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

Verbree, J.

CHAPTER 1

Introduction

The Rembrandt project *"Go with the flow: the heart-brain connection over the life-span"*

The studies described in this thesis were part of a larger project funded by the Rembrandt Institute for Cardiovascular Sciences aimed at studying the influence of cardiac functioning on cerebral blood flow. This project was executed within 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). The research described in this thesis was executed as an integral part of this joined project and the interested reader is also referred to other publications from this project as stated in the list of publications (see: author curriculum vitae).

INTRODUCTION

The brain is a highly metabolically 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 [1]. 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) [2]. 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 [3]. On the other hand, an increase in CBF to well above normal values may elicit (brain tissue) hyperperfusion with formation of edema leading to migraine-like headaches, seizures and intracerebral hemorrhage [4]. Therefore, safeguarding the brain from respectively, hypo- and hyperperfusion is of major importance.

The regulation of CBF is complex and comprises of multiple interlinked physiological mechanisms including the cerebral autoregulation, chemoregulation, neurogenic regulation and neurovascular coupling [5,6]. These mechanisms are largely unique to the cerebral vasculature and act directly on the cerebral vascular resistance. The highly effective and seemingly independent CBF regulation at the level of the brain itself is often treated as a separate entity [6]. 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 arrest [7] or by occlusion of a large cerebral artery [8] results in loss of consciousness within seconds. Thus, in addition to an effective set of cerebrovascular control mechanisms, the function of the heart and the condition of the large brain-feeding arteries are important in securing the blood supply to the brain. In other words, CBF is also dependent on factors beyond the brain [9]. The idea of considering the cardiovascular system as an integral component of CBF control has laid the foundation of the work presented in this thesis and will be discussed into more detail in the following paragraphs.

HEART-BRAIN CONNECTION

The circulation of blood starts with the heart pumping blood through the arteries to the tissue under consideration, in this case the brain. To guarantee a sufficient CBF, all elements of the circulation need to function properly (and) in concert. Evidence has emerged that cardiac dysfunction, impaired vessel patency or a critical reduction in central blood volume each may result in insufficient blood supply to the brain [10]. This affects CBF independently from cerebrovascular control whereas in turn, insufficient brain perfusion may eventually be followed by a decline in cognitive performance [11].

This followed, among others, from observations in patients with chronic heart failure in whom a lower CBF [12-14] was associated with a larger prevalence of cognitive dysfunction [15,16]. In

a longitudinal analysis, the Framingham Heart Study revealed a similar association between a low cardiac output and an increased risk of incident dementia and Alzheimer's disease [17]. In addition, about half of the patients in whom the patency of the large vessels to the brain is affected (for instance in carotid artery occlusive disease), have signs and symptoms of mild cognitive impairment [18,19]. Reinstitution of cardiac function by a heart transplantation, a left ventricular assist device or cardiac resynchronization therapy, improved or restored CBF with beneficial effects on cognitive performance [20-25], but the cognitive improvements after extracranial shunts remain an open issue [26]. These findings suggest that optimizing blood supply to the brain by improving cardiovascular function may become a new preventive or therapeutic target for cognitive disorders. Also, a decrease in central blood volume too large to secure cardiac output may affect CBF, for example during standing-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) [27]. 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. As yet, the current monodisciplinary approach from both clinicians and researchers leave the complete heart-brain connection as an unexplored 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.

AIM

From current knowledge on heart-brain interactions, we hypothesize that CBF control involves cardiovascular function in addition to the principal regulators of cerebral vessel resistance. Disentangling the contributions of systemic versus local brain blood flow regulation is challenging and requires expertise from multiple disciplines. At the start of this research project we had the good fortune to start a multidisciplinary collaboration and work closely with a MRI perfusion expert, a neuroradiologist, a pathologist, and an internist-physiologist sharing our special interest in the heart-brain connection. The primary aim of the project "Go with the flow: the heart-brain connection over the life-span" is to delineate the human heart-brain connection by integrating physiological concepts into the MR-environment and assess CBF and its regulation mechanisms at the macrovascular level (using Transcranial Doppler ultrasonography; TCD) and tissue level (using arterial spin labeling MR imaging; ASL-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. This thesis will mainly focus on the validation and comparison of the two main modalities of this project: TCD and ASL-MRI.

OUTLINE OF THIS THESIS

Chapter 1 introduces and outlines the thesis.

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 pulmonary parameters, followed by a description of the challenges that were used to assess autonomic cardio- and cerebrovascular control.

Chapters 4-6 addresses the validity of cerebral blood flow velocity measurements with transcranial Doppler ultrasonography (see methods section 2.1.2) under a variety of circumstances. It has thus far been assumed that the diameter of the large intracranial arteries remains unaffected by changes in $PaCO_2$ and brain perfusion pressure. Based on this assumption, changes in CBF*v* 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 therefore relevant for the interpretation of data on flow velocity obtained by transcranial Doppler ultrasonography. In **chapter 4** we investigated the effects of CO_2 on the diameter of a large cerebral artery using high resolution MRI at 7 Tesla and in **chapter 5** the distensibility of this artery driven by systolic-diastolic pressure differences. In **chapter 6** the effects of sympathetic activity by dynamic handgrip exercise on the diameter of a large cerebral artery using high resolution MRI at 7 Tesla.

Chapter 7 directly compares the CBF tissue response (ASL-MRI) with the CBF*v* (TCD) response in the middle cerebral artery to sympathetic activation by handgrip exercise in the same subject population to assess whether velocity changes in a large cerebral artery reflect perfusion changes in brain tissue.

Chapter 8 investigates the influence of cardiac pulsations on pseudo-Continuous ASL (pCASL) signal stability.

Chapter 9 summarizes the findings of this thesis and the findings followed by a general discussion in **chapter 10**.