New Insight of Morning Blood Pressure Surge Into the Triggers of Cardiovascular Disease—Synergistic Resonance of Blood Pressure Variability

Kazuomi Kario[1]

MORNING BLOOD PRESSURE SURGE AND EVIDENCE

There is significant diurnal variation of the onset time of cardiovascular events. Cardiovascular events occur most frequently in the morning. Ambulatory blood pressure (BP) also exhibits the significant diurnal variation with morning BP surge.[1] We first demonstrated that both ambulatory BP monitoring (ABPM)-defined measures of morning surge in systolic BP (sleep-trough and preawakening surge) were independently associated with stroke in the Jichi Medical University ABPM (JMU-ABPM) study in elderly hypertensive patients.[2] However, there is still debate on morning BP surge as the independent risk factor.[3,4]

In this issue, Pierdomenico *et al*. report that morning BP surge is associated with coronary events in medicated elderly hypertensive patients with dipper patterns of nocturnal BP fall.[5] In their study, Cox regression analysis showed that dippers in the third tertile (>23 mm Hg) of morning surge of systolic BP were at higher risk for both coronary events (hazard ratio = 1.912, 95% confidence interval (CI) = 1.048–3.488, $P = 0.03$).[5] In addition, they previously demonstrated that morning BP surge was independent risk for stroke events in the same database (hazard ratio = 2.08, 95% CI = 1.03–4.23, $P = 0.04$).[6] It is important that the hazard ratios in their elderly patients were nearly identical between stroke and coronary events, because this is the first study to demonstrate that morning BP surge has similar importance for both types of events.[5] In our previous studies we were unable to demonstrate a statistically significant association between morning BP surge and coronary events,[2] because of the small number of cardiac events occurred, while the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) demonstrated that exaggerated morning BP surge is independently associated only with cardiac events.[7] These differences may be partly due to differences in the subjects studied, since Asians are more likely to experience stroke events than coronary events. The IDACO may underestimate the risk of morning BP surge because it used a population-based adult sample whose members were at least 15 years younger than those in our study on hypertensive patients,[2] or those in the studies by Pierdomenico *et al*.[5,6]

In the study of Pierdomenico *et al*., the associations of morning BP surge with stroke and coronary events were independent of BP level and weighted SD of 24-hour BPs in dippers, but the risk of non-dippers overwhelmed the risk of morning BP surge.[5,6] They used the preawakening morning BP surge defined as the difference between the mean BP during the 2 hours after waking and the mean BP during the 2 hours before waking. The preawakening morning BP surge may underestimate the impact of morning BP surge, because the power of prewakening morning BP surge for the prediction of cardiovascular events was weaker than sleep-trough morning BP surge (mean BP during 2 hours after waking minus the lowest 1 hour-consecutive 3 BP readings) in both our JMU-ABPM study,[5] and the Pamela study on community-dwelling subjects.[8]

In addition, underestimation in the tertile analysis of morning BP surge with a low pathological threshold may affect the marginal impact of morning BP surge.[5,6] The risk of BP variability (BPV) may have a U-curve relationship with cardiovascular risk, and the extreme edges of both exaggerated BPV (hyperreactivity) and the absence of (or inverse) BPV (hyporeactivity) would be pathological.[3] Verdechia *et al*. demonstrated that morning BP surge was inversely associated with cardiovascular events.[9] The morning BP surge is partly associated with orthostatic hypertension,[10] extreme-dipping with exaggerated nocturnal BP falls,[11] and increased SD of daytime BPs assessed by ABPM, while riser/non-dipper status in nocturnal BP is associated with orthostatic hypotension and absence of or inverse morning BP surge.

SYNERGISTIC RESONANCE TO POTENTIATE MORNING SURGE

The study of Pierdomenico *et al*.[5,6] as well as previous studies did not strictly refer to the onset time of cardiovascular

Correspondence: Kazuomi Kario (kkario@jichi.ac.jp).

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[1]Division of Cardiovascular Medicine, Department of Medicine and Department of Sleep and Circadian Cardiology, Jichi Medical University School of Medicine, Tochigi, Japan.

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events.[5–9] In our study, the stroke events were significantly more likely to occur in the morning.[2] Even in high-risk hypertensives who are well controlled for the average values of home and ambulatory BPs, stroke may occur in the morning.[1] The morning BP surge is one of the various kinds of BPV, from short-term forms to long-term forms brought on by activities in daily living.[2,3] The morning BP surge would be potentiated by synergistic resonance of various components of BPV, resulting in the morning onset-cardiovascular events (Figure 1). These include beat-by-beat, orthostatic, physical, or psychological stress-induced, diurnal, day-by-day, visit-to-visit, seasonal and yearly BPV, and clinically these are detected by different methods of office, home, and ABPM. Almost all of these phenotypes of BPV are partly correlated with each other and are reported to be cardiovascular risk factors.[1,3,12,13]

The clinical implication of morning BP surge as a risk for triggering cardiovascular events is increased especially in high-risk patients with advanced vascular disease (small artery remodeling and advanced stiffness of the large arteries). We have recently proposed the concept of a vicious cycle between hemodynamic stress (increased variability of BP and blood flow) and vascular disease that damages organs and contributes to cardiovascular events such as systemic hemodynamic atherothrombotic syndrome (SHATS).[1,3,10,14,15] The power of morning BP surge, one of the BPV of SHATS, does not diminish during transmission from central to peripheral in those with stiffened artery. Vascular aging leads to increased vascular resistance and a reduction of baroreceptor sensitivity through both small and large artery remodeling. The baroreceptor sensitivity which is largely determined by vascular stiffness and sympathetic tonus should be the key mechanism of exaggerated morning BP surge and SHATS.[10]

In SHATS, synergistic resonance among the morning BP surge and different types of BPV may occur and could trigger cardiovascular events. In previous ABPM studies, morning BP surge was exaggerated in the winter, especially in elderly patients (winter morning surge in BP)[16] and on Mondays (Monday morning surge in BP).[17] These changes in morning BP surge may contribute to the increase in cardiovascular events in the winter in the elderly patients and on Mondays in working adults. Maximum systolic BP, one of the measures of day-by-day home BP monitoring most frequently found in the morning, has been significantly associated with measures of cardiovascular remodeling (left ventricular mass index, carotid intima-media thickness) even in hypertensives with a well-controlled average of home BP < 135/85 mm Hg.[18] In addition, the increased SD of morning BP is a significant independent predictor of cardiovascular death.[19] Thus, an unstable morning BP surge synergistically augmented by the resonance of other phenotypes of BPV may be more likely to advance organ damage and trigger cardiovascular events than a stable and reproducible morning BP surge.

PERSPECTIVES

Intermittent BP measurement at fixed intervals would underestimate the cardiovascular risk of morning BP surge. Repeated exaggerated BPV triggered only by specific conditions may advance organ damage, and 1 extremely large BP surge may trigger cardiovascular events. Ideally, beat-by-beat continuous BP monitoring is the best means of assessing BPV. Preparatory to the development of an accurate and validated noninvasive method of beat-by-beat continuous monitoring for clinical use, we developed a new hypoxia-triggered home nocturnal BP monitoring system, in which severe desaturation continuously monitored by pulse oximetry sends the signal of BP measurement to the device.[14,20] In patients with obstructive sleep apnea, exaggerated nocturnal BP surges triggered by hypoxic episodes during sleep could be successfully detected by this method of monitoring. Exaggerated nocturnal BP surge may partly explain why the sleep-onset cardiovascular events occur more frequently during sleep.

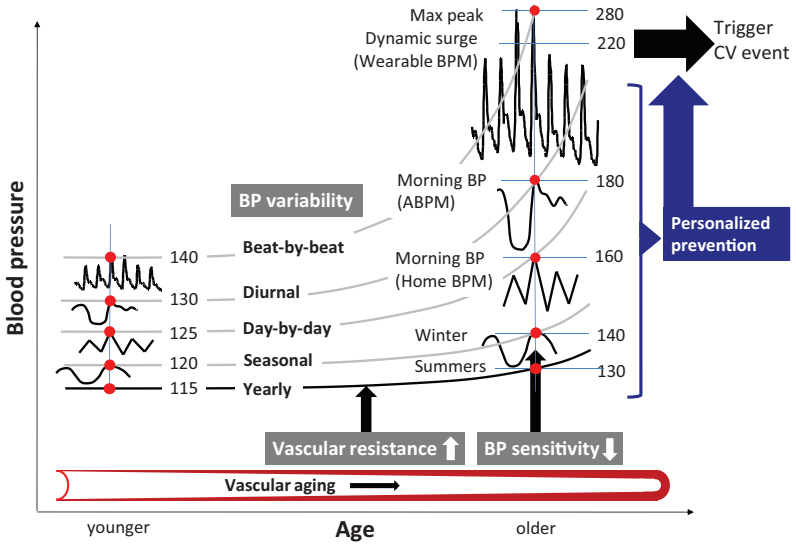

Figure 1. Vascular aging and synergistic resonance of morning blood pressure surge in systemic hemodynamic atherothrombotic syndrome (SHATS).

The BPV is the master biomarker of human health care, since it is not only a modifiable risk factor of organ damage and cardiovascular disease but also a sensor of cardiovascular dysregulation that is affected by individualized characteristics and stressors of daily behavioral factors and environmental conditions. In addition, the integrated risk of morning BP surge is augmented synergistically by the resonance of various BPV phenotypes in SHATS. Thus, in the future, management of hypertension based on simultaneous assessment of the resonance of all the BPV phenotypes by an Information and Communication Technology-based big-data engine driver will contribute to the ultimate personalized prevention of cardiovascular events (Figure 1).

DISCLOSURE

The author declared no conflict of interest.

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