATS), was recently proposed.[7,13,34,73,77,80,81] It is characterized by a vicious cycle between hemodynamic stress (BP variability, blood flow variability, pulse-wave form) and

vascular disease and is a risk factor for organ damage and cardiovascular events (Fig. 24). The phenotypes of BP variability in SHATS can be detected by home BP monitoring, ABPM, the active standing test, and so on. The novel contribution of SHATS is its synergistic consideration of various types of BP variability and hemodynamic stress in relation to vascular disease. Vascular disease, especially large artery disease, will augment the effects of exaggerated BP variability on atherosclerotic and small artery-related cardiovascular events. An increase in large artery stiffness decreases the attenuation of pulses transmitted to the peripheral arteries, resulting in advancing organ damage and the triggering of cardiovascular events at peripheral sites.

Increases in BP variability, central BP, and impaired baroreceptor sensitivity are the 3 BP measures of SHATS, and they are closely related. The overall underlying mechanism of SHATS may include impaired neural and vascular components of the baroreflex due to increased central sympathetic activity and decreased carotid dispensability, respectively. Additionally, small artery remodeling as well as large artery disease contribute to increases in BP variability. Arterial stiffness and pressure wave reflections are 2 important components of pulsatile hemodynamics. The measurements of ambulatory BP, including morning BP surge, can reflect pulsatile hemodynamics as influenced by arterial stiffness and wave reflections. The degree of central and peripheral neurohumoral activation and their related cardiovascular reactivity in each specific condition may determine the different phenotypes of BP variability.

The clinical relevance of SHATS is different between younger and older patients. SHATS is clinically important for predicting future sustained HTN in younger patients. The early detection of SHATS may sound an alert for the prevention of organ damage at this early stage. In older patients, SHATS is important as a direct risk for triggering cardiovascular events. The suppression of SHATS leads directly to a reduction in the rate of cardiovascular events. Nonetheless, the concept underscores that clinicians should recognize the synergistic risk posed by exaggerated BP variability and vascular damage in clinical practice.

Morning BP surge is one of the several types of BP variability.[34] Morning BP surge can be potentiated by a synergistic resonance of various components of BP variability, resulting in morning-onset cardiovascular events (Fig. 25).[82] In individuals with SHATS, a synergistic resonance among the morning BP surge and different types of BP variability may occur and could trigger cardiovascular events. In ABPM studies, the morning BP surge was exaggerated in the winter, especially in elderly patients (the winter morning surge in BP)[69] and on Mondays (the Monday morning surge in BP).[83] These changes in the morning BP surge may contribute to the increase in cardiovascular events in the winter among the elderly and on Mondays among working adults. Maximum SBP, one of the measures of day-by-day HBPM most frequently observed in the morning, has been reported to be significantly associated with measures of cardiovascular remodeling (ie, the left ventricular mass index and carotid intima-media thickness) even in hypertensives with a well-

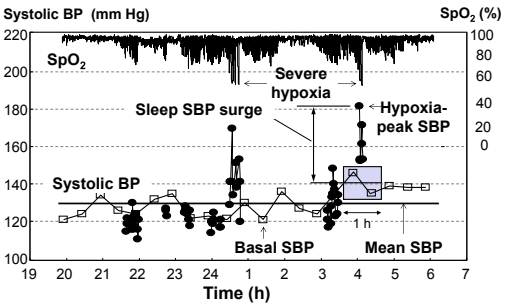

Figure 21. Definition of nocturnal blood pressure parameters by trigger nocturnal blood pressure monitoring (TNP). Reproduced with permission from Kario K, et al.[71] Abbreviation: SBP, systolic blood pressure.

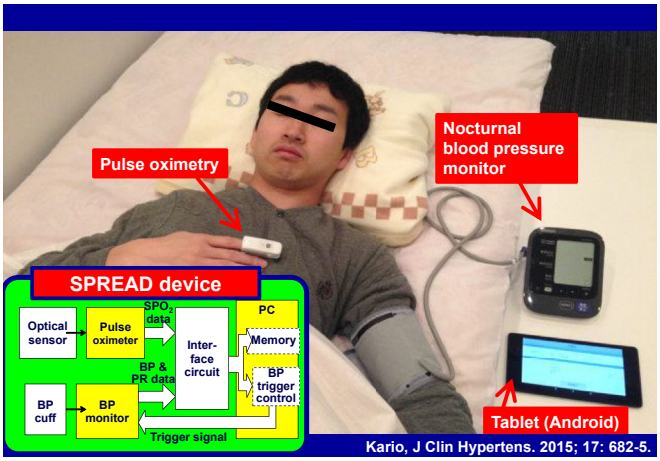

Figure 22. IT-based trigger nocturnal home blood pressure monitoring system with oxygen and heart rate triggers and Cloud system (ITN1, 2015) (Jichi Medical University, Omron Healthcare Co., Kyoto, Japan). Reproduced with permission from Kario, Hamasaki.[73] Abbreviations: BP, blood pressure; IT, information technology.

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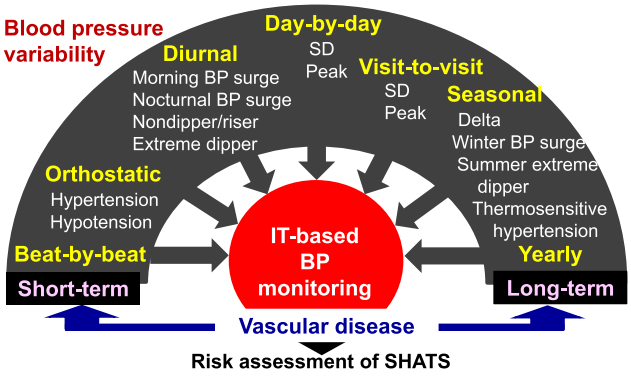

Figure 23. IT-based assessment of BP variability and vascular damage for SHATS. Reproduced with permission from Kario K.[34] Abbreviations: BP, blood pressure; IT, information technology; SHATS, systemic hemodynamic atherothrombotic syndrome.

controlled average of home BP of <135/85 mm Hg.[84] Additionally, the increased SD of morning BP is a significant independent predictor of cardiovascular death.[75] Thus, an unstable morning BP surge synergistically augmented by the resonance of other phenotypes of BP variability may be more likely to advance organ damage and trigger cardiovascular events than a stable and reproducible morning BP surge.

ANTIHYPERTENSIVE MEDICATION

In Japan, the most commonly used classes of antihypertensive drugs are calcium channel blockers (CCBs) and angiotensin receptor blockers (ARBs), as shown in the J-HOP study.[40] It is important to choose a long-acting antihypertensive drug with a longer half-life, such as amlodipine.[13] The BP-lowering effect of a CCB is independent of salt sensitivity and salt intake. Thus, a CCB is one of the most efficacious antihypertensive drugs for Asian patients. In fact, the ACS1 (Azilsartan Circadian and Sleep Pressure—the First Study) trial, a multicenter, randomized, open-label, 2-parallel group study comparing the effects of an ARB-II (azilsartan) and a CCB (amlodipine) demonstrated that amlodipine was superior to azilsartan for reducing ambulatory BP in hypertensive Japanese patients.[85]

A CCB lowers the higher baseline BP level more extensively than other antihypertensive drugs of the different class including renin-angiotensin system (RAS) inhibitors; however, it does not reduce the low baseline BP very much, resulting in reduced BP variability. Thus, a CCB seems to be the best choice for older patients with structural HTN with increased BP variability. On the other hand, a RAS inhibitor would be preferable for younger metabolic hypertensive patients with neurohumoral activation. Some guidelines concerning the management of HTN recommend selecting different drugs depending on the patient's age, but no studies, to our knowledge, have investigated the relationship between drug selection and age-related differences. In fact, the ACS1 trial demonstrated that azilsartan was superior to amlodipine for achieving a successful BP control rate in younger hypertensives.[85]

To further clarify the age- and sex-related differences in the ambulatory BP-lowering effect of CCBs and ARBs between younger adult hypertensives and older hypertensive patients, we conducted a post hoc analysis of the ACS1 results, and observed that azilsartan significantly reduced DBP values in the men <60 years compared with amlodipine, but amlodipine significantly reduced the SBP values in women ≥60 years compared with azilsartan.[86] Antihypertensive strategies considering these age- and sex-related differences in the BP-lowering effect of CCBs may increase cost-effectiveness in the long-term management of HTN.

The combination therapy of an ARB and a CCB is more frequently used than that of an ARB and a diuretic. Even the combination of an ARB with a small dose of diuretics is effective in Asians with higher salt intake and higher salt sensitivity.[87] There is a difference in diurnal BP-lowering effects between CCBs and diuretics. The use of a diuretic

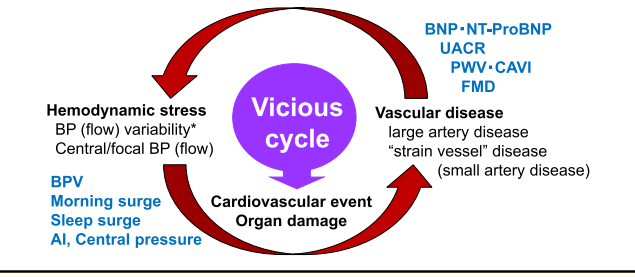

Figure 24. Systemic hemodynamic atherothrombotic syndrome (SHATS). *Acceleration of the risk for cardiovascular events and organ damage via a vicious cycle of hemodynamic stress and vascular disease. (Kario K. Editorial. Am J Hypertens 2014). Abbreviations: AI, augmentation index; BP, blood pressure; BPV, blood pressure variability; BNP, brain natriuretic peptide; CAVI, cardio-ankle vascular index; FMD, flow mediated dilation; NT-ProBNP, N-terminal pro-hormone brain natriuretic peptide; PWV, pulse-wave velocity; UACR, urinary albumin-to-creatinine ratio. Ref. Reproduced with permission from Kario K. Orthostatic hypertension—a new haemodynamic cardiovascular risk factor. Nat Rev Nephrol 2013;9:726–38.

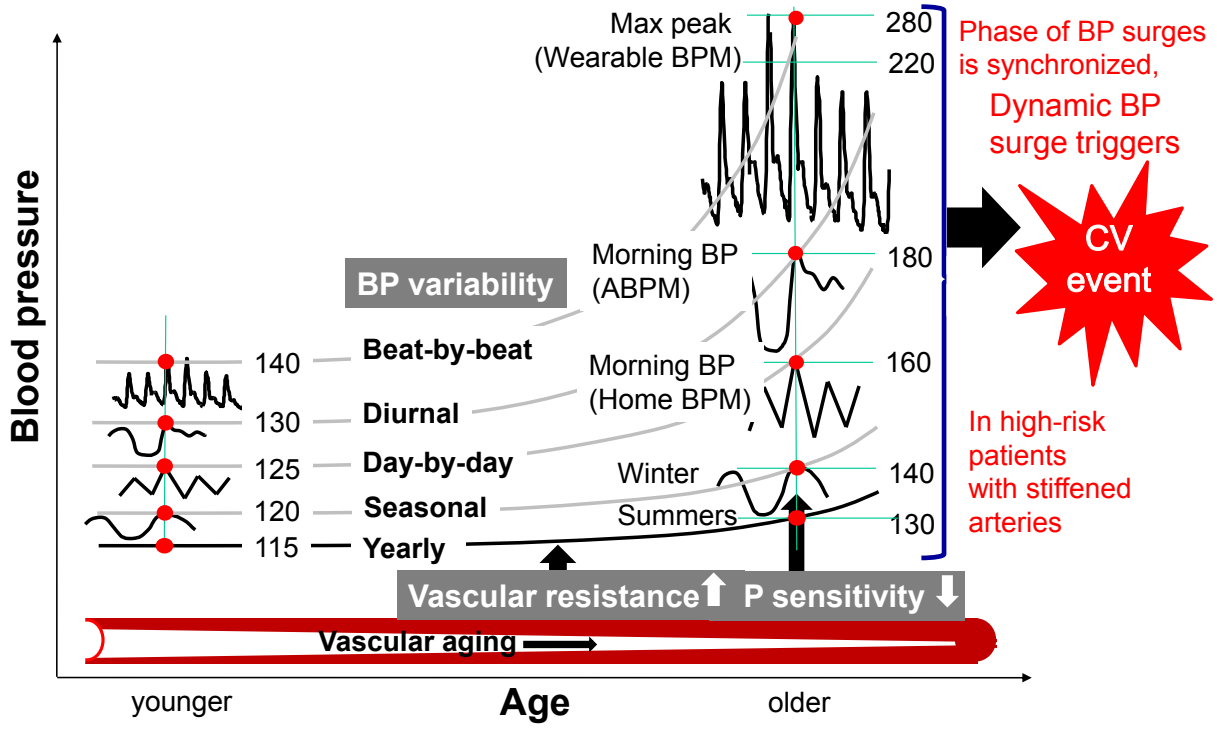

Figure 25. **The synergistic resonance of BP variability hypothesis. Reproduced with permission from Kario K.[82] Abbreviations: ABPM, ambulatory blood pressure monitor; BP, blood pressure; BPM, blood pressure monitor; CV, cardiovascular; HBPM, home blood pressure monitor.**

both as monotherapy and in ARB-diuretic combination therapy is more effective for reducing nocturnal BP, whereas CCB use is more effective for reducing higher daytime BP levels and BP variability.[88,89]

The bedtime dosing of antihypertensive drugs would be effective for reducing morning and nocturnal BP values, resulting in target organ protection. In the JMS-1 (Japan Morning Surge-1) study, the bedtime dosing of doxazosin reduced morning BP values and the UACR, and the reduction of the UACR was independent of the reduction of BP.[90] In the J-TOP study, the bedtime dosing of candesartan was more effective for reducing the UACR than morning dosing, even when the morning BP-lowering effects of bedtime and morning dosing were comparable.[91] In ARB combination therapy with a diuretic or CCB[92] and bedtime or morning dosing therapy,[93] the reduction of nocturnal BP is critically important for reducing the UACR.

A catheter-based renal denervation technique was recently introduced for the management of drug-resistant HTN. The HTN-1 and HTN-2 trials demonstrated a marked office BP reduction by renal denervation,[94,95] but the HTN-3 controlled trial using a sham group demonstrated no significant office BP-lowering effect by renal denervation compared with a sham group.[96] We conducted the HTN-J trial with Japanese patients with drug-resistant HTN.[97] In the HTN-J, the renal denervation arm tended to show more lowering of the 24-hour SBP compared with the control arm. But the trial was stopped because of the negative results of the HTN-3 trial. The SPYRAL HTN global trial is currently underway and is being conducted to determine the 24-hour BP-lowering effect of renal denervation in the absence and presence of antihypertensive medication.[98]

In the ABPM analysis of the combined data of the HTN-3 and HTN-J trials, renal denervation significantly reduced morning and nocturnal BP values, whereas it did not reduce daytime BP.[99] This can be partly explained by the close association between morning HTN and increased sympathetic activity. Asians are more likely to have an increased morning BP surge than Westerners, even among those with similar office BP values. Nocturnal

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HTN is frequently observed in patients with OSAS, who are likely to have increased sympathetic activity. In a recent study of OSAS patients, the sleep apnea-associated nocturnal BP peak was significantly suppressed by renal denervation.[100]

PERSPECTIVES

Practically, morning BP seems to be the most important target for antihypertensive treatment in current clinical practice for the management of HTN. The morning BP surge is one of the phenotypes of BP variability of SHATS. The specific treatment of morning HTN consists of selecting the optimal long-acting antihypertensive drug(s) and bedtime dosing. HBPM is the best method for diagnosing morning HTN and for the assessment of BP variability of SHATS. ICT-based HBPM and evaluation systems in combination with the evaluation of vascular disease may be feasible, and a morning BP-guided antihypertensive strategy would be more effective in clinical practice.

Ideally, wearable beat-by beat continuous BP monitoring is the best means of assessing all BP variabilities. Thus, in the future, the management of HTN based on the simultaneous assessment of the resonance of all of the BP variability phenotypes using wearable surge BP monitoring with an ICT-based big data analysis system will contribute to the ultimate individualized anticipation medication' for CVD.[101]

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