Cerebral small vessel disease

ADDENDUM

SUMMARY

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Cerebral small vessel disease (cSVD) is an umbrella term that covers all pathologies affecting the small arteries, arterioles, capillaries, and venules of the brain, as described in the introduction to this thesis (**Chapter 1**). The most prevalent form is the age- and cardiovascular risk factor related deep perforator arteriopathy. It is characterized by macrostructural brain tissue lesions that are visible on conventional magnetic resonance imaging (MRI), including white matter hyperintensities (WMH), lacunes, microbleeds and enlarged perivascular spaces. cSVD is an important cause of vascular cognitive impairment (VCI), lacunar strokes, deep intracerebral haemorrhage, and gait problems and mood disorders in elderly. Moreover, cSVD is assumed to be part of a systemic microvascular dysfunction.

Multiple processes have been proposed to be involved in the pathophysiology of cSVD, including a decline in microvessel density (microvascular rarefaction) and changes in cerebral blood flow (CBF), blood-brain barrier (BBB) dysfunction, endothelial and pericyte dysfunction, inflammatory and immunological processes, and impairment of the brain waste clearance system. These processes all occur and interact in the neurovascular unit (NVU). Nonetheless, the precise pathophysiological pathways underlying cSVD, their interaction, and the order in which they occur, remain elusive.

The general aim of this thesis was to gain more insight into the pathophysiological processes in the NVU in cSVD, by applying several advanced physiological MRI techniques, including vessel architecture imaging, arterial spin labelling (ASL), intravoxel incoherent motion (IVIM), and dynamic contrast-enhanced (DCE)-MRI. Additionally, we studied other vascular beds as a proxy for cerebral microvascular function.

In **Chapter 2**, we provided a review on microvascular rarefaction in human brain disorders. We pointed out impaired angiogenesis and active capillary regression, endothelial dysfunction and apoptosis, pericyte loss, and loss of shear stress as the four main pathophysiological pathways involved in microvascular rarefaction. Moreover, we summarized current evidence on the role of microvascular rarefaction in human brain disorders, which was mainly based on studies in animals and human post-mortem studies. Lastly, we elaborated on established and upcoming advanced MRI techniques that can be used to measure (a proxy for) microvessel density in the human brain *in vivo*, including dynamic susceptibility contrast-enhanced (DSC)-MRI, vessel size imaging, DCE-MRI, ASL and IVIM.

In **Chapter 3**, we applied vessel architecture imaging to investigate differences in microvessel density between 40 patients with cSVD and 21 controls from the CRUCIAL-VCI study, a observational cohort study (part of a larger international collaboration) designed to investigate the pathophysiological role of microvascular rarefaction in VCI. Vessel density was lower, and vessel size bigger in WMH compared to normal appearing white matter (NAWM). Vessel density was also lower, and vessel size bigger, in the gray matter, but not the NAWM, of patients

with cSVD compared to controls. Additionally, we showed a shift from capillaries to an arteriole vessel type in patients with cSVD. Higher age and male sex were also associated with lower vessel density, bigger vessel size and a shift from capillaries to arterioles. These findings comply with our hypothesis that the smallest vessels probably are the first to disappear, and support a possible role of microvascular rarefaction in the pathophysiology of cSVD. We also concluded that ageing and sex seem to affect these microvascular alterations.

In **Chapter 4**, we examined the relationship between baseline CBF, assessed with ASL, and cognitive decline over two years' time in 92 patients with VCI and 89 controls from the Heart-Brain study (a multicentre observational cohort study focussing on relationships between the hemodynamic status of the heart and brain, and cognitive impairment). Lower global CBF at baseline was associated with more global cognitive decline. This association was most profound in the domain of attention / psychomotor speed. Moreover, lower baseline regional CBF, in the temporal and frontal lobe, was associated with more decline in memory function. We found no differences in the effect of CBF on cognitive decline between VCI patients and controls. We concluded that impaired CBF at baseline is associated with faster cognitive decline in VCI and normal ageing, and we argued that impairments in CBF precede and contribute to the development of VCI.

In **Chapter 5**, we studied the relationship between the NVU, as a whole functionary unit, and cognitive performance, in 73 patients with cSVD, using canonical correlation analysis. Data were derived from a local observational cross-sectional imaging study on the pathophysiology of cSVD. The latent NVU function variable was composed of measures for BBB permeability, microvascular perfusion, and a proxy for perivascular clearance, which were assessed using DCE-MRI and IVIM. The latent cognition variable was composed of 13 cognitive test scores. We showed a strong canonical correlation between NVU function and cognitive performance, and all different NVU functions contributed to this correlation. This finding supports the concept of NVU dysfunction in cSVD, and stresses the need to target the NVU as whole in future studies.

In **Chapter 6**, we investigated the association between retinal and cerebral microvascular function in 70 participants from the Maastricht Study, a large observational population-based cohort study that focusses on the aetiology, pathophysiology, complications and comorbidities of type 2 diabetes mellitus. Vasoreactivity in response to a flicker light stimulus measured with a dynamic vessel analyzer was used to assess retinal microvascular function, whereas cerebral microvascular function was determined as the blood volume fraction and the microvascular diffusivity derived from IVIM MRI. We found an association between retinal arteriolar vasoreactivity and cerebral microvascular diffusivity. This finding highlights the potential of the eyes to be a window to the brain in early stages of disease. We did not observe any associations between retinal vessel vasoreactivity and the cerebral blood volume fraction, which might be due to other factors that can influence the measurement of the blood volume fraction, such as enlarged perivascular spaces and increased vessel tortuosity.

In **Chapter 7**, we examined the relationship between a combined measure of several microvascular function measures of different organ systems and macrostructural cSVD MRI markers in 1872 participants of The Maastricht Study. Our compound measure of peripheral microvascular function consisted of microvascular function measures of the retina, the kidney, the skin, and plasma biomarkers of endothelial dysfunction. The compound measure was independently associated with WMH volume, but not with the presence of lacunes or microbleeds. We did not find an association between single organ measures and WMH volume, supporting the hypothesis that an overall measure of multiple vascular beds reflects systemic microvascular function better than single organ measures. We concluded that peripheral systemic microvascular dysfunction biomarkers could be useful in the evaluation of the origin of brain microvascular damage.

In **Chapter 8**, the study protocol of the CRUCIAL study is described in detail. This study consists of four parallel observational cohort studies, and will examine the pathophysiological role of microvascular rarefaction and changes in perfusion in VCI and heart failure with preserved ejection fraction (HFpEF) using advanced physiological MRI techniques for both the brain and the heart. Moreover, by studying the microvasculature in the brain, heart, retina, and tongue, and blood biomarkers simultaneously in all subjects, further insights in the multisystem involvement of small vessel diseases will be gained.

Finally, in **Chapter 9**, we provided a general discussion on the meaning and implications of our results, and approached cSVD from three different points of view. Firstly, we discussed how cSVD can be regarded as a disease of the cerebral microcirculation characterized by hypoperfusion, which is probably partly caused by microvascular rarefaction. Secondly, we considered cSVD as a disease of the NVU comprising all its functions, and highlighted the importance of future research to target the NVU as a whole by using multimodal imaging protocols and by focussing on multiple-target, multiple-action drugs. Thirdly, we discussed cSVD in the context of a systemic disease, in which shared underlying pathways cause microvascular dysfunction in multiple organs. We underlined the importance of future research to prioritize these shared mechanistic pathways and of clinical trials to be extended to test benefits to multiple organ systems. Lastly, we discussed how these three different points of view come together.