Neuropathological changes in mouse models of cardiovascular diseases

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General introduction
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Cardiovascular disease (CVD) and cognitive decline are common conditions in the elderly, causing major morbidity and mortality. The social and economic burden that derives from CVD and cognitive decline becomes increasingly important in an aging population. Although there are treatment options available for CVD, no treatments are available to stop or slow the progression of cognitive decline into dementia. However, there is increasing evidence for a link between the presence of CVD and the development of dementia. Exploring this link is important, since understanding the underlying mechanisms will help to further understand the disease and may lead to the identification of new treatment targets for patients with cognitive decline and dementia. At the start of the 20th century it was already recognized that vascular diseases like arteriosclerosis were important contributors to dementia. However, research on causes and treatments of dementia at the end of the 20th century shifted towards amyloid beta deposition as the main cause for dementia, especially for its most prevalent subtype Alzheimer’s disease. In the last decade, the research community again recognizes the multifactorial nature of dementia, including the contribution of cardiovascular risk factors.

Dementia

The overall prevalence of dementia is 5-7% in people aged 60 years and above. In a recent approximation, the global prevalence of demented people was estimated to double every 20 years. The authors retrospectively estimated a total amount of 24.3 million dementia cases in the year 2010 and it is believed that this number will increase to approximately 65.7 million in 2030 and 115.4 million in 2050. These estimations are based on the population growth and demographic aging, with a constant dementia prevalence per age group. New evidence, however, suggests that the prevalence per age group is declining. This decline is limited to the population with a higher educational level (i.e. finished high school). Interestingly, this decline in dementia prevalence coincides with a decline in vascular risk factors, except for obesity and diabetes, within this same population subgroup. Nonetheless, this decline in dementia prevalence per age group does not mean that the total occurrence of dementia in the total population is reducing. The worldwide burden of dementia is still increasing due to the increase in life expectancy. Since dementia is estimated as the most burdensome neuropsychiatric disorder in elderly, this increase in patients will lead to an enormous increase in costs in the near future.
According to the World Health Organization International Classification of Diseases, dementia is “a syndrome due to disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement.” Several forms of dementia have been distinguished. Alzheimer’s disease is thought to be the most prevalent form of dementia, followed by vascular dementia. Other forms of dementia include pure Lewy body dementia, Lewy body variant of Alzheimer’s disease, frontotemporal dementia (including Pick’s disease) and miscellaneous dementia. The observed neuropathology and (strongest) affected cognitive domains differ between the dementia subtypes. In the following sections we will discuss the major dementia subtypes, vascular dementia and Alzheimer’s disease, and their relationship with CVD in more detail.

**Vascular cognitive impairment and vascular dementia**

Vascular dementia is the most severe form of vascular cognitive impairment (VCI), which is the collection of all cognitive changes from mild cognitive impairment to dementia, caused by any cardiovascular factor. Cognitive impairment in the milder forms of VCI does not always include memory impairment, but may also refer to impairment in attention, language, visuospatial or executive function domains. CVDs associated with an increased risk of vascular cognitive impairment and vascular dementia include heart failure, hypertension, atherosclerosis and cerebral small vessel diseases including ‘Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy’ (CADASIL).

One of the leading hypotheses is that cerebral hypoperfusion is the central player in the association between CVD and cognitive impairment. Heart failure, hypertension, and atherosclerosis have all been independently associated with reduced cerebral blood flow (CBF). In addition, reduced CBF is associated with increased brain pathology and cognitive decline. Brain pathology found in patients with VCI and vascular dementia include white matter lesions (visible as white matter hyperintensities on MRI scans), blood-brain barrier alterations, (micro) infarcts, inflammation and brain atrophy. Reduced CBF is thought to be an early event in the disease progression (chapter 2 figure 2). This is for example shown in hypertensive patients, in whom associations have been found between baseline cerebral hypoperfusion and cognitive decline during a 3 year follow-up period.
Alzheimer’s disease and vascular factors

Alzheimer’s disease is characterized by the accumulation of fibrillar amyloid beta peptides in the brain parenchym, called senile plaques, and by intracellular neurofibrillary tangles consisting of hyperphosphorylated tau. According to the amyloid hypothesis, the tangles, plaques and soluble forms of amyloid beta are the key initiators for the loss of neurons, synapses and white matter that will lead to cognitive impairment, especially memory impairment. Neurofibrillary pathology starts in the transentorhinal and entorhinal regions, which includes the hippocampus, and progresses into the limbic allocortex and neocortex. In addition, cerebral inflammation and oxidative stress are thought to be important factors in the disease initiation and progression.

There is accumulating evidence that vascular dysfunction and hypoperfusion also play an important role in the development of Alzheimer’s disease. Patients with Alzheimer’s disease and vascular dementia share common cardiovascular related risk factors and diseases. These include high blood pressure, aortic stiffening, increased carotid intimal medial thickness, coronary artery disease, atrial fibrillation, aortic and mitral valve damage. Regional CBF reduction has been observed in patients with Alzheimer’s disease compared to cognitively normal subjects and this decrease is associated with cognitive decline in domains corresponding with the regions with CBF reduction. Patients with mild cognitive impairment, which converted to Alzheimer’s disease in a follow-up period of 1-3 years, showed a reduction of baseline CBF in specific brain areas compared to patients who did not convert in the same time period. This suggests that CBF reduction is an early finding in Alzheimer’s disease patients and could possibly be used as a biomarker or treatment target in the future.

These links between Alzheimer’s disease and cardiovascular factors have led to the idea that the number of ‘pure’ Alzheimer’s disease cases is actually far less than has been estimated. Most patients probably have a ‘mixed’ form of dementia, combining both Alzheimer’s disease pathology and vascular dementia.

Cardiovascular diseases associated with cognitive impairment

There are several CVDs associated with an increased risk of cognitive impairment and dementia. CVDs most relevant for this thesis are atherosclerosis and heart failure.
Atherosclerosis

Atherosclerosis is a chronic inflammatory disease of the vessel wall. The development of atherosclerotic lesions starts with the accumulation of lipoproteins and macrophages in the intima of the arterial wall. This usually expands to fatty streaks characterized by lipid-laden smooth muscle cells and macrophage foam cells. Subsequently, extracellular lipid droplets will form between smooth muscle cells and adaptive intimal thickening is present. More advanced lesions are characterized by lipid cores, necrotic cores, thick layers of fibrous connective tissue and calcifications, and are called complicated lesions in the presence of hematoma and thrombus formation. Cerebral atherosclerotic lesions are usually less advanced compared to extracranial lesions. They develop approximately 20 years later in life and show a more stable phenotype. The presence of atherosclerotic lesions may lead to a reduction of the arterial lumen, thereby reducing the blood flow to distal organs. However, the thickening of the arterial wall does not always lead to lumen narrowing, but may instead increase the size of the external boundary of the artery, also known as outward remodelling. Although not all atherosclerotic lesions lead to lumen narrowing, both coronary and cerebral atherosclerosis have been associated with reduced CBF. The decline in CBF in patients with cerebral stenosis or occlusion was related to executive dysfunction. In addition, more severe coronary and cerebral atherosclerotic lesions have been found in patients with dementia compared to control subjects. The association between carotid artery atherosclerosis and CBF is still under debate. Differences in findings between distinct vessel beds could be caused by differences in studied populations. Carotid atherosclerosis associations studies have been performed in population-based cohorts, while coronary and cerebral atherosclerosis studies were performed in patient groups. Nonetheless, carotid artery atherosclerosis has been associated with an increased risk for dementia and associations have been reported of carotid intimal medial thickness and stenosis with poorer performance in cognitive tests and accelerated cognitive decline. In addition to the link between atherosclerosis, CBF reduction and cognitive decline, associations have also been shown between atherosclerosis and brain pathology. Calcifications in both peripheral and cerebral vessels have been associated with the presence of cerebral infarcts, increased volume of white matter lesions and decreased total brain volumes. Not only calcifications, but also carotid artery plaque score and intimal medial thickness correlate with brain atrophy and white matter hyperintensities. Furthermore, associations have been found between midlife aortic atherosclerosis and the presence of periventricular white matter lesions.
years later. The presence of white matter lesions, cerebral infarcts and smaller brain volumes in patients with atherosclerosis are associated with impairments in executive performance. In addition to cerebral pathologies associated with vascular dementia, patients with cerebral atherosclerosis also show increased Alzheimer’s disease pathology, such as an increased amount of amyloid plaques and neurofibrillary tangles. The existing link between atherosclerosis, CBF and cognitive function has been even further established by the improvement of cerebral perfusion and cognitive function after carotid artery stenting. This suggests that VCI and vascular dementia may be (partially) reversible processes and the recognition of the underlying risk factor or disease may lead to new treatment possibilities in these patients.

Heart failure
Heart failure arises due to an abnormality in the structure, function, conduction or rhythm of the heart. Underlying causes of heart failure include myocardial infarction, cardiomyopathy, degenerative or rheumatic valve disease, atrial fibrillation and high blood pressure. Heart failure can lead to reduced left-ventricular ejection fraction, which has been correlated to reduced cognitive performance. The low cardiac output may be the cause of the reduced CBF, CBF velocity, and cerebrovascular reactivity observed in heart failure patients, which in turn may lead to the observed brain atrophy, brain infarcts and lower cognitive performance.

Improving heart function by cardiac resynchronization therapy improves cognitive function within 3 months, while heart transplantation improves cognitive function 1 year after surgery. These findings support the hypothesis that an impaired heart function can influence cognitive performance and that this might be (partially) reversible.

Aims and outline of this thesis
Although many association and correlation studies have been published about cardiovascular risk factors and diseases in humans in relation to brain pathology and cognitive decline, the mechanisms underlying the disease progression of dementia are still largely unknown. In order to study these mechanisms, animal models with comparable etiology and neuropathology are needed. However, there is not yet a clear consensus on which animal models are suited to study the relationship between CVD and cognition and its underlying mechanisms.
The objective of this thesis is to study the neuropathological changes in different mouse models of cardiovascular diseases in order to get insights in which animal models are suited for mechanistic studies to investigate the relationship between CVD and cerebral hypoperfusion, brain pathology and cognitive decline.

Our main hypothesis is that different CVDs in mice contribute to the development of neuropathological changes related to cognitive impairment and dementia. Our first specific hypothesis is that intracranial atherosclerosis is not present in mice and thus does not contribute to the neuropathological changes.

Our second specific hypothesis is that, although the absence of the ApoE protein plays an important role in the development of neuropathological changes in atherosclerotic mouse models, severe extracranial atherosclerosis also contributes to the development of neuropathology. Our third specific hypothesis is that cerebral hypoperfusion is the common denominator in the different cardiovascular diseases and this is the key initiator of neuropathological changes and cognitive decline.

To achieve this goal we start in chapter 2 with reviewing the literature on different cardiovascular mouse models for which cerebral changes have been reported. Models included are mouse models for atherosclerosis, heart failure, hypoperfusion, hypertension and CADASIL.

Chapter 3, 4 and 5 focus on mouse models with atherosclerosis. In chapter 3 we assess whether mice develop intracranial atherosclerosis. This is important to determine, so we will know whether neuropathological changes in atherosclerotic mouse models can be triggered by intracranial atherosclerosis or whether they are an indirect effect of extracranial atherosclerosis. Because it is already known from humans that differences in atherosclerotic susceptibility exist between extra- and intracranial vessel beds, we also studied differences in vessel wall characteristics between extracranial and intracranial vessels in atherosclerotic mice. In chapter 4 we report on blood-brain barrier leakage and the presence of xanthomas in the brains of the atherosclerotic mouse models ApoE\(^{-/-}\) and ApoE\(^{-/-}\)Fbn1(C1039G)\(^{+/-}\), which is a recently described mouse model with severe extracranial atherosclerosis even containing features of complicated atherosclerotic lesions. In chapter 5 we evaluate whether extracranial atherosclerosis in ApoE\(^{-/-}\) and ApoE\(^{-/-}\)3L.CETP mice leads to neuropathological changes. In chapter 6 we investigate the effects of experimental induction of bilateral carotid stenosis, transverse aortic constriction or myocardial infarction in mice on CBF and neuropathological changes. The results obtained in this thesis are discussed in chapter 7 and summarized in chapter 8.
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CHAPTER 1


