The Risk of Waking-Up
Impact of the Morning Surge in Blood Pressure

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Through ambulatory blood pressure (BP) monitoring, we know that BP usually follows a distinct circadian rhythm, characterized by a nocturnal decline during sleep of 10% to 30%, followed by a moderate-to-marked increase coinciding with the time of awakening. For >2 decades, there has been great interest in the early morning period by preventive cardiologists and hypertension specialists, because it became evident that the onset of acute events, including sudden death, myocardial infarction, and stroke peak in the first 4 to 6 hours postawakening. Because BP, heart rate, and these cardiovascular events all follow the same temporal pattern, it has been suspected that a pathophysiological relationship exists between hemodynamic aberrations, such as the early morning BP surge and vascular damage.

Previous researchers have characterized the morning BP surge associated with increased target organ injury. Risk factors for a profile of excessive early morning hypertension, include older age, excessive alcohol and/or smoking, longer sleep times and later awakening times, cold weather climates, and day of the week (primarily Monday). Several studies performed in the past decade have found significant relations among the early morning BP surge and vascular disease, cardiac hypertrophy, and white matter lesions of the brain. Prospective studies in Japanese individuals have demonstrated a clinical impact of the early morning BP surge in predicting cardiovascular events. In one such cohort with 3.5 years of follow-up, for each 10-mm Hg increase in the early morning systolic BP surge obtained at baseline, the risk of stroke increased by 22%. Of note, this change of BP on arising predicted cardiovascular events independently of age, the average 24-hour systolic BP, and antihypertensive therapy. In a separate population in Ohasama, Japan, that had a 10-year median follow-up period, a large early morning BP surge was associated with the development of hemorrhagic stroke. Furthermore, in a smaller cohort study in France, a higher cardiovascular morbidity and mortality rate was observed in patients with the highest morning BP surge compared with those patients in the lowest morning BP surge group.

Thus, previous studies have suggested a parallel relationship between the early morning BP surge and cardiovascular outcomes but have been lacking in event numbers and enough statistical power to clarify at what level of the morning BP surge the risk will appear to become excessive. In this issue of Hypertension, Yi et al have used the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome to address these questions. It is clear that their analyses have more advantages than previous studies: first, the population is large and heterogenous (5645 people, and more than half are women from 8 countries on 3 continents); second, the follow-up period and event numbers are substantially greater than all of the previous studies with 11.4 years of median follow-up and >600 cardiovascular events. The investigators used 2 different definitions of the morning surge in BP; the first was called the “sleep-through morning surge” and was defined as the difference between the morning pressure during the first 2 hours after awakening and the average of the lowest nighttime BP. This was similar to the definition used by Kario et al in their seminal description of the impact of the morning BP surge on stroke events in an older Japanese cohort. The second definition was the “preawakening morning surge” and was the calculated difference between the morning BP during the first 2 hours after awakening and the BP during the first 2 hours before awakening. The top decile for these 2 definitions of morning BP surge was 37 and 28 mm Hg, respectively. In addition, the absolute morning surge in BP was 145.8 versus 123.7 mm Hg in those subjects who were in the 90th percentile versus those below the 90th percentile using the systolic sleep-through morning surge definition. In general, the trends for the 2 methods were similar: the morning BP surge was associated with a 30% to 45% increase in hazard for cardiovascular events. Of note, both definitions were fairly robust and similar for cardiac events but not for stroke events. The reason for this is unclear, but the authors did note demographic differences, because subjects in Asian countries were at a significantly higher risk for hemorrhagic stroke in the top morning surge decile but not for ischemic strokes, a finding at odds with the study by Kario et al. Of interest from the clinical perspective is the analysis of Yi et al to determine the “cutoff” point at which cardiovascular harm begins to occur. Using both definitions, the authors suggest that a systolic morning BP surge by either definition of <20 mm Hg is unlikely to be associated with increased risk. This is useful, and it would be important to know what absolute systolic BP correlates with the surge values used to plot against the adjusted hazard ratios. Lacking in this analysis, however, is characterization of the population as it relates to the morning BP surge. Might individuals with
a history of previous vascular events or major cardiovascular comorbidities (eg, diabetes mellitus or chronic kidney disease) show increased risk with lesser morning BP surge values compared with a healthier hypertensive patient group?

A substantial number of investigations have been conducted on the mechanism of the morning surge in BP and its potential relationship to cardiovascular harm. Increased, sympathetic nervous system activity and activation of the renin-angiotensin system have both been determined to be possible contributors to increases in vascular resistance and the morning BP surge. Whether these mechanisms of morning BP elevation independently convey vascular harm is not clear but is of theoretical concern, because it is known that α-adrenergic stimulation and renin-angiotensin-aldosterone activation can increase vascular tone, coronary vasospasm, and prothrombotic tendencies in the early morning period (see Figure).

Now that there is better characterization of the evidence linking an exaggerated morning BP surge of 28 to 37 mm Hg to cardiovascular morbidity and mortality, it seems reasonable to consider targeting this time of day with antihypertensive drug therapy. In fact, a substantial attempt to evaluate the benefit of a therapy that targeted BP and heart rate in the early morning period with controlled-onset extended-release verapamil versus conventional diuretic and/or β-blocker therapy on early morning cardiovascular events was initiated 12 years ago. The Controlled Onset Verapamil Investigation for Cardiovascular Endpoints Trial was a 17 000-patient study that defined morning cardiovascular events as those occurring in the first 6 hours postawakening and originally should have had enough statistical power to evaluate this prespecified outcome on targeted versus nontargeted therapy. Unfortunately, because of premature discontinuation of the trial 3 years early by the study sponsor, there were not nearly enough events to make any assessment of the early morning event outcomes.

It seems unlikely that another large-scale trial will be conducted to evaluate whether reduction of the morning surge in BP will reduce cardiovascular morbidity and mortality because, that trial would have to have an enormous sample size and be carried out for many years at a substantial cost. There are, however, a number of studies that demonstrate that it may not be difficult to intervene in morning BP surge values with targeted antihypertensive therapies. α-Adrenergic blockade at bedtime may be an effective means to both lower the morning BP surge and reduce left ventricular mass index, as well as microalbuminuria, in patients with uncontrolled “morning hypertension.” In addition, renin-angiotensin blocking agents that maintain pharmacodynamic effects into the early morning period have been shown to have a significant effect on the morning surge in BP. Because the early morning period coincides with the end of the dosing period of once-daily medications, attenuation of antihypertensive efficacy is relatively common. On the basis of the results of this important new study by Yi et al, new scrutiny should be given to control of the early morning BP, especially in patients at high risk for cardiovascular diseases and those who continue to smoke cigarettes.

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References


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