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COMMENTARY

Vascular mechanisms of cognitive impairment: roles of hypertension and subsequent small vessel disease under sympathetic influences

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Mild cognitive impairment (MCI) and vascular cognitive impairment are clinically important in the development of Alzheimer disease (AD)[1] and Binswanger disease/vascular dementia.[2,3] The vascular mechanisms of MCI/vascular cognitive impairment, as well as AD with vascular factors, are likely chronic cerebral ischemia due to both hypertensive lipohyalinotic small artery disease and arteriolar-capillary fibrohyalinosis with subsequent dysfunction of the blood–brain barrier.[4,5] These may ultimately cause multiple lacunes in the basal ganglia and the white matter, as well as white matter rarefaction by alteration in the glia and axons.[4]

Sympathetic nerve terminals exist not only in the innermost part of the adventitia, but also in the outer layer of the tunica media in human cerebral arteries.[6] Furthermore, the density of sympathetic terminals in cerebral arterial walls makes up over 30% of the total nerve terminals.[7] These may have roles in the development of angionecrosis/medial necrosis under excessive neurogenic control to smooth muscle layers by repeated arterial constrictions, while maintaining autoregulation of perfusion pressure under persistent hypertension. Thus, earthenware pipe-like subpial medial necrosis and medullary arteriolosclerosis accompanying diffuse white matter lesions in vascular cognitive impairment/Binswanger disease brains appear.[8,9] Moreover, blood–brain barrier alters with aging and even in some normal brain structures such as the olfactory bulb, hippocampus and periventricular areas,[10–12] and blood–brain barrier dysfunctions with the development of capillary collagenosis have been revealed not only in Binswanger disease brains,[13,14] but also spontaneously hypertensive rats and a rat model of chronic cerebral hypoperfusion.[15,16] Recently, it has been shown that the intra-cranial capillary diameter is regulated by pericyte contraction under noradrenergic and purinergic neurotransmitter influences.[17] All the above findings suggest that a failure in autonomic control of cerebral circulation and damage in blood–brain barrier under untreated hypertension have significant roles in the pathogenesis of MCI/vascular cognitive impairment.

The relationship, however, between hypertension and cognitive impairment has long been debated and still remains controversial. The majority of studies suggest that elevated blood pressure (BP) is associated with cognitive decline.[18] Longitudinal studies examining midlife hypertension have reported BP as a risk factor for dementia, suggesting its association with late-life atherosclerosis and vascular mechanisms of dementia. The Honolulu-Asia Aging Study—which tracked 2505 men, ages ranging from 71 to 93 years old, who were dementia-free over a mean of 5.1 years—demonstrated that dementia was significantly associated with high systolic BP, but not with pulse pressure.[19] Hypertension may be expected to predispose patients to the development of small vessel diseases, such as silent lacunar infarcts or white matter lesions, leading to cognitive impairment and finally, dementia.[20] Conversely, it has also been reported that relatively low BP is related to higher prevalence of dementia. The cross-sectional study of the Kungsholmen project—including 1642 subjects, aged 75–101 years—demonstrated that both systolic and diastolic BP were inversely related to prevalence of dementia in elderly people at baseline.[21] They further performed a 6-year follow-up study for community-based dementia-free cohort of 1270 subjects. Subjects with very high systolic BP (>180 *vs.* 141–180 mm Hg) and extremely low diastolic BP ($\leqslant 65$ *vs.* 66–90 mm Hg) showed a significant association with subsequent development of AD or other dementias.[22]

The Bronx Aging Study is a prospective study of 488 community-dwelling elderly individuals—over the age of 75, dementia-free at baseline, and followed at 12- to 18-month intervals. Low diastolic BP significantly influenced risk of developing AD, but not vascular dementia.[23] It can be postulated that BP changes in AD cause degeneration of neurons or reduction of the neurotransmitter pool, which regulate BP. Low BP may thus be a consequence of dementia, as neuronal loss itself may lower BP, particularly in AD. This mechanism may be reinforced by the dysfunction in the autonomic nervous system observed in patients with AD.[24] On the other hand, low BP may be an anticipatory factor for dementia if perfusion pressure decreases due to advanced atherosclerosis or cerebral dysautoregulation. Experimental cerebral hypoperfusion is reported to be associated with overexpression of β-amyloid precursor protein.[25] In follow-up study of lacunar infarction, BP tended to decrease in those who developed dementia, whereas BP tended

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to increase over time in patients with a fair outcome.[26] Autonomic functions, including sympathetic activity, might have a role in changes in BP during the course of cerebral infarction involving the autonomic nervous system and these fiber connections in spontaneously hypertensive rats[27] and hypertensive patients.[28]

Ambulatory BP monitoring is expected to evaluate the course of cognitive worsening in hypertensive patients than casual BP monitoring. On this issue, Guo Haiyan *et al.*[21] presented the valuable finding that abnormal nocturnal BP profile is associated with MCI. Although clinic BP was not significantly different between patients with and without MCI, 24-h nighttime BP level and BP values—especially nighttime systolic BP—were significantly higher in those with MCI than those without (P=0.008). Moreover, riser pattern showed strongest association with MCI, followed by non-dipper and extreme dipper. High absolute systolic BP and non-dipping status were strong indicators for reduced brain matter volume and cognitive impairment.[29] We prospectively studied the relationship between ambulatory BP monitoring values, stroke recurrence and subsequent cognitive decline (Figure 1).[30] High nighttime BP and/or non-dipping status were found to be significantly associated with both stroke recurrence and dementia progression. The Uppsala follow-up study consisted of 999 seventy-year-old men, because high diastolic BP at baseline examination at the age of 50 years was revealed to be related to impaired cognitive performance 20 years later—even after exclusion of men with a previous stroke.[31] Also, cross-sectional measurements at the age of 70 years showed that high 24-h diastolic BP and a non-dipping nocturnal BP pattern, as well as insulin resistance and diabetes, were related to low cognitive function.

A limitation of the study from Guo Haiyan *et al.*,[21] however, is that brain imaging study was lacking. Cognitive impairment has consistently been reported to be strongly associated with brain structural abnormalities; abnormalities such as brain atrophy, asymptomatic infarcts and white matter lesions. It has been suggested that progression of white matter lesions, in particular, correlate with cognitive impairment, not only in patients with cerebrovascular disease history,[32] but also in healthy elderly people.[33] The absence of nocturnal systolic BP decline, particularly riser pattern, was also strongly correlated with extensive white matter lesions.[34] We performed a long-term follow-up study of 177 patients with lacunar infarct for a mean of 8.9 years, using magnetic resonance imaging and ambulatory BP monitoring (Figure 2).[35] Male gender, confluent diffuse white matter lesions and non-dipping status were independent predictors for subsequent development of dementia. We further found in cross-sectional study of 200 patients with lacunar infarction that non-dipper and reversed dipper, as well

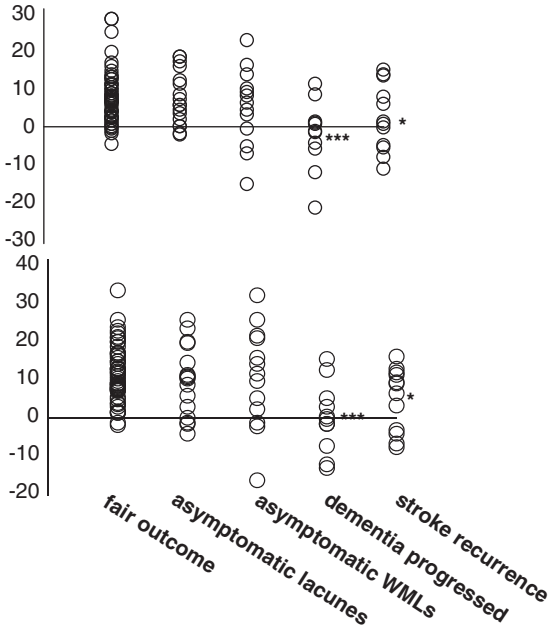

Figure 1 One hundred and five patients with lacunar infarcts were tracked for a mean of 3.2 years. Patients underwent repeated magnetic resonance imaging and 24-h blood pressure monitoring under treatment. The vertical scale indicates a percentage of nocturnal blood pressure decline. The upper figure shows systolic pressure decline. The lower figure shows diastolic pressure decline. Value for each patient is shown by circle according to five different outcomes. Patients with subsequent development of dementia and stroke recurrence showed significant association with reduced nocturnal blood pressure decline (***P<0.001, *P<0.05).

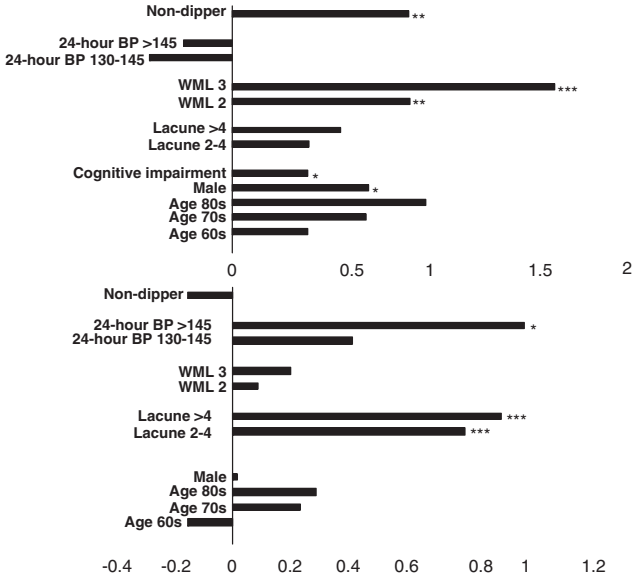

Figure 2 One hundred and seventy seven patients with lacunar infarct were tracked for a mean of 8.9 years of follow-up. Predictors for stroke recurrence (lower half of figure) and subsequent development of dementia appear to differ (upper half). Male gender, confluent diffuse white matter lesions and non-dipping status were independent predictors for subsequent development of dementia, whereas diabetes mellitus (not shown), multiple lacunae and high 24-h systolic blood pressure were independent predictors for stroke recurrence (***P<0.001, **P<0.01, *P<0.05).

as male gender and extensive white matter lesions, were independently associated with cognitive impairment.[36] High nighttime BP and/or non-dipping status, particularly reversed dipper, were significantly associated with extensive white matter lesions.

The underlying mechanism of riser BP or extreme dipper BP pattern is uncertain. Grassi *et al.*,[37] using measurement of muscle sympathetic nerve traffic, observed that sympathetic activation has a major role in BP dipping mechanism, and riser status is more strongly correlated with a sympathetic activation than any dipping status. They suggested that increased prevalence of hypertensive target organ damage or higher incidence of cerebro-cardiovascular events described in non-dipping status may depend, not just on the 24-h BP overload accompanying higher nocturnal BP values, but also on the increased sympathetic activation. Kario *et al.*,[38] on the other hand, investigated the relationship between ambulatory BP monitoring and postural BP variation in elderly hypertensive patients. They showed that abnormal diurnal BP variation closely related to postural BP variation with extreme dippers showing orthostatic hypertension and non-dippers showing orthostatic hypotension. Moreover, the orthostatic BP increase was selectively eliminated by α-adrenergic blocking—indicating that α-adrenergic activity is the predominant mechanism of orthostatic hypertension.[39] Morning BP may be closely associated with α-adrenergic activity. Thus, extreme dipper may potentially facilitate the process of cognitive impairment by morning hypertension, rather than nocturnal excessive BP decline.[40] In any event, it should be noted that a high prevalence of cognitive impairment was observed most frequently in the riser pattern. The vascular pathophysiologic mechanisms of riser pattern and its treatment need to be further explored.

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