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Letters to the Editor

Rhythm Control and Dementia in Patients With Atrial Fibrillation: A Role for Glymphatic System?

To the Editor:

We welcome the review by Blum and Conen, which deals with critical connection between atrial fibrillation (AF) and cognitive impairment in an objective and instructive way.[1] Indeed, AF-associated cognitive impairment (AFACI) is an underrecognised category of the dementia spectrum that is potentially targetable for prevention and treatment. Asymptomatic and symptomatic macro− and micro−cerebral embolism is the first to be proposed for AFACI mechanism. Cerebral hypoperfusion due to tachycardia and heart failure, impaired cerebral hemodynamic regulation during irregular cardiac cycles, and neuroendocrine and inflammatory perturbations also may play a role. In addition, the incidence of Alzheimer disease (AD) is higher in patients with AF, and AF is an independent risk factor for AD. Although the mechanism of AD-AF connection is unknown, the shared vascular and genetic risk profile is probably involved. We propose that a mechanistic hypothesis can be added.

Accumulation of neurotoxic forms of amyloid-β and tau proteins is the key in AD neuropathology. The insufficiency of the glymphatic system, which is the amyloid-β paravascular clearance system, is one of the critical steps in this accumulation.[2] The primary drivers of solute exchange between the interstitial space and the cerebrospinal fluid (CSF) in the glymphatic system are arteriolar pulsation and vasomotion. Cardiac diseases such as atrial arrhythmia and heart failure with low ejection fraction may decrease CSF flow with decreased arterial wall pulsatility.[3] In addition, causes of atherosclerosis, such as hypertension or diabetes, which also cause heart disease, reduce cerebral arteriolar compliance and ultimately pulsatility.

We would like to add that AF alone reduces glymphatic clearance by disrupting CSF flow rhythmicity. Even in such a distal circulatory bed, AF affects vascular wall wave dynamics and disrupts periodicity of the arteriolar systolic pulsation wave. This deterioration may be more pronounced, especially when there are highly irregular heart beats and pulses with extreme amplitude. Arrhythmia-caused disturbance in the perivascular convection leads to a decrease in its gain. In addition, this irregularity may cause loss of synchronization with vasomotion.[4] Once amyloid-β retention initiates, it directly affects vasomotion negatively, deteriorating neurovascular coupling gradually and perhaps increasing the need for systolic pulse drive. This may become more evident as the disease progresses. Therefore, AFACI cannot be completely eliminated, even if reduced, by anticoagulation. Stable and sustained AF rhythm control is necessary, at least theoretically, for dementia prevention. Amyloid clearance and cerebral blood flow increase provided by rhythm control contribute to the observed benefit.

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