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Blood pressure and cerebral blood flow in Alzheimer's disease

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Hypertension is very common in patients across the aging-mild cognitive impairment (MCI)-Alzheimer's dementia (AD) spectrum[1]. Although some studies suggest potential beneficial cognitive effects of antihypertensive agents in older adults[2], findings have been mixed with regard to treatment of hypertension in MCI and AD[3]. Diminished cerebral blood flow and degeneration of cortical regions critical for autoregulatory function (e.g., insular gyrus) are both observed as cognitive impairment progresses, potentially raising concerns over hypoperfusion events[4]. Some smaller studies have suggested possible deficits in cerebral autoregulation and baroreflex sensitivity in MCI and AD, but other studies have shown no differences between cases and controls[5–8]. In this issue of *Hypertension*, de Heus and colleagues report on a detailed study of cerebral autoregulation and baroreflex sensitivity in a relatively large group of older adults who were cognitively normal, MCI or diagnosed with AD[9]. In one of the larger and more comprehensive studies to date, the authors report no deficit in cerebral autoregulation or baroreflex sensitivity in either MCI or AD. These findings have major clinical implications since they could influence treatment decisions in hypertensive patients with cognitive deficits due to AD.

Leveraging baseline data from two clinical trials (NILVAD and Neuroexercise trials) and a separately collected set of older controls, de Hues and colleagues designed a case-control study to compare dynamic cerebral blood flow regulatory mechanisms across the aging-MCI-AD spectrum. Mean cerebral blood flow velocity was measured in the middle cerebral artery using transcranial Doppler ultrasound, continuous blood pressure was monitored by finger photoplethysmography and end-tidal carbon dioxide (CO_2) by nasal cannula. Unlike prior studies, hemodynamic fluctuations were investigated both at rest and during prodigious orthostatic challenges. These included sit-to-stand maneuvers that induced blood pressure changes of approximately 25% baseline, hypocapnia through hyperventilation, and hypercapnia via CO_2 gas inhalation. Cerebral autoregulation was quantified through transfer function analysis calculation of autoregulatory index, gain, normalized gain and phase for mean arterial blood pressure and mean cerebral blood flow velocity. Transfer function

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analysis between systolic blood pressure and R-R interval was used to estimate cardiac baroreflex sensitivity.

Despite being older and exhibiting lower mean cerebral blood flow velocity, AD dementia participants did not differ from controls on resting autoregulatory index or baroreflex sensitivity. Interestingly, they only differed from controls on one resting state transfer function analysis parameter (normalized gain), which actually showed better autoregulatory function. On orthostatic challenge, both normalized gain and autoregulatory index were higher in AD patients relative to controls, again indicating relatively better autoregulatory function in the AD group. No other differences were observed with regard to baroreflex sensitivity or cerebral vasomotor reactivity to CO_2.

A similar pattern of findings was revealed for the MCI group, which did not differ from the control group on resting autoregulatory index, baroreflex sensitivity or any other transfer function analysis parameters. Upon orthostatic challenge, gain was higher in controls than MCI patients but as in the AD group, the MCI group exhibited higher autoregulatory index, indicating enhanced cerebral autoregulation. Importantly, the authors conducted sensitivity analyses to ensure that the findings were not unduly influenced by sex, medications, cerebrovascular burden and cardiovascular risk factor differences, as well as power analysis to ensure that sufficient subject numbers were available to test the hypothesis. Overall the findings suggest that there is no deficit in cerebral autoregulation or baroreflex sensitivity in MCI or AD dementia. In fact, evidence indicated a potential augmentation of dynamic cerebral blood flow regulation in these patients.

Additional findings indicated that mean cerebral blood flow velocity was decreased at rest in AD patients but not MCI patients, yet the MCI group demonstrated greatly increased cerebrovascular resistance index (mean arterial pressure / mean cerebral blood flow velocity) relative to controls. These results are consistent with another recent report that cerebrovascular resistance changes may predate cerebral hypoperfusion in AD[10]. These findings could suggest that the preclinical phase of AD might be characterized by a hyperconstricted cerebrovasculature that is nonetheless functional in terms of dynamic autoregulation, and may even be hyper-reactive to autoregulatory triggers.

How can AD patients exhibit increased cerebrovascular resistance yet show no cerebral autoregulatory dysfunction? The authors offer two potential hypotheses that are not mutually exclusive as possible explanations for this pattern of findings. 1) The increased resistance could be occurring primarily within the arteriolar and capillary beds where AD-related microvascular abnormalities have been described[11]. The relative contribution of the microvasculature versus larger vessels to cerebrovascular resistance remains a matter of debate, but there is extensive evidence for microvascular dysfunction and neurovascular unit impairment in AD[12]. In this scenario, the more intact larger vessels may be able to temporarily compensate to maintain and stabilize cerebral blood flow through dynamic autoregulation during the preclinical disease phase. 2) Consistent with the observed increase in cerebrovascular resistance in the present study, enhanced vasoconstriction has been described in AD[11, 12]. Exaggerated vasoconstriction may facilitate cerebral autoregulation in response to age-related increases in blood pressure, which could ultimately lead to chronic

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hypoperfusion. The present study suggests that this process may leave vasodilation mechanisms intact. Future studies examining dynamic functioning of arteriolar and capillary vessels along with larger vessels may help disentangle the hemodynamic mechanisms involved within each vascular compartment.

There is now convergent evidence from pathological[11], animal model[12] and clinical studies[10] indicating that the cerebral arterioles and capillary vessels are prone to vasoconstriction and increased resistance. Molecular and cellular mechanisms responsible for this observation remain unclear, but may involve upregulation of endothelin-1[11], contractile proteins and calcium signaling in vascular smooth muscle cells, astrocytes, and pericytes[12], as well as superoxide from perivascular macrophages[13]. Cerebral amyloid and tau protein accumulations are the pathological hallmarks of AD, and it has been hypothesized that amyloid may be a causative agent in each of these scenarios. However, recent studies indicate that tau pathology may also impact vascular function[14], and some vascular factors may be independent of amyloid and tau[12]. Whatever the cause, chronic cerebral vasoconstriction may lead to imbalance of neuronal metabolic supply and demand, eventually precipitating cerebral hypoperfusion and contributing to brain injury and cognitive impairment in AD. Whether this increased cerebrovascular resistance may be improved through the use of antihypertensive agents is a critical question for preventative efforts. Some studies have suggested potential salutary effects of antihypertensive medications for cerebral blood flow[15] and cognitive function[2], but findings have been mixed and the mechanism of action remains unclear. The study by de Heus and colleagues suggests that cerebral autoregulatory function is intact in MCI and AD dementia, potentially easing concerns over aggressive blood pressure lowering in a population that is already at risk for hypoperfusion. Additional studies examining effects of antihypertensive medications on cerebrovascular resistance and contractility in this population may provide further insight for treatment guidelines.

The study has a number of strengths, including the size of the sample and the extent to which autoregulatory functions were studied. One study limitation was the lack of AD biomarkers to confirm cerebral amyloidosis and tau-mediated neurodegeneration as the cause of cognitive impairment. Future studies examining dynamic cerebral blood flow regulation in direct relation to AD biomarkers of amyloid, tau and neurovascular integrity may reveal further insights into how the disease impacts vascular function.

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