

Increased Blood Pressure Variability May Herald Cognitive Decline and Dementia

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A 68-year-old patient with well-controlled hypertension, asymptomatic since many years suddenly complains of vertigo, dizziness, and subtle loss of memory in daily life. Self-blood pressure (BP) measurement followed by 24-hour ambulatory BP measurement shows impressive BP variability. BP measurements on subsequent consultations vary from very high to low BP without an obvious explanation. Six months later, the patient's cognitive status worsens and he is diagnosed with dementia. Many of us have experienced such situations, when BP and more generally cardiovascular lability heralded, was accompanied or quickly followed by cognitive disturbance or dementia. Was increased BP variability the initial manifestation—or even more one of the causative factors—of subsequent cognitive decline, or was it the single manifestation that the busy hypertension specialist could detect during his 20 or 30-minute consultation?

Along with previous studies,¹ the work of Rouch et al published in this issue of *Hypertension*² further supports the strong correlation between BP variability and cognitive disorders. In over 3000 noninstitutionalized patients aged ≥65 years from the French S.AGES cohort who were followed every 6 months for 3 years, it was found that higher systolic and diastolic BP variability, but not pulse pressure variability—at least after adjustment for age—was associated with both cognitive decline and increased incidence of dementia, over and above mean baseline BP.²

Compared with previous work, this analysis has important strengths, from both hypertension specialists' and neurologists' perspective. First, the impact of visit-to-visit BP variability on cognitive decline has been evaluated using a wide array of BP

variability estimates, including the complex but particularly reliable variability independent of the mean introduced by Rothwell et al.³ Second, the impact of BP variability on cognitive deterioration has been further strengthened by similar results obtained for a harder end point, that is, the incidence of dementia. Third, this analysis was performed in moderately at-risk elderly subjects; therefore, its conclusions may be applicable to a wide range of individuals from the general population.

Still, nothing is perfect. While the hypertension specialist will frown at the lack of repeated BP measurements (everything rests on a single BP measurement at each visit) and may regret the lack of 24-hour BP measurement, at least in a subgroup, the neurologist may criticize the use of a simple but relatively insensitive tool such as the Mini-Mental State Examination rather than, for example, the Montreal Cognitive Assessment.⁴ He/she may also be disappointed by the absence of information on white matter lesions and other well-established imaging biomarkers associated with cognitive impairment¹ and frustrated by the lack of specification of the type of dementia in the almost hundred subjects who developed this complication during the follow-up. As 71% of enrolled subjects were on antihypertensive drug treatment at inclusion, it would also have been of interest to evaluate drug adherence and its potential impact on visit-to-visit BP variability. However, the aforementioned limitations do not fundamentally challenge the main conclusions of Rouch et al study.²

Very recently, the association between BP variability and dementia has been confirmed at an unprecedented scale in a South Korean data set including 7844814 subjects who underwent ≥3 health examinations from 2005 to 2012. Notably, 75% of cases of dementia were due to Alzheimer disease, only a minority being labeled as having vascular dementia.⁵

Overall, BP variability definitely appears as a predictive marker of cognitive decline, which may be added to an already long list including mean BP, arterial stiffness, intima media thickness, white matter lesions, microbleeds, and silent infarcts among many others.^{1,6} Nevertheless, it remains to be determined which combination of biomarkers more accurately predicts cognitive decline and, at the end of the spectrum, dementia, using the least invasive tests and at a lower cost. In particular, would integration of BP variability estimates in the assessment of the risk of dementia improve the prediction of cognitive decline over and above well-established factors other than mean BP? Such complex questions can be addressed in a well-established multi-step process.⁷ We are only at the beginning of the road and the Framingham study of cognitive decline is still awaited.

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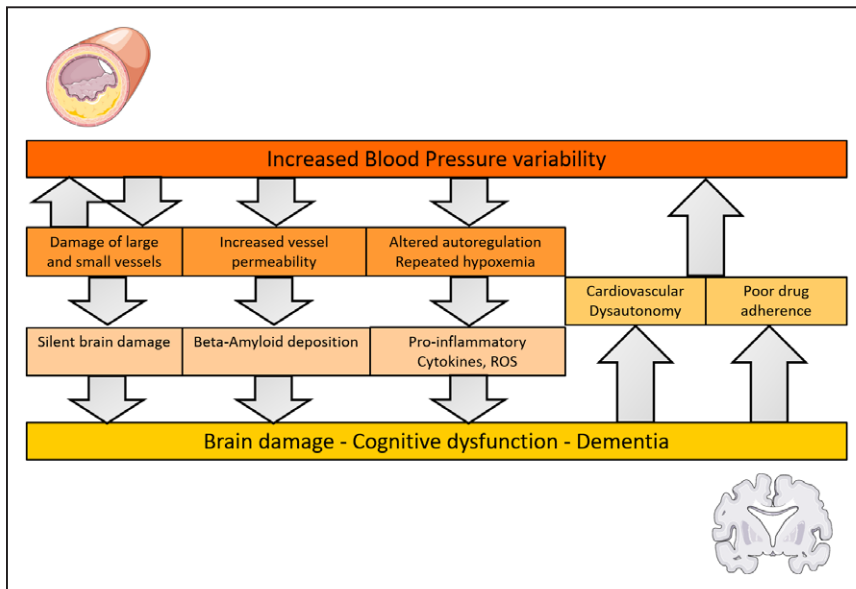


Figure. A simplified view of complex interactions between increased blood pressure variability, cognitive dysfunction, and dementia. ROS indicates reactive oxygen species. The figure was partly created using images from Servier Medical Art (<http://smart.servier.com>). Servier Medical Art by Servier is licensed under a Creative Commons Attribution 3.0 Unported License.

A second question is whether BP variability should be considered as a treatment target; more specifically, would lowering of BP variability decrease the risk of cognitive degradation and prevent dementia? As well known by the reader, this remains unclear not only for cerebrovascular function but also for cardiovascular events potentially associated with increased BP variability.⁸ In the International Database on Ambulatory BP in relation to Cardiovascular Outcome, including population-based cohorts, higher BP values over 24 hours and during the night, but not BP variability, were significantly associated with increased risks of death and composite cardiovascular outcome.⁹ Moreover, a minimum of 48 BP readings allowed an accurate assessment of the association between cardiovascular risk and BP variability.¹⁰

Waiting for stronger evidence, it is nevertheless reasonable to favor treatment strategies likely to decrease BP variability. First, particularly in older patients at risk of cognitive decline, it is advisable to simplify the treatment regimen to improve drug adherence and to opt for forgiving, that is, long-acting drugs to limit potential untoward consequences of irregular drug intake. Second, also according to Rothwell et al,³ it may be appropriate to give preference to calcium antagonists, shown to have a larger impact on BP variability.

However, the more fundamental question underlying discussions on the place of BP variability in risk assessment and prevention of cognitive decline is the nature and direction of the interaction between both. Is increased BP variability one of the drivers of cognitive decline, as suggested by the current study?² On the contrary, may primary brain damage induce BP lability? While a wealth of mechanisms have been proposed to account for BP variability-induced brain damage—structural alterations of large and small vessels, increased vascular permeability leading to β -amyloid deposition, repeated episodes of cerebral hypoxemia with release of proinflammatory cytokines and reactive oxygen species—other studies suggest that neuronal damage per se may be at the origin of autonomic dysfunction and increased BP variability, even before the onset of clinically detectable cognitive dysfunction.^{1,2}

It seems that nature hates unidirectionality and is more comparable to a basilica with multiple entrances than to a gothic church, where one may progress only in a single direction to reach the altar. The global picture is even more complex when one also integrates the uncertainties of human behavior in the jungle of pathophysiologic interrelations. Poor drug adherence favored by subclinical cognitive disturbances may lead to increased BP variability, paving the way for further cognitive decline. The figure provides a simplified view of complex interactions between increased BP variability, cognitive dysfunction, and dementia.

Whatever the chicken and the egg, increased BP variability may alert us to the eventuality of incipient cognitive decline and warrants optimization of cardiovascular and cerebrovascular preventive measures, as well as regular evaluation of cognitive performance.

From a wider perspective, the work of Rouch et al² supports the integration of BP variability in a comprehensive evaluation of arterial function aimed at identifying at an early stage subjects at risk of both cardiovascular disease and cognitive decline.

Disclosures

None.

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