Systemic and cerebral hemodynamics in response to cardiovascular challenges : the heart-brain connection

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CHAPTER 9

Summary

The brain is a metabolically active organ with little capacity for energy storage. This makes it highly dependent on a continuous supply of nutrients and oxygen. Multiple control mechanisms protect the brain against hypo- and hyperperfusion, which is so efficacious that the brain is often considered a hemodynamically separate entity from the rest of the body.

Despite these protective mechanisms, it is known that patients with cardiac dysfunction have a higher prevalence of cognitive dysfunction and higher risk of incident dementia and Alzheimer's disease. Fortuitously, the unfavorable effects of cardiovascular dysfunction on the brain seem reversible as improvement of cardiac function (for example cardiac transplantation or cardiac resynchronization treatment) restores brain perfusion and improves cognition. This suggests a new preventive and therapeutic target for improving cognition by ensuring blood supply to the brain based on improving cardiac function. Not only diseases of the heart are associated with loss of cognitive function, but diseases of the brain can also affect cardiac function. This bidirectional interrelationship is known under the term: heart-brain axis.

Understanding the heart-brain relation might guide future treatment decisions and give incentive for novel therapy development. The primary aim of the project "Go with the flow: the heart-brain axis" was to elucidate the interaction between heart and the brain, across the lifespan. This was done by integration of physiological concepts into the MRI-environment and by monitoring brain perfusion and its regulatory mechanisms at both the macrovascular level (using transcranial Doppler) and the tissue level (using arterial spin labeling MRI). This thesis focused mainly on the comparison and validation of these two modalities used in this project. Expertise from both the fields of cardiovascular physiology and MRI brain perfusion measurements were integrated into synergistic and comprehensive research protocols.

Chapters 1–3 provide a general introduction on the heart-brain axis, offer an overview of the underlying physiology, employed methodologies, and the physiological challenges and techniques applied in this project.

In **chapters 4, 5 & 6**, we considered the trustworthiness of the general assumption of middle cerebral artery diameter constancy. This assumption is applied to relate the TCD-measured cerebral blood flow velocity (CBFv) changes to changes in cerebral blood flow (CBF), i.e. brain perfusion changes. We applied high resolution MRI at 7 Tesla to investigate the middle cerebral artery (MCA) diameter during various environmental challenges. In **chapter 4**, we manipulated the end-tidal CO_2 concentration and showed that the MCA diameter increased at high levels of end-tidal CO_2. In **chapter 5**, high-resolution images of the MCA were obtained synchronized with the cardiac cycle. We found a subtle increase in MCA diameter during systole compared to diastole, suggesting that the diameter is sensitive to the pressure changes that occur within the heartbeat. Subsequently, in **chapter 6**, the effect of handgrip exercise on the MCA diameter was assessed, showing a small decrease in diameter suggestive of sympathetic influence on the

cerebral macrovasculature. These studies challenge the long-held assumption of MCA diameter constancy.

In **chapter 7**, we compared the CBFv response to rhythmic handgrip exercise in the MCA (measured by TCD) to the CBF response in the MCA flow territory (assessed with arterial spin labeling MRI (ASL)). Differences in arterial blood flow velocities are often used as proxy for changes in flow and brain tissue perfusion. We found that during rhythmic handgrip the CBFv increased, whereas no change in the MCA flow territory could be observed. Therefore, whole-brain CBF-measurements by ASL do not support the claim that a change in MCAv measured by TCD can be used as a proxy for regional CBF during rhythmic handgrip exercise. The observed decrease in MCA diameter during handgrip as observed in **chapter 6** can only explain a small part (approximately one fifth) of the observed discrepancy. Shunting of MCA blood flow during exercise (i.e. not feeding the brain tissue) could explain this discrepancy; however, evidence for such a hypothesized mechanism is currently lacking. Implications for understanding the underlying physiological mechanisms could be far reaching for either one or both modalities, indicating the need to further explore the relation of arterial blood flow and tissue perfusion.

In **chapter 8**, we investigated the influence of cardiac pulsations on pseudo-Continuous ASL (pCASL) signal stability. Due to the long labeling duration in pCASL the relative contribution of the label created at the end of labeling to the detected ASL-signal will be the largest, while this could be highly dependent on the moment of the cardiac cycle when labeling stops. Simulations showed only modest influence of the cardiac cycle, with variations both originating from the amount of label created at the end-of-labeling as well as from different transport times of the label to the imaging region during the post-labeling delay. An end-of-labeling triggering scheme was implemented on the scanner to validate these simulation-findings. In-vivo human experiments did also not show measurable effects of triggering on the ASL-signal intensity or stability. Combined with earlier studies on cardiac triggering, it was concluded that cardiac triggering at the start or the end of labeling has little benefit to pCASL signal stability.