Maintaining cerebral blood flow
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Introduction and outline of the thesis
1.1 INTRODUCTION

‘…Claude Bernard also repeatedly insists, and this deserves especial notice, that when the heart is affected it reacts on the brain; and the state of the brain again reacts through the pneumo-gastric (vagus) nerve on the heart; so that under any excitement there will be much mutual action and reaction between these, the two most important organs of the body...’ Darwin C. (1872)1,2

The brain is a highly metabolic active organ and although it accounts for a small fraction of total body weight (2%), it consumes in the resting condition about 20% of total body oxygen and 25% of total body glucose.3 Interestingly, the brain by itself has hardly no capillary recruitment and lacks almost any form of energy storage. This requires sufficient and uninterrupted supply of blood to the brain and, to this end, it receives ~15% of the cardiac output (amount of blood being pumped by the heart in one minute).4 Acute interruption of the cerebral blood flow (CBF) and with that oxygen delivery to brain tissue, even for a few seconds, has deleterious effects and results in loss of consciousness.5 On the other hand, an increase in CBF to well above normal values may elicit (brain tissue) hyperperfusion with edema development leading to migraine-like headaches, seizures and intracerebral hemorrhage.6 Therefore, safeguarding the brain from respectively hypo- and hyperperfusion is of major importance.

The regulation of CBF is complex and involves a powerful set of control mechanisms including the cerebral autoregulation, chemoregulation, neurogenic regulation and neurovascular coupling.7,8 These mechanisms are largely unique to the cerebral vasculature and act directly on the cerebral vascular resistance. CBF regulation at the level of the brain itself is often assumed to be so efficacious that it is treated as a separate entity.8 The perfusion of the brain is, however, also reliant on a sufficient supply of blood from the heart: acute interruption of CBF due to cardiac arrest9 or occlusion of a large cerebral artery10 results in loss of consciousness within seconds. Thus in addition to an effective set of cerebrovascular control mechanisms, the function of the heart and condition of the large brain-feeding arteries are also important in securing the blood supply to the brain. In other words, CBF also depends on factors beyond the brain.11-14 The idea of considering the cardiovascular system as an integral component of CBF control has laid the foundation of this thesis.

1.1.1 Heart-brain connection

The circulation of blood starts with the heart pumping blood through the blood vessels to the tissue under consideration, in this case the brain. To guarantee a sufficient CBF, all of these elements need to function properly. Evidence has emerged that cardiac dysfunction, impaired vessel patency or a critical reduction in central blood volume lead
to insufficient blood supply to the brain. This affects CBF independently from cerebrovascular control mechanisms whereas, in turn, insufficient brain perfusion may lead to a decline in cognitive performance.\textsuperscript{15}

This followed, among others, from observations in patients with chronic heart failure who showed a lower CBF\textsuperscript{16-18} which is associated with a larger prevalence of cognitive dysfunction.\textsuperscript{19,20} More recently, the Framingham Heart Study revealed in a longitudinal cohort a similar association between a low cardiac output and an increased risk of incident dementia and Alzheimer’s disease.\textsuperscript{21} In addition, about half of the patients with impaired patency of large brain-feeding vessels (for instance in carotid artery occlusive disease), have signs and symptoms of mild cognitive impairment.\textsuperscript{22,23} In patients with chronic heart failure, improvement or reinstitution of cardiac function by, respectively, a left ventricular assist device, cardiac resynchronization therapy or a heart transplantation, improved or restored CBF\textsuperscript{24-26} with beneficial effects on cognitive performance.\textsuperscript{27-29}

There is, as yet, no conclusive evidence that extracranial-intracranial bypass surgery improves cognitive function in patients with a symptomatic internal carotid artery stenosis.\textsuperscript{30} A decrease in central blood volume too large to secure cardiac output may also affect CBF. An example for this phenomenon follows from the daily life physiological observation when healthy humans stand-up. Changing body position from the supine to the upright posture leads to a gravity induced shift in blood from the upper body towards the legs affecting the return of blood towards the right heart (venous return).\textsuperscript{31} The postural reduction in the amount of blood that is directly available to the heart (central blood volume) results in a decline in cardiac output with a drop in CBF and CBF velocity.\textsuperscript{3,32-35}

Aforementioned observations suggest a functional link between the effective arterial blood volume, the heart and brain-feeding vessels on one hand, and brain perfusion and cognition on the other. Optimizing blood supply to the brain by improving cardiovascular function may become a new preventive or therapeutic target for cognitive disorders. As yet, the current monodisciplinary approach by clinicians and researchers alike, leaves the complete heart-brain connection as an incompletely explored territory. A synergy of different expertise fields may provide more insight into the interesting and clinically increasingly important relationships between the heart and the brain.

1.1.2 Aim

From current knowledge on heart-brain interactions, we hypothesize that maintaining CBF requires cardiovascular functional integrity in addition to cerebrovascular autoregulatory control. The challenge of disentangling the contributions of systemic versus local brain blood flow regulatory mechanisms requires expert contribution from various disciplines. At the onset of this research project we had the good fortune to start a multidisciplinary collaboration, working closely with a MRI perfusion expert, a
neuro-radiologist, a pathologist, and an internist-physiologist sharing an interest in the heart-brain connection. The primary aims of the studies presented in this thesis are the delineation of the human heart-brain connection by integrating physiological concepts into the MRI environment and quantification of CBF and its regulation mechanisms at the macrovascular level (using transcranial Doppler ultrasound) and at the tissue level (using arterial spin labeling MRI). This brought together expertise on the characterization of the systemic and cerebrovascular response to physiological challenges in health and disease as well as on brain perfusion at the tissue level using high resolution MRI. From observations in healthy volunteers and in patients with heart failure this thesis attempts to provide at least a partial answer to the following questions:

1. How to challenge the cardiovascular system in a controlled and reproducible manner (Chapter 4.1) and how to apply these interventions in a MRI setting (Chapters 4.2 and 4.3)?
2. Can central hypovolemia be detected non-invasively by arterial pressure wave analysis (Chapter 4.4) and, if so, is cerebral perfusion under those conditions predominantly related to arterial pressure or systemic blood flow (Chapter 6.1)?
3. Is the postural cardiovascular response affected in patients with chronic heart failure and, if so, related to multidrug blockade treatment or the cardiac condition (Chapter 4.5)?
4. What is the effect of CO₂ partial pressure (Chapter 5.1) and of sympathetic activation (Chapter 5.2) on the diameter of the middle cerebral artery as one of the main brain-feeding arteries? Does transcranial Doppler determined CBF velocity in a large cerebral artery reflect CBF in brain tissue as measured with arterial spin labeling MRI (Chapter 5.3)?
5. Does aging influence the relationship between cardiac output and CBF velocity as measured with transcranial Doppler ultrasound (Chapter 6.2)?

1.2 OUTLINE OF THE THESIS

The studies described in this thesis have been performed in two different centers: the Laboratory for Clinical Cardiovascular Physiology of the Academic Medical Center (AMC; affiliated with the University of Amsterdam) and the C.J. Gorter Center for High-Field MRI, Department of Radiology of the Leiden University Medical Center (LUMC).

Chapter 2 provides a brief overview of the physiological principles involved in systemic and cerebral blood flow control. Chapter 3 describes the methods of continuous and non-invasive monitoring of systemic, cerebral and respiratory parameters, followed by
a description of the physiological interventions that were used to assess autonomic cardio- and cerebrovascular control.

**Chapter 4** focuses on the identification and development of cardiovascular challenges that will bring the circulatory system out of balance while being suitable for application in the physiology laboratory as well as inside the MRI scanner. To be able to study the effects of systemic blood flow on brain perfusion, such a challenge need to acutely and reversibly affect cardiac output while being patient friendly (e.g. safe, non-invasive and easily applicable). In **Chapter 4.1** we investigated the reproducibility and robustness of the cardiovascular response to lower body negative pressure (LBNP). LBNP has the potential to serve as a MRI compatible surrogate of orthostatic stress as it also reduces the magnitude of the central blood volume while the subject remains in the supine position. In **Chapter 4.2** we tested whether the cardio- and cerebrovascular response to LBNP performed in the supine body position is representative for the response induced by passive head-up tilt. In **Chapter 4.3** we tested whether we could reduce head movement with a custom designed compact LBNP box (covering only the pelvic region and upper legs) while imposing a similar cardiovascular challenge compared to conventional LBNP. This would be essential to increase the reliability of MRI measurements of cerebrovascular hemodynamics during LBNP.

Whereas the desired effect of cardiovascular challenges applied in this thesis have in common that they modulate the central blood volume, quantifying the central blood volume itself remains difficult. In **Chapter 4.4**, we investigated the value of respiration-related variation in arterial pressure (e.g. pulse- and systolic pressure variation) as potentially useful biomarkers in the detection of central hypovolemia in spontaneously breathing subjects. In addition to studies in healthy volunteers, we determined in **Chapter 4.5** the cardiovascular response to orthostatic stress in patients with a chronically compromised cardiac function.

**Chapter 5** addresses the validity of CBF velocity measurements with transcranial Doppler ultrasound under a variety of circumstances. It has thus far been assumed that the diameter of the large intracranial arteries remains unaffected by changes in arterial CO$_2$ partial pressure and cerebral perfusion pressure. Based on this assumption, changes in CBF velocity are considered directly proportional to changes in CBF. However, inconsistent findings in literature do not exclude the possibility of diameter changes in large intracranial arteries under the conditions of the studies presented in this thesis. Validity of this assumption is relevant for the interpretation of data on CBF velocity obtained by transcranial Doppler ultrasound. We therefore tested the effects of CO$_2$ partial pressure (**Chapter 5.1**) and sympathetic activation by dynamic handgrip exercise (**Chapter 5.2**) on the diameter of the middle cerebral artery using ultra-high-field MRI at 7 Tesla.
Chapter 5.3 addressed whether CBF velocity changes in large brain feeding arteries reflect perfusion changes at the brain tissue level. We therefore compared the CBF velocity response measured in the middle cerebral artery by transcranial Doppler with the CBF tissue response as assessed with arterial spin labeling MRI to sympathetic activation by dynamic handgrip exercise.

Chapter 6 focuses on the relationship between cardiac output and transcranial Doppler determined CBF velocity. In Chapter 6.1 we report on the relationship between CBF velocity and cardiac output on one hand and CBF velocity and arterial pressure on the other when manipulating the central blood volume from depletion to repletion by head-up tilt. Chapter 6.2 describes the influence of aging on the CO-CBF velocity relationship.