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Multi-Scale Modelling of the Cerebral Lymphatic System and Its Failure

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Abstract : Alzheimer's disease (AD) is the most common form of dementia and although it has been researched for over 100 years, there is still no cure or preventive medication. Its onset and progression is closely related to the accumulation of the neuronal metabolite Aβ. This raises the question of how metabolites and waste products are eliminated from the brain as the brain does not have a traditional lymphatic system. In recent years the rapid uptake of Aβ into cerebral artery walls and its clearance along those arteries towards the lymph nodes in the neck has been suggested and confirmed in mice studies, which has led to the hypothesis that interstitial fluid (ISF), in the basement membranes in the walls of cerebral arteries, provides the pathways for the lymphatic drainage of Aβ. This mechanism, however, requires a net reverse flow of ISF inside the blood vessel wall compared to the blood flow and the driving forces for such a mechanism remain unknown. While possible driving mechanisms have been studied using mathematical models in the past, a mechanism for net reverse flow has not been discovered yet. Here, we aim to address the question of the driving force of this reverse lymphatic drainage of Aβ (also called perivascular drainage) by using multi-scale numerical and analytical modelling. The numerical simulation software COMSOL Multiphysics 4.4 is used to develop a fluid-structure interaction model of a cerebral artery, which models blood flow and displacements in the artery wall due to blood pressure changes. An analytical model of a layer of basement membrane inside the wall governs the flow of ISF and, therefore, solute drainage based on the pressure changes and wall displacements obtained from the cerebral artery model. The findings suggest that an active role in facilitating a reverse flow is played by the components of the basement membrane and that stiffening of the artery wall during age is a major risk factor for the impairment of brain lymphatics. Additionally, our model supports the hypothesis of a close association between cerebrovascular diseases and the failure of perivascular drainage.

Keywords : Alzheimer's disease, artery wall mechanics, cerebral blood flow, cerebral lymphatics
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