Day-by-Day Blood Pressure Variability
Cause or Consequence of Vascular Brain Injury?

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Dementia represents an important public health issue in developed countries because of increasing longevity of the elderly population. Cerebral damage is mediated by changes in cerebral vasculature affecting both large and small vessels. The microvascular disease results in chronic ischemic changes affecting the white matter, which in the long run can lead to cognitive alterations, which may progress to overt vascular dementia. It is thus important to identify and counterbalance the risk factors for cognitive decline at a population level. Although high midlife blood pressure (BP) is associated with an increased risk of late-life dementia, the pathophysiology of the relationship between elevated BP and low cognition remains unclear. In particular, it is uncertain whether, to preserve cognition, it is better not only to lower the mean BP level but also to achieve a more stable BP. Both high and, especially in the elderly, low BP have been linked to cognitive decline and dementia. Patients with hypertension may be especially vulnerable to swings of pressure including episodes of hypotension, because in elderly persons with chronic hypertension, the shift of cerebral autoregulation toward higher BP levels makes the brain more exposed to hypoperfusion. BP variability (BPV) increases with age, and recent studies have reported an association between long-term BPV and silent cerebral lesions, in particular white matter hyperintensities. Of note, the association of BPV with poorer outcome was found in subjects with higher as well as in those with lower BP levels. In a cohort of 6506 elderly individuals followed-up for 8 years, Alpörovitch et al found that an increase of 1 SD in the coefficient of variation of BP measured on 3 visits was associated with a 10% increased risk of dementia.

BP measured out of office predicts cardiovascular outcomes better than traditional BP measured by the doctor. In addition it allows for an easy and detailed assessment of BPV, which may have relevant implications for the clinical evaluation of patients with hypertension. Clinical studies have shown that short-term BPV evaluated from 24-hour ambulatory monitoring was associated with white matter hyperintensities and silent infarcts. A cross-sectional association with short-term BPV has been found also for cognitive function, especially in elderly hypertensives with no history of cerebrovascular disease.

The relationship between cognitive function and home BP is less known. Self-measured BP is a better predictor of cardiovascular outcomes than office BP and might also have a stronger association with the incidence of cognitive dysfunction. Indeed, in this issue of Hypertension, Matsumoto et al demonstrated that home BP level was significantly higher in people with cognitive decline than in those without cognitive decline. For each 1 SD increase in the home systolic BP level, there was a 48% increase in the adjusted risk of cognitive decline. At variance, no differences in conventional BP were observed according to cognitive function. These results were obtained within 486 participants from the general population of the Ohasama study followed for a median of 7.8 years. However, the most intriguing finding of this study was that also day-by-day BP SD was a predictor of cognitive decline with a 51% increase in risk for each 1 SD increase in the home systolic BPV. This relationship held true also when mean home BP was included in the regression models. When participants were divided into 4 groups by the median home systolic BP and the median SD of the home systolic BP (8.55 mmHg), the group with higher home mean systolic BP and home BPV had the greatest risk for cognitive decline among the 4 groups. Another interesting finding was that an elevated SD of the home systolic BP was associated with an increased risk of cognitive decline even when mean systolic BP was below the median value, in keeping with the data by Brickman et al obtained with traditional office BP measurement.

Mechanistic Relationship Between BPV and Cognitive Deterioration

These interesting results call for some pathophysiological considerations. Factors involved in BPV may differ according to the type of BPV. In current clinical practice, one can measure short-term BPV within the 24 hours using noninvasive ambulatory monitoring or longer-term BPV derived from day-by-day home BP readings or from visit-to-visit BP measurements spaced by months or even years. Previous research has shown that both long-term and short-term BPVs were associated with silent cerebral infarctions, brain atrophy, and deep white matter hyperintensity. As mentioned above, swings of pressure can cause cerebral hypoperfusion increasing the risk of silent vascular brain lesions, cognitive decline, and dementia. However, it should be pointed out that increased BPV could be the consequence rather than the cause of brain injury. The neuronal damage occurring during the dementia process may affect the brain structures involved in BP regulation thereby causing BP instability. Another possibility is that...
high BPV may reflect an underlying atherosclerotic process, and that large artery stiffness caused by aging and hypertension may magnify naturally occurring BP oscillations. In the Matsumoto et al study,11 pulse pressure was not a determinant of home BPV. However, in a recent study by Giordano et al17 in a population-based cohort aged 53 to 94 years, pulse pressure resulted to be an independent predictor of cognitive decline. Increased BPV may be the consequence of cardiovascular autonomic dysfunction. Short-term heart rate and BP variabilities have been shown to be inversely associated, and previous research has documented that reduced heart rate variability, a marker of autonomic dysfunction, was associated with impaired cognitive function, even after controlling for traditional cardiovascular risk factors.12 Previous results from the Ohasama study obtained with 24-hour ambulatory monitoring have shown that increased short-term BPV and reduced ambulatory heart rate variability independently contribute to cardiovascular mortality, suggesting that impaired baroreflex function is not the sole mechanism explaining the relation between high BPV and poorer prognosis.13 In a more recent analysis of the Ohasama study, the same group of investigators showed a combined direct effect of BP and heart rate variabilities defined as within-subject SDs of day-by-day home measurements on cardiovascular outcomes.14 This suggests that high day-by-day BPV may not only be the result of impaired baroreflex control but also the effect of sympathetic activation causing simultaneous elevations in BP and heart rate in response to occasional mental or physical triggers. Another possibility is that elevated day-by-day BPV might reflect poor compliance to treatment by patients on antihypertensive therapy, which could result in inadequate BP control favoring cognitive impairment. However, in the Matsumoto et al study,11 high home BPV was a predictor of cognitive decline only among the untreated participants and was not associated with cognitive dysfunction in treated patients. This argues against poor adherence to treatment as a cause of elevated day-by-day BPV in the Ohasama population. In conclusion, available evidence suggests that a constellation of environmental, behavioral, humoral, physical, and neural factors all contribute to determining BPV (Figure), and that the relative contribution of these factors may differ for short-term and longer-term BPV.

Limitations of the Study
A possible limitation of the Matsumoto et al study11 is that the data come from a Japanese population and might, therefore, not be representative of non-Asian or non-Japanese subjects. In Asian populations, the association of home BP with cerebrovascular morbidity is stronger than that between BP and cardiac events.14 Thus, these findings may be because of specific characteristics of the Ohasama population and await testing in different ethnic groups.

Another possible limitation is that only SD was used as a measure of day-by-day BPV. In studies of the association of long-term BPV with health outcomes, it is not clear which metrics of BPV are better representative of true BPV.15 Other measures of home BPV have shown closer association with cardiovascular outcomes than SD15 and might have a better predictive value for cognitive impairment.

Figure. Mechanistic relationship between increased blood pressure variability and cognitive decline. The association between blood pressure variability and cognitive decline can be explained through different pathways. High blood pressure variability can be the cause of silent vascular brain lesions leading to cognitive dysfunction but may also be the consequence of brain injury. In addition, a chronic underlying disease can simultaneously increase blood pressure variability and favor cerebral damage directly. BP indicates blood pressure.

Future Perspectives
Day-by-day BPV largely depends on the number and timing of measurements and on how BP is measured.16 To establish objective criteria for the definition of high day-by-day BPV for clinical use, the procedures for self-BP measurement should be standardized. Besides results for metrics of overall variability, it is advisable that in future clinical trials also results for metrics of variability between consecutive days such as average real variability should be reported. Finally, if BPV is an important predictor of adverse outcome, it is possible that pharmacological reduction of BPV in hypertension confers additional cardiovascular protection to that provided by the decrease in mean BP. In clinical trials comparing 2 antihypertensive regimens, Rothwell et al16 found that the regimen associated with lower intraindividual or interindividual visit-to-visit variabilities was associated with a lower incidence of stroke. Some data indicate that calcium antagonists are more effective than other antihypertensive drugs for reducing BPV suggesting that the beneficial effect shown by these drugs for prevention of dementia might be because of their action on BPV.17 However, if BPV is simply a marker of an underlying chronic illness, targeting of antihypertensive treatment toward stabilizing BPV would be a fruitless exercise. Only future long-term clinical trials encompassing the current main classes of antihypertensive drugs will reveal whether different drug classes have a different action on BPV and whether reduction of day-by-day BPV may help to prevent or delay cognitive decline in hypertension.

Disclosures
None.

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