INTRODUCTION

As our life expectancy increases, the number of older people is growing and will keep growing in the future. The prevalence of dementia and cardiovascular disease will continue to increase as a consequence of the aging population. Currently, the number of patients with dementia is expected to rise from 36 million in 2010 to 115 million in 2050 worldwide. It is estimated that 1.5 million patients suffer from cardiovascular disease in the Netherlands (CBS). Cardiovascular disease is the number one cause of death globally, with nearly 18 million annual deaths (World Health Organization). However, dementia is about to overtake the leading cause of death worldwide. Both dementia and cardiovascular disease pose a large burden on patients, caregivers and the society as a whole. Recent studies suggest that dementia and cardiovascular disease are closely related. Patients with dementia and cardiovascular disease share common risk factors such as age, diabetes, smoking and physical inactivity. In addition, patients with cardiovascular disease are at risk for cognitive decline and dementia. Despite these findings, few studies have addressed the connection between the heart and brain. The monodisciplinary approach in which health care and research are currently organized leads to neglecting the cardiovascular status in patients presenting with cognitive complaints at the memory clinic. Vice versa, in patients presenting with cardiovascular disease at cardiology departments little attention is paid to cognitive decline. So, the connection between the heart and brain is an incompletely explored territory in research and in clinical practice.

Research in this thesis is focused on vascular determinants of cognitive functioning and depressive symptoms. In the following paragraphs of this introductory chapter, I first describe the characteristics of dementia and Alzheimer’s disease. Second, I focus on vascular pathology in the brain by describing the characteristics of vascular cognitive impairment and introducing cerebral blood flow. Third, I introduce important gaps in knowledge about the role of cerebral blood flow in the connection between heart and brain. Finally, I end with the aims of this thesis.

**Dementia and Alzheimer’s disease**

Cognitive functioning encompasses different cognitive domains including memory, problem solving and decision-making, attention and production and comprehension of language. Cognitive functioning is assessed using neuropsychological tests that identify the presence and extent of cognitive deficits and the affected cognitive domains. A neuropsychological assessment is essential for a diagnosis of dementia. Dementia is a syndrome that is characterized by significant cognitive decline from a previous level of performance in one or more cognitive domains. The cognitive decline should be of such severity that it interferes with independence in activities of
daily living and is not attributable to a delirium or a psychiatric disorder. Dementia develops gradually and is often preceded by a phase with cognitive impairment that is not sufficient for a dementia diagnosis. This stage is often called mild cognitive impairment or MCI. Patients with MCI have an increased risk of developing dementia. In addition, before the stage of MCI, patients can experience cognitive complaints that cannot be objectified with neuropsychological assessment, meaning that patients perform within the normal range on cognitive tests. The majority of these patients with subjective cognitive decline (SCD) are worried well and can be reassured, but a small part of them will develop dementia.

The most common cause of dementia is Alzheimer’s disease (AD), a neurodegenerative disease accounting for 60-80% of individuals with dementia. Patients with AD typically present with difficulty to remember newly learned information, but also problems with orientation and executive functioning (i.e. organization, planning, flexibility and other higher order cognitive functions). Neuropathologically, AD is characterized by loss of neurons and synapses in the cerebral cortex. Histopathological characteristics of AD are amyloid β plaques and neurofibrillary tangles. Although AD is the most common form of dementia, it is increasingly recognized that vascular brain injury is an independent cause of, and an important contributor to cognitive impairment.

**Vascular cognitive impairment**
The term vascular cognitive impairment (VCI) captures the entire spectrum of vascular brain injuries that contribute to any degree of cognitive impairment, ranging from SCD and MCI to full blown dementia. Both pathological and clinical studies showed that a diagnosis of dementia due to pure vascular brain injury (i.e. vascular dementia) accounts for only <10% of all dementia cases. However, pathological studies also showed that the prevalence of any form of vascular brain injury in elderly is extremely high (up to 75% of patients with dementia). Furthermore, co-existence of multiple pathologies (also known as dementia due to mixed pathology) is common, in particular at old age. The most common mixed pathology is AD with vascular brain injury. In order to make a diagnosis of VCI, an important role is attributed to structural brain imaging, since it provides evidence of vascular brain injury. Vascular brain injury is broadly divided into manifestations of large vessel disease, e.g. large (sub-)cortical infarcts, and small vessel disease. Common manifestations of small vessel disease on magnetic resonance imaging (MRI) are white matter hyperintensities (WMH), lacunes and microbleeds (Figure 1). The type, severity and location of vascular brain injury contributes to the phenotype and/or severity of cognitive impairment. Typically, patients with VCI have mental slowness and problems with executive functioning, but also memory problems, behavioral changes and neuropsychiatric symptoms including depression or apathy are common. Main risk factors for VCI and dementia are hypertension (high
blood pressure), hypercholesterolemia (high cholesterol), diabetes mellitus, obesity, physical inactivity and smoking. A recent study in the UK showed that around 35% of all dementia cases are attributable to a combination of risk factors. This would suggest that management of vascular risk factors has potential to prevent dementia.

Figure 1. Examples of vascular brain injury in four different patients. A: White matter hyperintensities; B: multiple microbleeds indicative for cerebral amyloid angiopathy (CAA); C: lacunes; D: large vessel infarct.

A main hitch in dementia research is the limited knowledge about how vascular brain injury contributes to cognitive impairment or neuropsychiatric symptoms in individual patients, as the severity of symptoms not always correspond to the burden of vascular brain injury. For example, we see patients at the memory clinic with extensive WMH or lacunes and no or mild cognitive impairment, whereas other patients with similar vascular brain injury might have severe dementia. As neuropsychiatric symptoms are common in patients with vascular brain injury, psychiatric disorders such as depression are often included in the differential diagnosis. In addition, we know little about the potential effect of mixed brain pathologies, such as AD, which could explain a substantial part of the symptoms in patients with VCI. To improve our understanding of VCI and to allow for a more accurate diagnosis, we need to investigate the role of vascular brain injury in cognitive impairment and neuropsychiatric symptoms. This would lead to a larger understanding why some people with severe vascular brain injury develop dementia with or without neuropsychiatric symptoms, while others appear to be cognitively normal. Therefore, in this thesis, we aimed to investigate the role of vascular changes on cognitive functioning and neuropsychiatric symptoms in non-demented patients and memory-clinic patients.

Cerebral blood flow

Biological markers or biomarkers are measurable indicators that reflect a biological state or condition. Biomarkers of amyloid plaques, measured in cerebrospinal fluid (CSF) or
with amyloid position emission tomography (PET), represent the earliest detectable changes in the course of AD and can be detected up to decades before the first clinical symptoms occur.\textsuperscript{16,19} However, amyloid markers have already plateaued by the stage of mild cognitive impairment (MCI) (Figure 2). Also, the amount of amyloid does not correlate well with the clinical course of AD or cognitive functioning,\textsuperscript{20} which make amyloid markers less suitable as a measure for disease severity. Functional and metabolic markers, such as glucose metabolism or cerebral blood flow (CBF), are abnormal in the MCI stage but continue to change well into the dementia stage (Figure 2).\textsuperscript{18} Therefore, functional markers are potentially more suitable as a measure for disease severity.

Figure 2. Hypothetical model of biological markers in Alzheimer’s disease.\textsuperscript{18}

Cerebral blood flow (CBF) is defined as the blood supply to the brain in a given time frame. Previous studies have found that global and regional CBF decreases in aging and in neurodegenerative diseases.\textsuperscript{21,22} It is hypothesized that this decrease in CBF is associated with vascular risk factors and risk factors for AD. There is increasing evidence that CBF is reduced in patients with mild cognitive impairment and AD, compared to healthy individuals.\textsuperscript{23,24} Reduced CBF has been found to predict conversion to mild cognitive impairment or dementia.\textsuperscript{25} In addition, reduced CBF has been associated with cognitive impairment in the general population and in patients with cognitive complaints.\textsuperscript{23,26–28} Previously, we found that reduced CBF not only reflects neurodegenerative changes (i.e. atrophy), but is also associated with vascular brain injury.\textsuperscript{29}
Although there is convincing evidence that changes in haemodynamics contribute to the development of cognitive impairment, the mechanisms involved are incompletely understood. Most studies investigating CBF and cognitive functioning had small sample sizes and used only a cognitive screening test (i.e. Mini-Mental State Examination (MMSE)) or a few neuropsychological tests to evaluate cognitive functioning. It is currently unclear to what extent haemodynamic changes determine cognitive impairment in patients with memory problems. In addition, it is currently still unknown if reduced CBF is a consequence of the neurodegenerative disease process in AD (i.e. less demand of oxygen as a consequence of atrophy of the brain) or whether it reflects impaired vascular function and as such is a causative factor in the disease process of AD.

**Arterial spin labeling**

Arterial spin labeling (ASL) is a relatively new MRI technique to measure CBF in the brain. With ASL, arterial blood water is magnetically labeled at the site where the blood flows through the carotid and vertebral arteries into the brain. In Figure 3 this is depicted as the label plane. The labeled arterial blood water is then used as an endogenous tracer. After a certain amount of time (transit time), the tracer reaches the brain tissue and imaging is performed at the acquisition plane. In addition, a control image without labeling is acquired. The perfusion signal or the CBF map is calculated by subtracting the control or unlabeled image from the labeled image. ASL is usually expressed as volume of blood that flows through 100 grams of brain tissue per minute (mL/100g/min). An important advantage of ASL is that it is a non-invasive imaging technique (i.e. without a radioactively labeled tracer) and that it can be derived during the same scanning session as structural images, making it a feasible technique in a routine clinical setting. In addition, distinct patterns of regional CBF changes, measured with ASL, can help in the differentiation between neurodegenerative diseases, such as AD, frontotemporal dementia and dementia with Lewy Bodies. In this thesis we use ASL to measure CBF.

![Figure 3. Schematic overview of arterial spin labeling acquisition. MRI sequence in which two acquisitions are carried out: one with the labeling of arterial blood water and one without labeling (the control acquisition). The subtraction of the control image from the labeled image provides a perfusion image, the CBF map.](image)
The heart-brain axis

The adult human brain accounts for only 2% of the body weight, but it receives about 20% of the cardiac output (amount of blood being pumped by the heart in one minute). As CBF is reliant on a sufficient supply of blood from the heart, it is obvious that heart and brain are related to each other. Insufficiency in blood supply may lead to essential damage of the brain. Therefore, blood flow to and blood flow in the brain is securely controlled by a complex set of control mechanisms including cerebral autoregulation, chemoregulation and neurovascular coupling. Ineffective control mechanisms could lead to an insufficient blood supply to the brain. Earlier studies showed that patients with impairment in systemic haemodynamics (i.e. changes in dynamics of blood flow) such as chronic heart failure or carotid occlusive disease have reduced CBF, which is associated with a larger prevalence of cognitive impairment. A longitudinal study in participants from the Framingham Heart Study showed that low cardiac output is associated with an increased risk of dementia. In addition, studies showed that strategies to restore the haemodynamics, for example cardiac transplantation or extracranial-intracranial bypass surgery, improved cognitive functioning. Despite this evidence, if and how changes in CBF contribute to the development and progression of VCI are relatively unexplored. In addition, cardiovascular disease and vascular risk factors are highly prevalent in elderly and ultimately these diseases may have its consequences on CBF. To understand the contribution of haemodynamic changes to VCI, the Heart-Brain Connection study has been initiated: a unique national multidisciplinary collaborative network with different disciplines, from neurologists to cardiologists, radiologists and neuropsychologists. The Heart-Brain Connection study focuses on the role of haemodynamic abnormalities along the heart-brain axis in VCI to provide more insight in the relationship between the heart and the brain. Currently treatment of VCI is restricted to secondary prevention by prescribing either platelet antiaggregants or anticoagulants and treating vascular risk factors, such as high blood pressure. Although the prevalence of VCI is increasing, few intervention studies focus on treatments for this specific group. Optimizing the blood flow to and in the brain by improving cardiovascular function or treating vascular risk factors could potentially lead to a new preventative and therapeutic target for patients with cognitive impairment. The Heart-Brain study also focuses on potential treatment options for patients with VCI, aiming at improving the haemodynamic status.

General aim

This thesis, focusing on cerebrovascular aspects of cognitive functioning and neuropsychiatric symptoms has three aims: First, to investigate the relationship between CBF and cognitive functioning. Second, to establish the role of haemodynamics...
along the heart-brain axis in cognitive functioning. And third, to investigate the implication of small vessel disease on depressive symptoms.

**Thesis outline**

In the first part of this thesis we provide an overview of the Heart-Brain study *(chapter 2)*, a multicenter cohort study with follow-up measurements in patients with heart failure, carotid occlusive disease and VCI. We also present the design and methods of the ExCersion-VCI study, an experimental sub study of the Heart-Brain study *(chapter 3)*, which is a randomized controlled trial testing the effect of aerobic exercise on CBF in patients with VCI.

The second part focuses on haemodynamic changes and cognition. First, in *chapter 4*, we studied the relationship between CBF and cognitive functioning in a memory clinic cohort in patients with subjective cognitive decline, mild cognitive impairment and AD. In addition, we investigated the prognostic value of CBF in patients with AD in the same cohort *(chapter 5)*. Second, in *chapter 6* we examined the association in a population-based cohort with three ethnic groups: European, African-Caribbean and South-Asian healthy elderly. Third, we investigated the occurrence and profile of cognitive impairment in three patient groups with dysfunctioning in dynamics of blood flow along the heart-brain axis *(chapter 7)*. And finally, in *chapter 8* we investigated the association between CBF and cognitive functioning in the Heart-Brain study: in patients with heart failure, carotid occlusive disease and VCI.

In part three of this thesis, markers of small vessel disease in relation to depressive symptoms are investigated. In *chapter 9* the relationship between severity of small vessel disease markers and depressive symptoms was studied in a memory clinic cohort in patients with subjective cognitive decline, mild cognitive impairment and AD. In *chapter 10* we investigate the relationship between the location of WMH and depressive symptoms in patients with VCI using a lesion symptom-mapping technique. Finally, the last part of this thesis *(chapter 11)* summarizes the main findings of this thesis, followed by a general discussion of the results. The thesis ends with suggestions for further research.
REFERENCES


