

**EDITORIAL**

# What Is Blood Pressure Variability? Is It Associated With Cognitive Decline and Dementia?

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**B**lood pressure (BP) is one of the key elements for evaluation of health status and one of the older concepts in medicine, introduced by William Harvey in the 17th century. The first published measure was made by Stephen Hales in England in 1733.<sup>1</sup> It was not until the invention of the sphygmomanometer in 1896 by Scipione Riv-Rocci<sup>2</sup> and the description by Nikolai Korotkoff of the sounds using the stethoscope in conjunction with the sphygmomanometer cuff in 1905 that clinical measurements became possible.<sup>3,4</sup> In the first half of the 20th century, insurance companies played a significant role by providing statistical data demonstrating the association of elevated BP with heart disease, renal disease, and strokes.<sup>3</sup> In early years, efforts to treat hypertension included bloodletting and a range of ineffective chemical interventions. Not until the 1950s was the diuretic, thiazide, introduced as the first effective treatment.<sup>5</sup> The levels of systolic and diastolic BP were the primary focus until the concept of BP variability (BPV) was first raised in the 1970s.<sup>6</sup> This concept has gained increased attention in the literature as a potentially significant aspect of BP-related pathology.<sup>7</sup> Today, the American Heart Association has specific guidelines to measure BP in the clinic setting that do not include BPV.<sup>8</sup> The use of ambulatory measures of BP using monitors to assess BP at more regular intervals and different times of day has demonstrated an association between nighttime and early morning dips in BP that may be associated

with all-cause mortality.<sup>9,10</sup> Such observations lend strength to the notion that BPV, in some form, may play a role in cardiovascular health that is essential to general health, including brain health.

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**See Article by Ernst et al.**

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The discovery of Alzheimer disease (AD) brain changes, early on known as "presenile dementia," replaced "vascular hardening" as the underlying pathology, "although vascular changes" and AD often occur together.<sup>3</sup> The distinction of cerebral atherosclerosis and brain changes associated with Alzheimer dementia presents significant diagnostic challenges. A multitude of studies associated BP control in midlife and vascular changes in the brain leading to cognitive impairment.<sup>11–15</sup> Most of these do not address the presence of specific pathological changes identified with AD that until recently have been made primarily postmortem. Recently, evidence of vascular effects on cognitive function that are independent of the presence of AD suggest that vascular disease of the brain does have its own independent effect and that the combination of the 2 may accelerate decline in cognition.<sup>16,17</sup>

In this issue of the *Journal of the American Heart Association (JAHA)*, the report by Ernst et al adds to the issue of BPV and cognitive function but also exposes some of the important missing elements.<sup>18</sup> It describes

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a large population of older adults who were subjects of the ASPIrin in Reducing Events in the Elderly study not originally designed for the purpose of this report.<sup>19,20</sup> Nevertheless, it has some key components that provide a unique opportunity for the longitudinal analysis of BP and BPV, cognitive decline, and dementia. This longitudinal study in Australia and the United States was of older individuals ( $\geq 70$  years and  $\geq 65$  years if a minority) in good health, with preserved cognition, and no life-limiting conditions at enrollment in the ASPIrin in Reducing Events in the Elderly study. People with uncontrolled hypertension or early measured signs of cognitive decline were excluded. Participants were randomized into groups receiving 100 mg of aspirin daily and an equal number receiving placebo who were then followed up for a mean of 4.7 years. Publications of the original study did not demonstrate a significant effect of aspirin on longevity nor did it lower the risk of cognitive decline.<sup>19,20</sup> The current study and analysis by Ernst et al uses the multiple assessments with several different instruments for cognitive function from the ASPIrin in Reducing Events in the Elderly study. Participants were seen annually for clinical assessments, including standardized measures of BP (American Heart Association Guidelines), and were contacted by telephone quarterly for follow-up of general health but no BP data were obtained. BPV was defined as "within-individual SD of mean systolic BP obtained from the baseline, first and second year annual visits." Dementia triggers from any of the battery of standardized assessments were followed up with additional assessments, and the data were reviewed by an expert panel, blinded for study arm, for adjudication of the dementia end point. A total of 16 758 participants of the original 19 114 enrolled remained in the study of BPV. A total of 16 600 were free of evidence of dementia after 2 years, and 396 developed dementia over a median of 2.7 years. A total of 14 105 were free of cognitive impairment at 2 years of follow-up (those developing incident dementia or cognitive decline in the first 2 years of the original study were excluded in this study to minimize immortal time bias during the first 2 years used to estimate BPV). A total of 1993 demonstrated cognitive decline over a further median follow-up of 2 years. In this study, the authors used time-to-event models to calculate the hazard ratios and 95% CIs for incident dementia using tertile stratification of BPV and as a continuous variable. After further 2 years of follow-up, they then demonstrated a significant risk for both dementia and cognitive decline for those in the highest tertile of BPV compared with the lowest. There was similar incident dementia in men (2.6%) and women (2.2%) and similar cognitive decline occurred in 14.7% of men and 13.6% of women. There was a highly significant association in men between BPV in the highest compared with lowest tertile but not in women. The

use of BPV as a continuous variable gave results consistent with those using the tertile. Sensitivity analyses suggested that the relationship between BPV and dementia remained for men, but not for cognitive decline. Finally, neither systolic BP nor diastolic BP nor use of antihypertensive drugs nor hypertension had any measurable effect on either dementia or cognitive decline in men and women.

This study has many of the important characteristics required to assess BPV impact on cognitive decline and dementia: standardized measures of BP, a prospective study with multiple instruments to measure cognition, and a standardized means of defining BPV, dementia, and cognitive decline. Nevertheless, there remain unresolved elements. These include the definition of BPV. In this study, and most others, an SD from the individual mean BP was used as the criterion for BPV. What is the ideal frequency and interval for measuring BPV? Is it sufficient to measure BPV using annual standardized measurements? Does BPV require more frequent measures and perhaps under different conditions to truly reach an empirical and more functional definition of BPV? What might be the physiologic/metabolic process underlying BPV? Ambulatory measures of BP have been suggested as a better means of measuring BPV that allows measures of BP under different conditions and at different times of the day. Do these ambulatory measures of BP dips in BP suggest a different measure of BPV would be more useful?<sup>9,10</sup> Most current busy clinics would not qualify for a standardized measure of BP; it is often conducted through a shirt sleeve, standing up, sitting down, or even on an examination table. Only one measure is typically made. So, use of electronic health records or primary clinic data would not likely suffice to assess BPV. What is the impact of treatment of hypertension on BPV? From the study by Ernst et al and other studies, treatment of high systolic BP does not seem to affect BPV? So, if BPV is a key element for vascular health, what approaches to treatment might be required?

A second issue is the assessment of AD in conjunction with BPV. Although clinical criteria for dementia were applied in the study by Ernst et al, there is no assessment of the presence of characteristic pathological changes associated with AD, other than clinical measures of cognition, at any point in the study, raising the ongoing issue of the role of AD versus vascular disease in dementia. So, in this particular study, there is no means to separate the 2 into independent variables. So, what might make up a more robust, even definitive, study of the role of BPV and vascular health in general and AD in the pathway to cognitive decline and dementia? First, a broader measure of BPV that could accommodate the standardized clinical measures as well as a much more frequent and varied measure of BPV under a range of conditions and associated outcomes.

The use of ambulatory measures of BP has pointed to how this might be done, but there are commercially available wearables emerging that might provide even more data on BPV that could be subjected to newer methods of unbiased analysis to better define what is BPV. This could be done in parallel with the current standardized means of clinical BP measurements to assess their relevance to BPV. Assessments of vascular physiology (eg, flow-mediated dilatation) and other physiologic and metabolic measures in parallel with the wearable BPV measures might provide much more insight into the physiologic and metabolic understanding of BPV that is currently lacking. There seems to be few causative hypotheses around BPV. In such a prospective study, the use of newer imaging technology for AD, such as positron emission tomography scans, would be of great benefit to perform along with the assessment of BPV to help disentangle the relationship between vascular causes and intrinsic AD pathology. No doubt this would be a complex and costly study. Nevertheless, at the moment, we have few offerings to prevent AD; there are many that might be available for preventing the vascular component and in a global epidemic of aging associated with serious cognitive decline and dementia that would be a welcome advance.

## ARTICLE INFORMATION

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### Disclosures

None.

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