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CARDIOVASCULAR RISK AND HYPERTENSION (PW DE LEEUW AND AH GRADMAN, SECTION EDITORS)

Nocturnal Blood Pressure, Morning Blood Pressure Surge, and Cerebrovascular Events

Yuichiro Yano · Kazuomi Kario

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Abstract Cerebrovascular disease is a common cause of death and major cause of disability worldwide. Even in silent cases (e.g., silent cerebral infarction, white matter lesion), cerebrovascular disease can lead to physical and cognitive impairment, thereby substantially reducing the activities of daily living. Accordingly, the earliest possible action to prevent not only symptomatic but also silent cerebrovascular disease has become a major public health challenge. Hypertension is a potent risk factor for both symptomatic and silent cerebrovascular disease. Twenty-four–hour blood pressure (BP) rather than office BP is closely associated with cerebrovascular disease and/or poor physical and cognitive function. In particular, nocturnal BP and morning BP surge have attracted much attention as risk factors for cerebrovascular diseases independently of 24-h BP level. This review is an attempt to summarize some of the evidence on nocturnal BP level or nocturnal BP dipping status, and morning BP surge as potent risk factors for cerebrovascular disease.

Keywords Nocturnal blood pressure · Nocturnal dipping · Morning blood pressure surge · Cardiovascular risk · Hypertension · Cerebrovascular event

Introduction

For older adults, the fastest-growing segment of the population, it is crucial not only to extend life limits, but also to maintain activities of daily living and to limit disability in the last periods of life. Stroke is a common cause of death and major cause of disability worldwide, and the burden will increase dramatically during the next 20 years because of the aging population [1]. Even in silent cerebrovascular diseases, such as silent cerebral infarction (SCI) and white matter lesion (WML), associations with increased risk of stroke, gait and balance disorders, tendency to fall, and cognitive impairments, including declining attention and declining speed of mental processing, have been reported [2–6]. Accordingly, performing the earliest possible actions to prevent not only symptomatic but also silent cerebrovascular disease has become a major public health challenge. To this end, clarifying the risk factors contributing to cerebrovascular disease has become a top priority for research.

Hypertension is a potent risk factor for both symptomatic and silent cerebrovascular disease and in turn leads to poor physical function and cognitive dysfunction in middle-aged and older individuals [5–8]. Twenty-four–hour blood pressure (BP) rather than office BP is closely associated with cerebrovascular disease or poor physical and cognitive function. In particular, BP at a specific time, such as nocturnal BP or morning BP increase from sleep, has been shown to be a risk factor for cerebrovascular disease independently of 24-h BP level [9–13, 14••, 15, 16, 17•]. This review is an attempt to clarify the clinical implications of nocturnal BP level or nocturnal BP dipping status, and morning BP surge as potent risk factors for cerebrovascular disease.

Nocturnal Blood Pressure Evaluation

Nocturnal BP can be measured only by using ambulatory BP monitoring (ABPM). There are some newly developed, programmed home BP measurement devices (HEM-5041 and HEM-7471C-N; OMRON, Kyoto, Japan) that can

Y. Yano · K. Kario (✉)
Division of Cardiovascular Medicine,
Jichi Medical University School of Medicine,
3311-1 Yakushiji,
Shimotsuke, Tochigi 329-0498, Japan
e-mail: kkario@jichi.ac.jp

measure nocturnal BP automatically at various time points [18, 19], but their predictive power for cardiovascular disease (CVD) has not yet been determined.

The standard definition of nocturnal BP remains unclear, but one simple and popular method of determining the time of awaking and sleeping is to assess this information from a diary card. The diary should also include information about whether or not the patient took daytime naps that otherwise might have contributed to the misclassification of nocturnal BP dipping status. Another method to define nocturnal BP is to use arbitrarily defined wide (10 p.m.–6 a.m.) or narrow (midnight–6 a.m.) clock time intervals. The use of narrow fixed intervals excluding the transition periods in the morning and nighttime provides a more accurate estimate of nocturnal BP.

Nocturnal Blood Pressure and Cerebrovascular Disease: Cross-Sectional Study

Physiologically, most individuals experience a reduction in nocturnal BP relative to daytime BP known as nocturnal BP dipping. Although arbitrary, the average systolic or diastolic BP decline from daytime to nocturnal BP is 10 %–20 %, which is referred to as *normal dipping*, and the nocturnal BP decline is less than 10 %, which is referred to as *nondipping*.

The dipping/nondipping classification was first introduced in 1988 by O'Brien et al. [20], who reported a more frequent history of stroke in nondippers, defined as those having a nocturnal systolic/diastolic BP decline of less than 10/5 mm Hg compared with dippers. Although subsequent investigators used a variable definition of nondipping, several cross-sectional studies [21–27], but not all [28, 29] demonstrated that less nocturnal BP dipping, rather than another BP index, such as 24-h, daytime, or office BP levels, was associated with SCI, WML, or brain atrophy in older individuals with or without hypertension. The inconsistent results between nocturnal BP dipping and silent cerebrovascular diseases might be due to the differences in the study populations (e.g., age and ethnic differences) or the presence of antihypertensive medications or preexisting cerebrovascular disease, and there is no general consensus in the definition of nocturnal BP dipping or the quantification of such cerebrovascular diseases.

From the nature of the cross-sectional analysis in these studies [21–29], it remains uncertain whether nondipping is the cause or consequence of cerebrovascular disease. We previously reported the case of a 79-year-old hypertensive man whose diurnal BP pattern changed after a lacunar infarction in the left internal capsule, suggesting that abnormal diurnal BP might originate from minor cerebrovascular abnormalities [30]. Yamamoto et al. [31] reported that some patients with recurrent cerebrovascular events expressed further reduction of the nocturnal BP dipping after a second attack from that at the study recruitment. These results suggest that cerebrovascular disease caused by hypertension leads to disrupted diurnal BP variation through functional impairment of the central autonomic nervous system. An additional explanation of the association between nondipping and cerebrovascular disease is that both conditions could be linked to common pathophysiologic mechanisms, such as increased sympathetic nerve activity, chronic kidney disease, and sleep apnea (Fig. 1).

Nocturnal Blood Pressure and Cerebrovascular Disease: Prospective Study

Although the findings have been inconsistent, a reduced extent of nocturnal BP dipping has been suggested to be a potential predictor of CVD morbidity and mortality, including cerebrovascular events, in both general and hypertensive populations [9–13, 14••]. Staessen et al. [9] showed a 10 % increase in the night-to-day ratio of systolic BP was associated with cardiovascular morbidity, including stroke, independent of the 24-h BP level (hazard ratio [HR], 1.41 [95 % CI, 1.03–1.94]; $P<0.05$), among untreated older hypertensive patients with systolic hypertension (≥60 years). Ohkubo et al. [10] have shown that each 5 % attenuation of nocturnal BP dipping conferred an approximately 20 % rise in the risk of cardiovascular mortality (half of the events were cerebrovascular disease) among the general population; even when the 24-h BP was within normal range (<135/85 mm Hg), reduced nocturnal BP dipping was still a significant risk factor for cardiovascular mortality. Conversely, a recent meta-analysis of an International Database on Ambulatory BP in relation to Cardiovascular Outcome (IDACO) study ($n=7,458$; mean age, 57 years) indicated that an 8 % increase in the night-to-day ratio of systolic BP was associated with all-cause mortality (HR, 1.13 [95 % CI, 1.07–1.19]; $P<0.001$), particularly in non-CVD mortality, whereas it was not associated with an increased risk of stroke or combined cardiovascular end points independently of 24-h BP levels [11]. Furthermore, a systematic review of 23,856 hypertensive patients and 9,641 subjects from population cohorts from Asia, Europe, and South America by Hansen et al. [14••] revealed that a 10 % increase in the night-to-day ratio of systolic BP was associated with cardiovascular morbidity, including stroke, in general populations (HR, 1.08 [95 % CI, 1.01–1.16]; $P=0.04$) or in hypertensive patients (HR, 1.13 [95 % CI, 1.00–1.27]; $P=0.04$), although it added only 0.1 % prognostic value beyond the 24-h BP levels.

In contrast to nocturnal BP dipping, evidence is increasing that the mean nocturnal BP level itself is the most sensitive predictor of not only total mortality, but also of

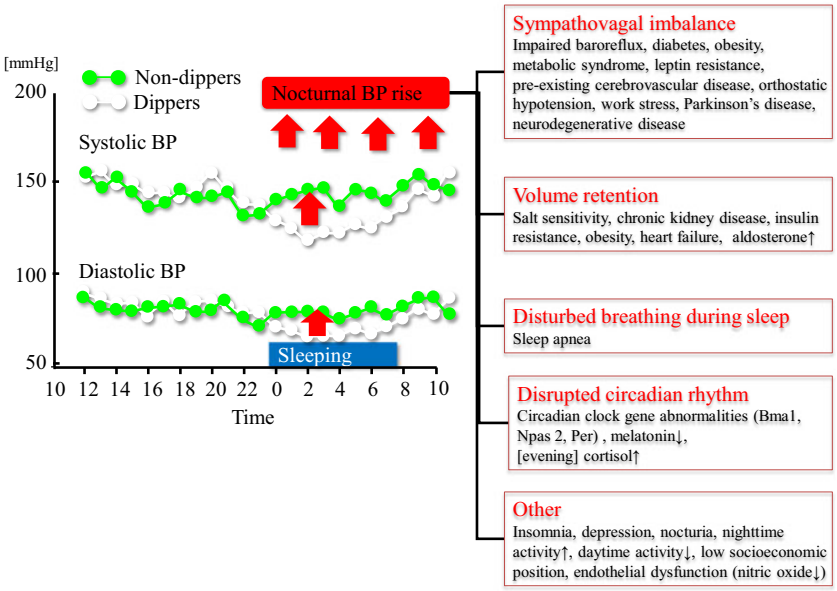

Fig. 1 Pathophysiology of altered diurnal blood pressure (BP) variation and/or nocturnal hypertension. The pathophysiology of nocturnal BP risk is multifactorial

stroke among 24-h BP components in individuals with or without hypertension [11–13]. According to the IDACO database, a 16-mm Hg increase in the nocturnal systolic BP was associated with stroke events (HR, 1.08 [1.01–1.16]; $P<0.001$), whereas an 8 % increase in the night-to-day ratio of systolic BP was not associated with stroke events. Intriguingly, the predictive value of nocturnal BP was especially important in treated hypertensive patients, as antihypertensive medications can easily affect daytime BP; thus, daytime BP was no longer a significant predictor of cardiovascular events in such patients [11].

High nocturnal BP is frequently accompanied by non-dipping status. However, both phenotypes are not always concomitantly present; hence, the pathophysiologic and clinical implications of each may differ. Although the results were not conclusive, less nocturnal BP dipping has been associated with excess CVD mortality as well as non-CVD mortality rather than CVD morbidity [11–13], which raises the possibility that less dipping is (though not in all cases) a marker of preexisting or concurrent diseases (Fig. 1). In particular, reverse dipping or a riser pattern, which means the night-to-day BP ratio is 1 or more, consistently showed the poorest outcomes among several dipping statuses [11, 12, 14••, 32]. Our previous data showed that among older hypertensive patients ($n=575$; mean age, 72 years), subjects with reverse dipping ($n=63$ [11 %]) had the highest incidence of stroke (22 % during 41 months of follow-up), particularly fatal type stroke, and hemorrhagic stroke was more common in reverse dipping (29 % of stroke) than in other dipping groups (7.7 % of stroke; $P=0.04$) [32]. According to the IDACO database, subjects with reverse dipping had the highest incidence rates of total mortality (27 %) and stroke events (11 %) over the median follow-up of 9.6 years as compared with other nocturnal BP dipping patterns [14••]. Death from reverse dipping occurred at an older age, raising the issue of reverse causality (i.e., reverse dipping, an extremely unphysiologic diurnal variation of BP, may be a marker of poor health conditions rather than a cause of them). To understand whether nondipping or reverse dipping is a reversible risk factor or not, interventional studies are required to show the clinical benefit of restoring the disrupted diurnal variation of BP. Unfortunately, such evidence is scarce, but recently, Hermida et al. [33•], who prospectively treated 3,344 subjects with or without hypertension (mean age, 53 years) for a median follow-up period of 5.6 years, showed that a 5-mm Hg reduction in nocturnal systolic BP during treatment with antihypertensive medication was associated with a 17 % reduction in CVD morbidity and mortality ($P<0.001$). They also showed that a 10 % increase in nocturnal BP dipping during follow-up was associated with a 25 % reduction in CVD morbidity and mortality ($P<0.001$) independently of any other ambulatory BP parameters [33•]. This means that in addition to lower office or 24-h BP, decreasing nocturnal BP or restoring the abnormal diurnal BP variation to normal would be a treatment target for the reduction of CVD events. The study patients were middle-aged, and half of them were defined as having obesity or metabolic syndrome. Therefore, it remained unclear whether or not a similar benefit could also be achieved in older hypertensive patients or subjects who had preexisting CVD.

Treatment of Nocturnal Blood Pressure Increases

While there is no evidence-based approach for the treatment of nocturnal hypertension or nondipping that can lead to the reduction of cerebrovascular disease in a hypertensive or

general population, it seems promising to treat the pathophysiology underlying the altered diurnal BP variation, including nocturnal hypertension. The etiology of nocturnal hypertension or nondipping is complex and may be encountered together with a number of clinical backgrounds, such as autonomic dysfunction, volume overload secondary to salt sensitivity and chronic kidney disease, poor quality of sleep, disruption of biological circadian rhythms, and other factors (Fig. 1). We previously reported that an intervention that can reduce sympathetic nerve activity by nighttime dosing with an α-blocker (i.e., doxazosin) markedly reduced nocturnal BP in nondippers and reverse dippers in uncomplicated hypertensive patients [34]. Salt restriction, thiazide diuretics, or aldosterone antagonists can force nondipping into dipping status [35, 36]. The effectiveness of obstructive sleep apnea treatment with continuous positive airway pressure was modest but significant [37]. Finally, the potential benefit of chronotherapy in the treatment of hypertension has been reported. The administration of at least one antihypertensive drug at bedtime has been reported to be more effective than morning administration, not only for lowering nocturnal BP and restoring circadian variability in BP, but also for reducing cardiovascular events and total mortality [33•].

How to Evaluate Morning Blood Pressure Surge

The incidence of most adverse cardiovascular events appears to follow a circadian pattern, reaching a peak in the morning shortly after waking. The activities of many physiologic parameters, including hemodynamic, hematologic, and humoral factors, also fluctuate in a cyclical manner over 24 h. Accordingly, it has been suggested that during the postwaking hours, the phases of these cycles synchronize to create an environment that predisposes to atherosclerotic plaque rupture and thrombosis in susceptible individuals, thereby accounting for the heightened cardiovascular risk at this time of day [38, 39, 40••].

An increase in BP after waking is a physiologic phenomenon. However, a marked and rapid morning BP surge, which is determined by a sum of physiologic and unphysiologic factors (Fig. 2), is associated with increased cardiovascular risk. Thus, the association between the degree of morning BP surge and cardiovascular risk seems not to be linear, but rather to have a threshold. There is no consensus on a single definition or on the threshold of pathological morning BP surge, but two main definitions that have been proven to have prognostic value for predicting CVD have been used in the previous research [16, 17•, 40••]. One is the sleep-trough surge, defined as the morning systolic BP (2-h average of four 30-min systolic BP readings just after waking) minus the lowest nocturnal systolic BP (1.5-h average of the three BP readings centered on the lowest nighttime reading). The second definition is the prewaking surge, defined as the morning systolic BP (2-h average BP after waking) minus the prewaking systolic BP (2-h average of four BP readings just before waking). The differences in clinical implications between the two definitions remain unclear, but the sleep-trough surge can express more dynamic diurnal BP change during the specific time period from sleep to early-morning. Recently, the use of self-measured home BP measurement has become widely accepted, and its measurement in the morning and evening is used as the morning BP increase (ME difference: morning systolic BP minus evening systolic BP). However, home BP self-measured in the morning in a seated position may underscore the risk of ambulatory morning BP surge, which is augmented by morning physical activity [41]. Ultimately, an optimal definition of morning BP surge should be supported by data showing its ability to predict cardiovascular outcomes.

Morning Blood Pressure Surge and Cerebrovascular Disease

There is mounting evidence suggesting significant associations between morning BP surge and cardiac [42, 43], cerebral [15, 44], renal [45], and vascular damage [46–48], even though the definitions of morning BP surge are not uniform across the investigations (Fig. 3). In our previous study with older hypertensive patients (n=519; mean age, 72 years), multiple SCIs were more frequently detected by brain MRI in the morning BP surge group (≥55 mm Hg, top decile group) than in subjects without morning BP surge (57 % vs 33 %; P<0.001) [15]. Another study (n=98; mean age, 70 years) revealed that α-adrenergic morning BP surge, defined as a reduction in morning BP surge by α-adrenergic blocker (doxazosin) therapy, rather than morning BP surge itself was closely associated with multiple SCIs [44]. Morning BP surge is known to be mediated by sympathetic nerve activity, although not exclusively [49–51]. Recently, it was demonstrated that sympathetic nerve activity in patients with morning BP surge can be suddenly activated after waking, rather than the activation being maintained evenly under steady-state basal conditions [52].

Because sympathetic nerve activity is involved in not only BP elevation, but also other adverse effects, such as hemostatic abnormalities (including platelet aggregation, increased blood viscosity, and endothelial dysfunction), these factors may in part explain the higher prevalence of multiple SCIs in patients with morning BP surge [15, 44]. In fact, we recently reported that in older hypertensive patients (n=60; mean age, 71 years), there was a close association between the extent of morning BP surge and that of platelet

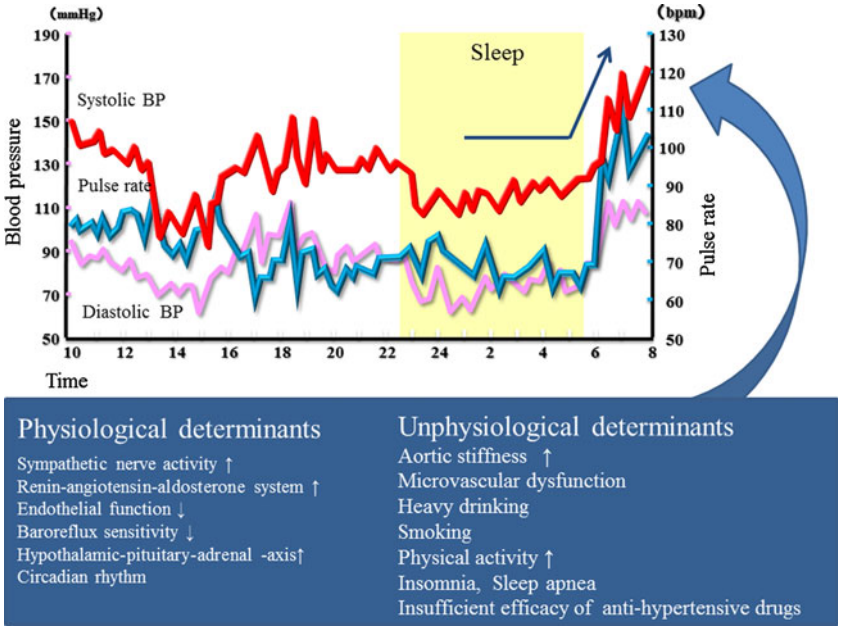

Fig. 2 Physiological and unphysiological determinants of morning blood pressure (BP) surge. Morning BP is determined by physiological and unphysiological factors. (*Reprinted from* Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. Hypertension. 2001; 38: 852–7. American Heart Association; Council for High Blood Pressure Research [American; Interamerican Society of Hypertension]. Copyright 2001 by Lippincott Williams & Wilkins; reproduced with permission from Lippincott Williams & Wilkins.)

aggregation, as assessed by the spontaneous small-sized platelet aggregation detected by a light scattering intensity method (R=0.62; P<0.001) [53]. The OR for multiple SCIs with a +1 SD increase of morning BP surge (+16 mm Hg) was 2.0, and that of morning spontaneous small-sized platelet aggregation (+19,884×10^5×2 mV counts 10 min) was

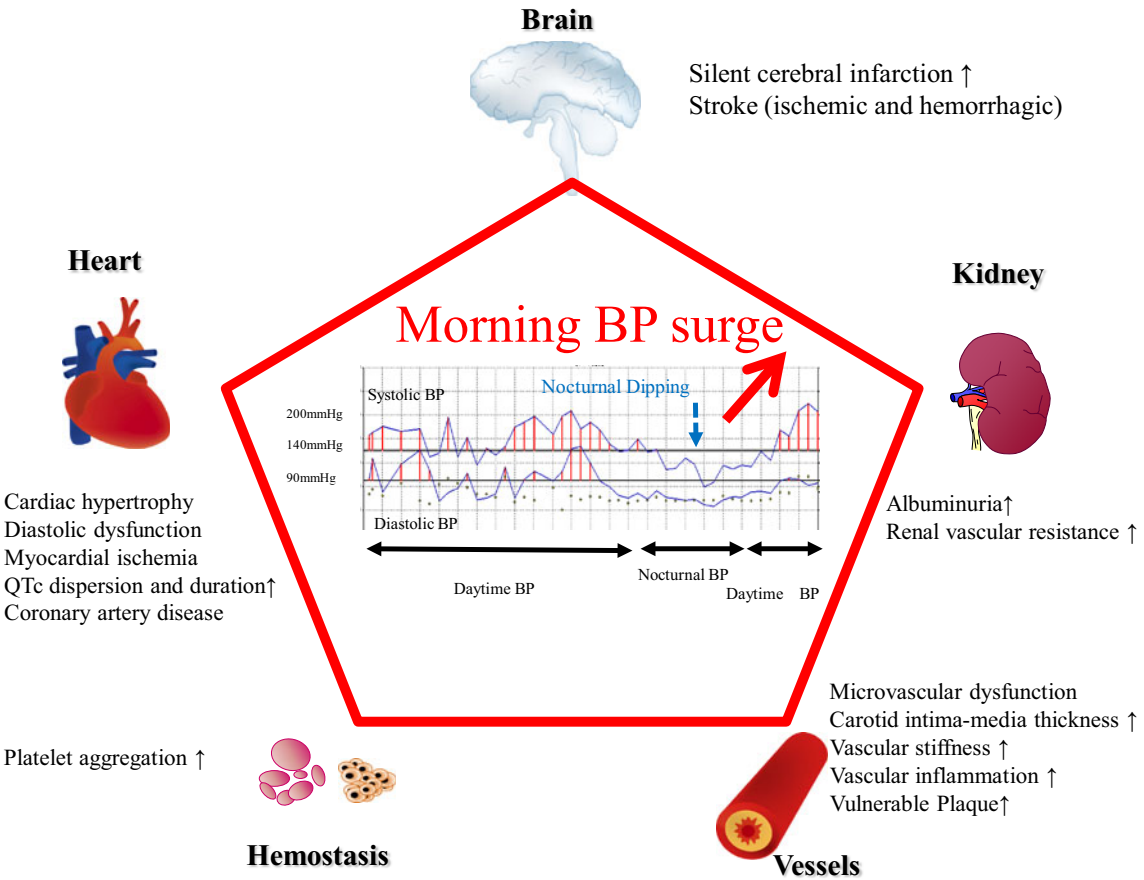

Fig. 3 Morning blood pressure (BP) surge and cardiovascular risk. Several reports have shown significant associations between morning BP surge and cardiovascular diseases. IMT, intima-media thickness

3.0 (both $P<0.05$), but when both factors were entered into the same model, only the latter remained significant in association with multiple SCIs ($P<0.05$). From the nature of these cross-sectional studies [44, 53], there is also concern of a reverse association—that is, that multiple SCIs themselves may increase in BP variability and undergo a more pronounced morning BP surge through an alteration of central sympathovagal balance toward increased sympathetic nerve activity. Against this concern, in our prospective cohort study (3.5 years) of 519 older adult Japanese hypertensive patients (mean age, 72 years), we first showed that an excessive morning BP surge (≥55 mm Hg, top decile of the population) was associated with an increased risk of stroke as compared with the nonsurge group (19 % vs 7.3 %, respectively; $P=0.004$) [15]. After matching for age and 24-h BP, the relative risk of morning BP surge remained significant (relative risk, 2.7; $P=0.04$). The increase in morning BP surge (+10 mm Hg) was associated with stroke events (relative risk, 1.25; $P=0.008$) independently of 24-h BP level, nocturnal BP dipping status, and the baseline presence of SCI. Using the same database [15], we recently reported another novel aspect of this subject—namely, that morning BP surge (>44 mm Hg, top quartile), as well as high levels of plasma plasminogen activator inhibitor-1 (≥58 ng/mL, top quartile), a principal inhibitor of fibrinolysis, and prothrombin fragment 1+2 (≥1.78 nmol/L), a marker of thrombin generation, were independently and additively associated with an increased risk of stroke in older hypertensive patients [54]. Our findings indicate that regardless of the extent of baseline cerebrovascular damage, morning BP surge can trigger stroke onset, possibly though the direct hemodynamic effect of the BP peak on the vascular wall, which was proven to result in an inflammatory-dependent unstable plaque vascular phenotype via the activation of ubiquitin–proteasome activity [48]. Other pathophysiologic changes occurring in the morning (e.g., hemostatic alteration) also made important contributions to stroke onset independently of morning BP surge.

Recently, Li et al. [17•] used the IDACO database to clearly confirm the risk conferred by morning BP surge (8 countries; $n=5,645$; mean age, 53 years; median follow-up, 11.4 years). They showed that while accounting for the night/day BP ratio, the 24-h BP level, and other covariates, a morning BP surge, defined as the top decile of sleep-through surge (≥37 mm Hg), was associated with a 30 % increase in hazard for total mortality and cardiovascular morbidities. In this study, a morning BP surge was associated with a higher risk of hemorrhagic stroke (51 cases; HR, 2.28 [95 % CI, 1.09–4.26]; $P=0.03$), but not ischemic stroke. About half of the hemorrhagic stroke events ($n=27$) were derived from the Ohasama Study, a Japanese general population–based study; therefore, the increased risk of hemorrhagic stroke in the morning BP surge was consistent with a report from the Ohasama Study [16], but different from our findings, in which the morning BP surge significantly predicted ischemic stroke. Different characteristics of the populations under study, such as age or the presence of antihypertensive medications, might explain this diversity. Li et al. [17•] also suggested that a morning BP surge of less than 20 mm Hg is unlikely to be associated with increased risk. It will be important to determine the optimal cutoff of morning BP surge that is unlikely to be associated with increased cardiovascular risk; this cutoff may depend on a patient age, ethnicity, comorbidity (e.g., diabetes, chronic kidney disease), or the presence of antihypertensive medication or preexisting CVD.

Treatment of Morning Blood Pressure Surge

The fundamental approach to suppressing morning BP surge is to use long-acting antihypertensive drugs, such as long-acting calcium channel blockers or inhibitors of the renin-angiotensin-aldosterone system. Lifestyle interventions, such as moderating alcohol intake and sleeping well, are also important. A chronotherapeutic approach, such as bedtime dosing and a drug delivery system that incorporates extended-release or delayed-onset antihypertensive agents, is useful for reducing morning BP surge [55, 56]. Previously, we demonstrated that bedtime dosing of an α-adrenergic blocker or an angiotensin II receptor blocker could reduce morning BP and ameliorate surrogate markers (i.e., cardiac hypertrophy and albuminuria) in patients with morning hypertension [57–59]. However, no study has investigated whether or not the suppression of an exaggerated morning BP surge can lead to a reduction of cardiovascular morbidity and mortality, in particular cerebrovascular disease. The Controlled Onset Verapamil Investigation of Cardiovascular Endpoints trial, which evaluated the benefits of a therapy that targeted BP and heart rate in the early morning with controlled-onset, extended-release verapamil versus conventional diuretic and/or β-blocker therapy in early-morning cardiovascular events, showed that extended-release verapamil did not reduce stroke events to a greater degree compared with the other therapy [60]. However, that study was flawed because its sponsor discontinued the trial 3 years early. Recent findings from the MAPEC (Monitorización Ambulatoria para Predicción de Eventos Cardiovasculares [Ambulatory Blood Pressure Monitoring for Prediction of Cardiovascular Events]) study, designed to investigate prospectively whether bedtime treatment causes specific changes in the circadian BP profile that reduce CVD risk, indicated that a reduction in the morning BP surge during follow-up could not lead to a reduction in CVD events, including stroke [33•]. The level of morning BP surge was not described in the MAPEC study, but it seems to be lower

even in patients who had CVD events (mean daytime systolic BP was 139 mm Hg, and mean nocturnal systolic BP was 134 mm Hg) as compared with previous reports [17•, 32]. The MAPEC study was performed in a middle-aged population (mean age, 53 years), and half of them were defined as having obesity or metabolic syndrome, which may be one of the reasons why the nocturnal BP in the MAPEC study was higher, while the morning BP surge in the MAPEC study was lower than in previous reports [17•, 32]. A future interventional study with pharmacologic or nonpharmacologic therapy, particularly in older hypertensive patients, will be needed to examine the clinical benefit of morning BP surge–lowering therapy on cardiovascular morbidity and mortality.

Conclusions

In this review, we summarized the findings on nocturnal BP, nocturnal BP dipping, and morning BP surge, all of which have been reported as potent risk factors for cerebrovascular disease. To establish the clinical implications of these BP parameters, we have to perform interventional studies to examine whether or not a reduction in nocturnal BP or morning BP surge, or a restoration of abnormal nocturnal BP dipping status with pharmacologic or nonpharmacologic therapy, can lead to an improvement of cardiovascular morbidity and mortality in hypertensive patients independently of 24-h BP reduction. In addition, we have to consider the best way to improve these BP parameters, and to what optimal level, in order to achieve a clinical benefit by these interventions.

Disclosure No potential conflicts of interest relevant to this article were reported.

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- •• Of major importance

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