Cognitive Decline and Dementia
Are We Getting to the Vascular Heart of the Matter?

Jurgen A.H.R. Claassen

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Human lifespan has increased linearly during the past 170 years. Not only do we live to an older age but also we do so in better health and with less disability. Healthcare advances have turned previously fatal or crippling diseases into chronic comorbidities. Especially in the field of cardiovascular medicine, medical advances have shifted the age of onset of common disorders, such as myocardial infarction, to higher age, together with improved functional outcome after treatment. This has led to what is known as compression of morbidity: serious disability caused by chronic diseases occurs only in the last years of life.

Looming over this prospect of a long life in good functional status is the threat of cognitive decline. Rough estimates of the prevalence of dementia show a strong increase with age from 5% at the age of years 65 to 20% at the age of 80 years and 40% at the age of 90 years. The majority (>70%) of these dementia cases results from Alzheimer disease. A distressing note is that, despite tremendous research efforts, all (mainly antiamyloid) Alzheimer drugs that have been developed since the cholinesterase-inhibitors (1996–2001) have failed to produce clinical benefit. For other prominent causes of dementia (vascular dementia, Lewy body dementia, and frontotemporal dementia), there is an equal lack of effective treatment.

However, hopeful news emerges from a previously unforeseen corner: the cardiovascular field. Recent population cohort studies have found that the relative prevalence of all-cause dementia has declined1 (absolute numbers continue to rise because of the growing number of elderly), and this decline has been attributed to the improved cardiovascular care that has been available in the lifetimes of these cohorts. In addition, lifestyles that are known to promote cardiovascular health are associated with lower risk of dementia.2 These observations suggest that the most promising route toward reduction of dementia is through cardiovascular disease.3 However, how cardiovascular disease is linked to dementia is insufficiently known.

In this issue of Hypertension, Böhm et al4 have analyzed ≈25,000 patients at high risk for cardiovascular disease, who had participated in hypertension trials. Patients with cognitive impairment at baseline were excluded, as were patients with uncontrolled hypertension (on-treatment blood pressure [BP] >160/100 mm Hg). This excluded group contained mainly older elderly with more severe comorbidity. Cognitive function was assessed at baseline, after 2 years (100%) and at study end (>90% of patients), which was between 3 and 5.5 years. BP and heart rate were recorded at regular intervals (6 months), with an average of 11 recordings during a period of 4.5 years. These patients provide a wealth of data that are highly welcome in a field that is obscured by cross-sectional studies, short follow-up studies with only a single measurement of BP or cognition, and underpowered intervention studies.

Critics will scrutinize the use of the Mini Mental State Examination as the sole determinant of cognitive function, and the absence of clinical, imaging, or pathological confirmation of diagnosis. The Mini Mental State Examination is insensitive to dementia in patients with higher education and those with vascular dementia and is sensitive to confounding (eg, depression). However, the power here is in the large numbers and repeated assessments. The patterns of decline in Mini Mental State Examination that emerge in this study, taking into account what we have learned from other studies, most likely truly reflect trends of cognitive decline in this population. Approximately 5% of patients developed cognitive impairment (suggesting that they were somewhere on the continuum of mild cognitive impairment and dementia), which is consistent with what would have been expected based on population studies of dementia in this age group.1 Because of this, and because the Mini Mental State Examination is more sensitive to cognitive decline because of Alzheimer disease than to vascular dementia, we can postulate that the causes of cognitive decline in these patients reflect the causes observed in the larger population (ie, mostly Alzheimer, mixed Alzheimer/vascular pathology followed by vascular dementia). This is supported by the fact that exclusion of patients with stroke did not alter the results.4

Before moving to the major and new findings, an important confirmatory finding is that high systolic BP (>145 mm Hg) was associated with incident cognitive impairment (although not as an independent predictor), and that low-normal BP (<124 mm Hg) was not, the latter contradicting conclusions from cross-sectional studies that a low BP may be detrimental for cognitive function. However, the oldest and most frail patients were not included in this analysis, and specifically in this group, optimal BP levels remain unknown.
The new and striking observations reported by Böhm et al are that the risk to develop cognitive impairment was highest (≈10% compared with ≈5%) with (1) higher variability in visit-to-visit BP, independent of the level of BP and (2) higher heart rate. Higher visit-to-visit BP variability has been associated with grater stroke risk, but stroke did not explain the present findings. High heart rate has been linked with poorer cardiovascular outcome, but not previously with cognition. However, it is of interest that cross-sectional studies in patients with Alzheimer have consistently noted higher heart rates than in controls.5,5

How should we interpret these findings? Of course, they may be associations without causality. Patients with cognitive impairment may have poorer adherence to medication and hence more variation in BP. High vascular stiffness may lead to both cognitive decline and BP variation or high heart rate. However, there is also sufficient theoretical evidence to warrant exploration of causality. The direction of any such causality cannot be determined in this study, but on theoretical grounds both directions are plausible. For example, Alzheimer disease is a slowly progressive disease, and amyloid accumulation in the brain precedes clinical symptoms by >10 years. This early accumulation of amyloid, with consequent neurodegeneration, could affect central BP control. Indeed, baroreflex function was reduced in patients with Alzheimer disease, progressing from early stage (mild cognitive impairment) to dementia stage.5 Impaired baroreflex function could explain increased BP variability. Of interest, degeneration of the brain cholinergic neurons is also a prominent finding in Alzheimer disease,5 and the question is whether this extends to the parasympathetic nervous system. Reduced parasympathetic (cholinergic) neurotransmission could well explain higher resting heart rate. Intriguing is that cholinesterase-inhibitors (drugs that stimulate cholinergic neurotransmission) partially restored baroreflex function in patients with Alzheimer disease.5

For the reverse direction, how could variability in BP or high heart rate cause dementia? The brain critically depends on brain perfusion (15%–20% of cardiac output in resting state). Instability in BP, present over long periods of time (as in the patients in this study), may jeopardize perfusion. For example, in a patient in the highest quintile of variability in this study (coefficient of variation >10%) and an average systolic BP of 150 mm Hg, systolic BP could vary between 120 and 180 mm Hg. Even with effective cerebral autoregulation, such changes will affect cerebral blood flow.7 Chronic repetitive mismatches between neuronal demand and supply could lead to neuronal injury and degeneration.8 In turn, and more speculatively, low heart rate, based on animal data, may have beneficial effects on atherosclerosis and endothelial function and thus on cerebral blood flow, and these protective effects may be lost with high heart rates.4

Thinking outside the box, beyond the supply of oxygen and glucose, the brain’s vasculature may play an important role in clearance of toxic waste from the brain, including Alzheimer amyloid-β.9,10 The paravascular circulation of brain interstitial fluid and cerebrospinal fluid along penetrating arterioles is dependent on adequate pulsatile flow.7 Could high BP variation or high heart rate be causes or markers of a reduced vascular clearance?

All in all, the observations by Böhm et al should stimulate a strong research effort, uniting the cardiovascular and neuroscience fields, aimed at elucidating the links between vascular disease and onset and progression of cognitive decline.

Disclosures

None.

References

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Jurgen A.H.R. Claassen

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