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COMMENTARY

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Blood pressure variability and neurocognitive functioning

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Cognitive impairment is a worldwide public health and social care concern. It has striking consequences to patients, caregivers, and the healthcare system, and is an exponentially raising disease burden due to the aging population. Dementia affects approximately 1.5% of people aged 65-70 years and the prevalence increases up to 25% among people aged 85 and over.[1] According to the World Health Organization, around 50 million people currently suffer from dementia, and the number is continuously growing, with nearly 10 million of new cases every year.[2] At this alarming rate, more than 115 million people are expected to be living with dementia by 2050.[3] Hence, the development of measures aimed to prevent and delay the onset and progression of the cognitive deterioration represents a critical priority and emerging need.

1 | BLOOD PRESSURE VARIABILITY: A NOVEL VASCULAR RISK FACTOR

Blood pressure (BP) is well known to fluctuate as the effect of complex interactions between external environmental and behavioral stimuli, intrinsic cardiovascular regulatory mechanisms, humoral influences, and rheological factors.[4] The variations in BP levels can be measured either as the overall variability during a defined time interval—synthesized by means of the standard deviation and coefficient of variation, with or without adjustment for the time trends in underlying mean BP values—or, alternatively, as the average absolute difference between adjacent readings—expressed as the successive variation.[5] The BP fluctuations can be assessed both within minutes and hours (short-term) and across time intervals of days, weeks, and months (long-term) through ambulatory BP monitoring, home measurements, or repeated clinical visits.[5] Far from being a background noise or a phenomenon occurring at random and able to dilute the prognostic value of the average BP measurements, the BP variability (BPV) is increasingly recognized as a causative factor of the alterations in brain structure and function.[6] In the recent years, a growing evidence about the role of the BPV on the onset and course of cognitive impairment and dementia has become available: several cross-sectional and longitudinal, prospective cohort studies have clearly demonstrated that increased daytime, day-to-day and visit-to-visit BP oscillations are significantly associated, independently of average and absolute BP levels, with the cognitive dysfunction both in non-demented and demented patients, and are independent risk factors for the incidence of cognitive impairment and dementia, including Alzheimer's disease and vascular dementia, and the progression of the neuropsychological decline.[7-21]

Different explanations can be proposed for the relationship between the raised BPV and impaired neurocognitive functioning. Hemodynamic instability is one of the putative mechanisms. The shear stress on the vessel wall induced by the steep BP variations can lead to the endothelial injury and disturbances in vascular smooth muscle functioning and, in turn, promote micro-vascular damage and arterial remodeling. The cerebral microcirculatory dysfunction can influence the integrity of the blood-brain barrier and result into neuronal injury and accelerated neuronal loss.[22,23] The artery remodeling can act as an upstream factor of the cerebral blood flow imbalance and favor the β-amyloid deposition and reactive gliosis.[6] Furthermore, exaggerated BPV can have detrimental effects on the cerebral blood flow and hemodynamics.[24,25] Marked oscillations in the arterial BP can favor inconsistent perfusion and repeated episodes of tissue hypoxia-ischemia that are able to promote the microglia activation and brain amyloidogenesis. This may cause neuronal damage and cellular death, particularly in the most vulnerable regions, including the subcortical white matter and the hippocampi.[6,26,27] Notably, the reduced elasticity of the vascular bed and the shift in the limits of the cerebral autoregulation toward higher levels, which are common findings among the elderly individuals or patients with long-lasting hypertension, can make cerebral blood flow highly dependent on the systemic BP and magnify the effects of the BP fluctuations.[28] Accordingly, the high short- and long-term BPVs can be reasonably

responsible of white matter lesions, cerebral micro-bleeds, cortical infarcts, and brain atrophy, all of which may contribute to the cognitive dysfunction.[13,29]

Inflammatory response and oxidative stress may be adjunctive mediators. Endothelial cells and blood-brain barrier damage induced by the BP fluctuations and perfusion unbalances, can induce the over-activation of the microglia and increase the secretion of pro-inflammatory cytokines and reactive oxygen species.[30] The up-regulation of the neuro-inflammatory milieu and the reactive gliosis are strongly hypothesized to further contribute to the neuro-degeneration.[26] In this regards, the BPV has been significantly associated with the markers of inflammation and endothelial activation,[31] and there is strong evidences that supports the role of anti-inflammatory and anti-oxidant treatments in the reduction of target-organ damage, secondary to the BP variations.[32]

Finally, one interesting issue is the interplay between BPV, neuro-degeneration, and autonomic dysfunction. Although it cannot be excluded that BPV may, at least in part, represent an epiphenomenon and a marker of the neuronal loss and cholinergic dysfunction associated with the cognitive deterioration,[33] the autonomic instability can contribute to the pathologic processes underpinning the cognitive decline through the dysregulation of the homeostatic functions and the resulting impairment in the modulation of brain blood flow.[34]

2 | CLINICAL IMPLICATIONS AND FUTURE RESEARCH DIRECTIONS

The perspective suggesting additive or synergistic effects between the cerebrovascular impairment and neuro-degeneration is, undoubtedly, extremely interesting and stimulating since it points out the opportunity to develop preventive and therapeutic strategies.[35] So far, a large body of evidence has shown the association of vascular pathology with impaired cognitive performance and dementia, and the BPV has recently emerged as a reliable risk factor for both brain vascular lesions and cognitive deterioration. To date, however, little attention has been paid to monitoring and controlling BP variations.

First, clinicians and investigators should record the BP values as accurately as possible to analyze the short- and long-term fluctuations. However, in this regard, it should be noted that the assessment of the BPV still lacks standardization. The number and frequency of the measurements and the follow-up intervals varied across the studies. Therefore, further effort would require determining the most appropriate schedule to obtain reproducible and valid estimates of the BPV, define the normality ranges, and identify the pathological thresholds.

Second, the control of the BP stability could represent a significant goal in the clinical management to preserve the cerebral functions and prevent or delay the cognitive decline. Antihypertensive medications have different effects on the intra- and inter-individual BP fluctuations,[36,37] and the calcium channel blockers and diuretics are the most effective options for minimizing the BPV.[38] Notably, the decrease of the BPV limited the end-organ disease in experimental models, and the diuretic use was associated with a significantly reduced risk of Alzheimer's disease in participants with mild cognitive impairment, in addition to, and independently of, mean systolic BP.[39] Also, a pooled analysis of randomized, double-blind, controlled trials found evidence of benefit attributable to nimodipine in the measures of cognitive functions for patients with degenerative, multi-infarct and mixed dementia.[40] Future well planned, prospective, long-term investigations that evaluating (in parallel) the BP fluctuations, imaging markers of brain disease, and cognitive functions that encompass the current main classes of antihypertensive drugs are warranted to examine whether the strategies to reduce the BPV can effectively decrease the risk of the cognitive impairment, revealing whether treatment-effect heterogeneity exists across the different BP lowering agents.

In conclusion, the understanding of the pathogenesis of cognitive deterioration is one of the most effective strategies to confine its global burden. It is suggested that BPV is one of the underlying causes that takes part in processes that leads to neuro-cognitive dysfunction; therefore, it may be a promising interventional target for preventing dementia.

CONFLICT OF INTEREST

None.

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