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MODEL-BASED APPROACHES TO CHARACTERIZE CEREBRAL ARTERIAL STIFFNESS AND CSF TRANSPORT WITH MRI

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Akademisk avhandling

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Abstract
Cerebral small vessel disease (cSVD) is prevalent in the aging population and is believed to be an important contributor to cognitive decline, dementia, and stroke. The underlying mechanisms of cSVD remain largely unknown but are potentially linked to cerebral arterial stiffening. With age and vascular risk factors, the arteries lose their elasticity, facilitating transmission of pulsatile blood flow to the brain which potentially harms the microvasculature through processes involving blood-brain barrier (BBB) disruption. However, the association between cerebral arterial stiffness and cSVD is understudied, likely due to the lack of measurement techniques.

Another potential pathway through which brain health can be affected in aging is via its waste clearance system. It entails flow of cerebrospinal fluid (CSF) from the subarachnoid space (SAS) through the brain via perivascular pathways, enabling clearance of interstitial solutes along the way. Here the CSF production, as well as the cyclic motion of the arterial walls are thought to drive the fluid flow. In line with this, studies have demonstrated that injected contrast agents propagate along the major cerebral arteries, although the separate contributions from diffusion and bulk flow are still to be determined.

The aim of this thesis was to propose methods to assess key parameters believed to influence brain health in the ageing population, specifically stiffness of, and CSF transport along, the major cerebral arteries. Furthermore, the aim was to employ the proposed techniques in relevant cohorts to study physiological and pathological processes.

Using whole-brain 4D flow MRI and leveraging the stiffness-dependent time-delays between blood flow waveforms sampled at increasing depths in the cerebral arterial tree, allowed the quantification of a global cerebral pulse wave velocity (gcPWV). We demonstrated that challenges introduced by low temporal resolution could be handled by utilizing the vast number of potential measurement points along the extent of the cerebrovascular tree (Paper I). We also showed that gcPWV did not critically depend on the included vascular depth (Paper II), or the inclusion of specific arterial branches, and that it demonstrated robustness to large reductions in the amount of input data, as well as the expected sensitivity to age (Paper I).

In a population-based cohort, higher gcPWV was associated with white matter hyperintensity (WMH) volume, the most frequently recognized feature of cSVD (Paper II). gcPWV was also associated to change in WMH volume over a 2.5-year period (Paper III). However, controlling for baseline WMH volume suppressed this relationship, suggesting that the predictive nature of gcPWV at an already old age and over a short time window was limited.

Furthermore, gcPWV showed no association with BBB permeability. Combined with an absence of the previously suggested link between WMH volume and BBB permeability, this finding suggests that increased BBB permeability is unlikely to be a primary pathway for cSVD progression in its early stages (Paper III).

To investigate CSF diffusion and bulk flow, we studied contrast propagation following intrathecal gadolinium injection in patients evaluated for idiopathic normal pressure hydrocephalus (Paper IV). Quantitative MRI was used to measure contrast concentrations at baseline and 3, 5, and 7 hours post-injection. By applying an optimization approach based on the 1D advection-diffusion equation, we identified contributions from both diffusion and bulk flow, with movement occurring in an antegrade direction along the major cerebral arteries in the SAS. The measured diffusivity was significantly higher than that of self-diffusion, indicating enhanced diffusion-like behavior. Notably, the bulk flow component matched the magnitude expected from intrinsic CSF production and absorption.

In conclusion, using 4D flow MRI we developed a robust measurement approach to assess global cerebral arterial stiffness, quantified as gcPWV. Our findings showed that gcPWV was associated with both age and cSVD features, suggesting a role for macrovascular dysfunction in cSVD. However, from a longitudinal perspective, gcPWV had limited predictive value for cSVD development. Additionally, BBB leakage was not associated with gcPWV or WMH volume, indicating that BBB disruption was unlikely to be the primary pathway for disease progression in this cohort. Using a novel approach to assess gadolinium propagation along major arteries in the SAS, we identified an enhanced diffusion behavior and a bulk flow magnitude consistent with intrinsic CSF production and absorption. This highlights the role of classical CSF circulation in delivering fresh CSF for brain clearance.

Keywords
Magnetic resonance imaging, 4D flow MRI, imaging, arteries, arterial stiffness, pulse wave velocity, diffusion, advection, bulk flow, CSF, small vessel disease, optimization

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