Editorial Comment

Unresolved Issues of the Morning Blood Pressure Surge: The Next Stage of Clinical Applicability for the Morning Surge

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The morning blood pressure surge (MS) has attracted interest as a potentially novel risk factor for cardiac, cerebral, renal, and vascular damage (1–8). Although the information derived from MS may be valuable, there are several methodological limitations in applying this information in patient management in the clinical setting. These limitations include different criteria for defining MS, relatively poor reproducibility, and the influence of physical activity on morning blood pressure (BP) level. Moreover, the pathological mechanisms of MS are poorly understood, and it is unknown whether the therapy aimed at improving abnormal MS may have a favorable effect on a patient's prognosis.

The Definition of MS

There is no consensus on the definition of MS. In our prospective cohort study (3.5 years) of 519 elderly Japanese patients with hypertension (1), an excessive MS (≥ 55 mmHg: top decile of the population) was found to be associated with an increased risk of stroke as compared with a non-surge group (19% vs. 7.3%, respectively; $p=0.004$), independent of the ambulatory 24-h BP level. In our case, the level of MS was calculated using the difference between the mean systolic BP (SBP) during the 2 h after waking and the average of 3 readings centered on the lowest BP taken while patients were asleep (sleep-trough MS). Pre-waking MS, defined as the dif-

ference between the mean SBP during the 2 h after waking and the average BP during the 2 h before waking, was also analyzed in our study; however, there were no significant findings. Metoki *et al.* (2), who used the same definition of MS that we did, demonstrated that both sleep-trough MS (≥ 40 mmHg) and pre-waking MS (≥ 25 mmHg) were associated with a higher risk of hemorrhagic stroke. Other studies showing the risk of excessive MS have used various definitions of MS. For example, Gosse *et al.* (3) defined the waking surge as the difference between the SBP measured precisely upon waking and the last values before waking. Kuwajima *et al.* (4) showed that the BP change from the level upon waking to maximum SBP during the first 3 h after arising was correlated with cardiac hypertrophy.

The pathological mechanisms of MS vary according to the definition. Our definition of MS, which includes the lowest BP during sleep, shows an amplitude and steep change in the morning BP after waking; in contrast, the pre-waking MS showed a change in BP during the time between waking and arising. Because a major component of MS is mainly determined by arising from sleep, our definition seems more feasible. However, an optimal definition of MS should be supported by the data showing its ability to predict cardiovascular outcomes. Rizzoni *et al.* (5) recently evaluated the risk of MS in subcutaneous small-artery remodeling using different definitions. They showed that the strongest correlation

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between MS and small-artery remodeling was found when our definition (sleep-trough MS) was used. Previously, we found that excessive sleep-trough MS was associated with lacunar infarcts from cerebral small-artery occlusion (1). Marfella *et al.* (6) demonstrated that exaggerated sleep-trough MS was significantly associated with vulnerable plaques in atherosclerotic lesions *via* the activation of oxidative stress and the ubiquitin–proteasome system. These data indicate that sleep-trough MS may be the best definition of MS for predicting vascular damage.

Our definition of MS could be determined by the balance between nocturnal and morning BP. As shown by Metoki *et al.* (2) as well as our study (1), the degree of MS is inversely correlated with nocturnal BP fall, both of which are reported to have opposite prognostic values, which makes the their clinical interpretation more difficult. In fact, among participants with an extreme dipping pattern (nocturnal BP reduction is >20% from diurnal BP) in our study, 24% had excessive MS (≥ 55 mmHg); *vice versa*, the prevalence of an extreme dipping pattern of BP was 51% among the excessive MS group (1). Our studies showed that both excessive MS and extreme BP dipping pattern were risk factors for stroke (1, 9), but the latter risk was largely explained by excessive MS (1). However, because the degree of MS is not always correlated with 24-h BP variability (5), and the rate of BP variation during MS correlated independently with atherosclerosis progression after adjustment for 24-h BP variability (10), we assume that the time-specific aspect of BP variability plays an important role in the cardiovascular burden; namely, the impact of BP variability is more markedly enhanced in the morning periods.

The regulation of nocturnal BP is easily influenced by various physiological states; *i.e.*, sleep apnea is less likely to influence nocturnal BP elevation in elderly person, whereas a middle-aged or young person would be more prone to be influenced by morning and nocturnal BP elevation *via* sleep apnea (11, 12). Thus, the balance between nocturnal and morning BP becomes more complex in different clinical settings. Such complexities could lead to controversy about whether the risk of excessive MS is independent of BP dipping status (1, 2). Further research is needed to elucidate the interaction between nocturnal BP dipping status and MS, and whether there is a synergic action of these factors on cardiovascular risks.

Reproducibility of MS

Another aspect of MS that is relevant to its potential use as a therapeutic target is its reproducibility, because a high reproducibility might strengthen the prognostic significance of MS. In this issue of *Hypertension Research*, Stergiou *et al.* (13) compared the reproducibility of five different definitions of MS by measuring two ambulatory BP profiles recorded 2 weeks apart among untreated hypertensive subjects. The five MS definitions were as follows: MS1, average BP 1 h after

rising minus the average BP at 1 h before rising; MS2, BP 2 h after rising minus 2 h before rising; MS3, BP 3 h after rising minus 3 h before rising; MS4, BP 2 h after rising minus the average BP during sleep; and MS5, sleep-trough MS as used in our study. The reproducibility of each MS definition was assessed by using a concordance correlation coefficient, the standard deviation of differences, and the coefficient of variation between repeated MS assessments and the agreement in detecting excessive MS defined as subjects at the top quartile of the MS distribution. Although the two ambulatory BP levels recorded 2 weeks apart were similar, there were substantial differences in the reproducibility of MS by each definition. Overall, the MS4 definition appeared to have the minimum difference between the first and the second reading; however, there was still a large difference exceeding 10 mmHg. Recently, Wizner *et al.* (14) demonstrated similar findings that both the short- (1 month) and long-term (10 months) sleep-trough MS (MS5) definitions are poorly reproducible in older patients with isolated systolic hypertension. Both studies showed the correlation coefficients between the first and second readings of MS to be about 0.4–0.5. This is due in part to the fact that physical activity and posture could easily cause morning as well as nocturnal BP variations (15, 16). The reactivity of BP to physical activity is highest in the morning, irrespective of individual differences in wake time, BP status, medication use, age, and sex (17). Although the underlying reason for this observation has not been determined, some of the possible mechanisms are activated neurohumoral function, including α -adrenergic activity and the renin–angiotensin–aldosterone system, and impaired baroreflex function or endothelial cell function in the morning (18, 19). In the present study, Stergiou *et al.* did not perform actigraphy (13), which is now widely used both for the quantitative assessment of physical activity during the day and for the assessment of sleep quality and duration (9). Thus, differences in physical activity between BP recording days may play a role in the limited reproducibility of MS. Because moderate morning BP elevation is a physiological phenomenon, and MS has a likelihood of exaggerating the pressor response to mental stress and physical stimuli, resulting in increased BP variability, the relatively poor reproducibility of MS may be somewhat inevitable. Moreover, as mentioned above, MS can be affected by two factors (nocturnal and morning BP); thus there is more significant variation compared with parameters that are determined by a single factor (*e.g.*, 24-h BP variability or morning or nocturnal BP).

In contrast, in a categorical analysis using the top quartile as an arbitrary cutoff for excessive MS (13), about 70–80% of patients categorized as having excessive MS at first exam were also classified as the surge group at the time of the second reading (κ -statistic: 0.2–0.5). This means that there was a slight improvement in the reproducibility of MS when it was quantified as a proportional (%) rather than absolute (mmHg) BP change. Indeed, it is important to note that excessive MS, but not moderate MS, appeared to be characterized by the

intrinsic pathophysiological characteristics of the behavior of an individual's BP; therefore, a categorical analysis of MS rather than a continuous variable seems more feasible. If so, there is a considerable need to define the thresholds of MS to predict cardiovascular events among general or hypertensive patients. Although our previous finding (1) using sleep-trough MS as a continuous variable showed a significant association between MS and stroke risk (10-mmHg increase, relative ratio 1.25, $p=0.008$), further research should clarify whether MS should be considered a continuous or categorical variable in terms of predicting cardiovascular outcome.

In spite of the limitations of MS reproducibility, the available evidence showing the clinical value of MS has been based entirely on a single recording of 24-h ambulatory BP (1–8). This means that excessive MS poses a significant cardiovascular risk even when it occurs only once. In our view, the risk associated with an excessive MS is attributable to internal causes based on an individual's specific situation, regardless of reproducibility. Among the hypertensive subjects, if an exaggerated MS is detected even once among several times, an increased risk would be identified when the trigger events occur, when compared with those with stable BP in whom an exaggerated BP surge is never detected. Thus, we need to examine whether the matter of reproducibility of MS has a significant impact on the prognostic significance of MS.

Treatment Strategy of MS

Finally, what is missing in this field to fully support the clinical relevance of MS is a convincing demonstration that a pharmacological or non-pharmacological correction of an abnormal MS level is associated with better target organ protection and prevention of subsequent cardiovascular diseases. Recently, we demonstrated that adding a bedtime dose of an α -adrenergic blocker to reduce an abnormal morning BP (≥ 135 mmHg) titrated by self-measured home BP significantly reduced BP and urinary albumin excretion rate (20, 21). Because microalbuminuria is now a well-recognized cardiovascular risk factor, its reduction may be connected with an improvement of cardiovascular outcome. Further prospective and interventional studies aimed at not only strict BP control but also atherosclerotic plaque-stabilizing strategies using statins, peroxisome proliferator-activated receptor- γ agonists, and inhibitors of the renin-angiotensin system are necessary to fully support the clinical applicability of the prognostic value of MS (22).

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