

# Heart failure and Alzheimer's disease

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**Abstract.** Cermakova P, Eriksdotter M, Lund LH, Winblad B, Religa P, Religa D (Karolinska Institutet, Huddinge, Sweden; International Clinical Research Center and St. Anne's University Hospital, Brno, Czech Republic; Karolinska University Hospital; Karolinska Institutet, Karolinska University Hospital; Karolinska Institutet, Stockholm, Sweden). Heart failure and Alzheimer's disease (Review). *J Intern Med* 2015; **277**:406–425.

It has recently been proposed that heart failure is a risk factor for Alzheimer's disease. Decreased cerebral blood flow and neurohormonal activation due to heart failure may contribute to the dysfunction of the neurovascular unit and cause an energy

crisis in neurons. This leads to the impaired clearance of amyloid beta and hyperphosphorylation of tau protein, resulting in the formation of amyloid beta plaques and neurofibrillary tangles. In this article, we will summarize the current understanding of the relationship between heart failure and Alzheimer's disease based on epidemiological studies, brain imaging research, pathological findings and the use of animal models. The importance of atherosclerosis, myocardial infarction, atrial fibrillation, blood pressure and valve disease as well as the effect of relevant medications will be discussed.

**Keywords:** Alzheimer's disease, dementia, heart failure, neurocardiology, neurovascular unit.

## Introduction

Dementia and heart failure (HF) both represent growing social, healthcare and economic problems. It is estimated that there were more than 35 million persons worldwide with dementia in 2010, and this number is expected to double every 20 years [1], largely due to an ageing population but also to an increasing prevalence of risk factors for dementia. The annual worldwide costs of dementia were 604 billion dollars in 2010 [2]. The most common form of dementia is Alzheimer's disease (AD), and the major risk factor for its development is increasing age [3]. Other known risk factors include family history, hypertension and hypotension, high cholesterol levels, low levels of physical activity and of education, obesity, and the presence of epsilon 4 allele of the apolipoprotein E gene (*APOE4*) [4–6]. A recently proposed risk factor for AD is HF [7].

Chronic HF is a progressive condition that may be defined as inadequate cardiac output to meet metabolic demands. The most common causes of HF in developed countries include ischaemic heart disease with myocardial infarction, hypertension, cardiomyopathy and degenerative valve disorders.

The prevalence of HF is about 2% [8], increasing sharply with age, with up to 10% of individuals over 65 years [8] and 20% over 75 years affected [9]. It has been shown that HF is more 'malignant' cancer overall [9]. Hospitalization for HF accounts for 1–2% of all healthcare expenditure in Europe [10], and HF is the most common cause of hospitalization in patients over 65 years of age [11].

Alzheimer's disease and HF often occur together and thus increase the cost of care and health resource utilization [12]; this highlights the need to investigate the relationship between these two conditions. Impaired cognition in HF patients leads to significantly more frequent hospital readmissions [13] and increases mortality rates [14].

The relationship between HF and AD remains largely unclear. In this review, we aim to explain how HF contributes to the development of AD, focusing mainly on reduced cerebral blood flow (CBF) [15] and dysfunction of the neurovascular unit [16]. However, multiple cardiovascular conditions often coexist, suggesting that several mechanisms underlying cardiovascular dysfunction may contribute to cognitive decline. HF in the

elderly is often underdiagnosed, because the symptoms of HF are mimicked or masked by comorbidities in this population [17]. Causes of HF and common comorbidities will be discussed with emphasis on their contribution to dementia and specifically AD.

Early identification and correct medical treatment of cardiovascular conditions can reduce the prevalence of AD [18]. Indeed prevention of AD may be more effective than current pharmacological treatment [19, 20]. It has been estimated that delaying the onset of AD by just 1 year would lead to 9 million fewer cases by 2050 [21]. During the past 3 years, the results of at least five studies have been published suggesting that the incidence of dementia and AD may have decreased over the last two decades [22–26]. The mortality improvements are generally attributed to better awareness of cardiovascular disease risk factors. In addition, successful management of hypertension and increase in the use of statins and antithrombotic drugs may play an important role.

#### Cognitive disorders: dementia and delirium

Cognition is a group of mental processes which include memory, attention, learning, decision making, problem solving, language processing and executive functions. Dementia is a progressive cognitive disorder which usually primarily affects memory. In addition, aphasia, apraxia, agnosia and disturbances of executive functioning are common symptoms. Delirium, on the other hand, is characterized by an abrupt impairment of cognition and a fluctuating course. It is very common amongst elderly patients undergoing a surgery [27]. Precipitating insults include infection, intoxication, high volume load, electrolyte imbalance, fever or administration of anticholinergic drugs [28, 29]. Delirium has been generally viewed as an acute state, but may in fact persist for several months [30]. Delirium and dementia often coexist [31]; indeed, delirium may be both a prognostic factor for dementia and worsen cognitive impairment in pre-existing dementia [32].

#### HF with preserved ejection fraction

Heart failure was originally a clinical diagnosis that relied on classical symptoms and signs of neurohormonal activation, in particular fluid retention,

as summarized in the Framingham criteria. The availability of and over-reliance on echocardiography led to a focus on reduced ejection fraction, generally considered to be <40–50%, as a tool and sometimes even a criterion for diagnosis. However, it has become increasingly clear that HF also occurs with preserved ejection fraction and is equally common and perhaps equally serious [33]. Because HF with preserved ejection fraction is associated with diastolic dysfunction, that is, impaired active relaxation and passive filling during diastole, it is often termed diastolic HF [34], but impaired systolic contractility occurs, too [35]. HF with preserved ejection fraction is associated with older age, female gender, hypertension and atrial fibrillation. There is continuing debate as to whether HF with preserved ejection fraction is a distinct syndrome or a consequence of ageing and the associated subtle renal insufficiency, vascular changes and anaemia [36]. However, given the multifactorial nature of this syndrome and its close correlation with age and other risk factors for dementia, HF with preserved ejection fraction is likely to be highly relevant for the development of dementia even though causality may be difficult to establish.

#### HF and cognition

Since 1977 when the term 'cardiogenic dementia' was first introduced [37], it has been confirmed that HF contributes to cognitive decline [38] and the grade of cognitive impairment correlates with the severity of HF [39]. Even though heart disease and AD share similar genetic backgrounds and risk factors such as *ApoE* polymorphisms, it is becoming increasingly clear that there is also an association through their dependency on an adequate blood supply. Insufficient blood circulation may contribute to changes in all organs and lead to the multiple organ dysfunction syndrome. Decreased cardiac output due to HF is associated with abnormal brain ageing and cognitive impairment [40]. Data from the Framingham Heart Study confirmed that reduced cardiac index and left ventricular ejection fraction are associated with impaired cognition [41]. Lower values of cardiac index were even found to be related to smaller brain volumes [42]. Findings of other studies demonstrated that left ventricular ejection fraction is linked to cognitive decline in patients with HF [43]. A low left ventricular ejection fraction was related to memory [44], reasoning and sequencing impairment [45].

Data from a recent study demonstrate some degree of cognitive decline in almost 47% of patients hospitalized for HF [46]. HF increases the risk of delirium [28] and, on the other hand, delirium is associated with a more advanced stage of HF [47]. Few studies have investigated the prevalence of dementia or its subtypes in subjects with HF. Recently, in a Swedish population-based longitudinal study, it was found that 40% of patients with HF also had dementia. By contrast, dementia was present in 30% of individuals without HF [48]. There is growing evidence that HF is a risk factor for both vascular dementia and AD [7, 49], but the prevalence of AD in HF patients is not known.

#### HF and structural brain changes

Growing evidence from neuroimaging studies suggests an association between HF and structural brain abnormalities, which further supports a relationship between dysfunction of both the heart and brain. Total and regional brain atrophy or demyelination are common in patients with HF [50]; indeed, Kumar and colleagues found reduced axonal integrity of several brain circuits that are involved in cognition in these patients [51]. Serber *et al.* [52] reported abnormalities of the frontal cortex which were correlated with reduced cognitive functioning.

In a study comparing HF patients with both healthy control subjects and patients diagnosed with heart disease other than HF, it was found that HF was related to more white matter hyperintensities, lacunar infarcts and medial temporal lobe atrophy. Medial temporal atrophy is an early feature of AD and is associated with lower cognitive function and an increased risk of progression to dementia [53]. However, these pathological findings were more likely to be found even in patients with heart disease other than HF compared with healthy individuals, thus cannot be considered as a specific consequence of HF [50].

Considerable data suggest that heart disease may precipitate neurodegenerative changes seen as white matter hyperintensities [54], which have been associated with cognitive functions [55]. However, the clinical significance of these changes is not clear, as they are extremely common in the elderly population and in many studies were not related to cognitive performance [56, 57].

#### CBF in AD

It has been demonstrated extensively that vascular changes and reduced blood supply of the brain are involved in the pathogenesis of AD [58]. There is a large body of evidence demonstrating that AD is characterized by reduction in both total and regional CBF with resulting brain hypoperfusion. Total CBF is about 20% lower in patients with AD compared with individuals without dementia [15]. Lower CBF has been reported and confirmed in many studies using single-photon emission computed tomography (SPECT), positron emission tomography, spin-labelling magnetic resonance imaging (MRI) or transcranial Doppler measurements [59–61]. It seems likely that reduced CBF can cause neuronal dysfunction or death [62].

Results of the Rotterdam Study, a prospective population-based cohort with 1730 participants, suggested that cerebral hypoperfusion precedes and possibly contributes to the onset of clinical dementia [63]. This is supported by the findings of a delay in CBF response in patients with mild cognitive impairment (MCI) and an even longer delay in patients with AD in a study using functional MRI and blood oxygenation level dependent contrast [64]. Because MCI may be considered the earliest clinical feature of AD, this evidence suggests that CBF reductions are present in early stages of AD pathogenesis. This is consistent with results from a longitudinal study using SPECT to investigate CBF in MCI patients with a high predictive value for conversion to AD. Significant reductions in the parietal lobule, angular gyrus and precuneus were found [65], which implies that reduced CBF precedes neurodegeneration.

Furthermore, decreased CBF may negatively affect the synthesis of proteins required for memory and learning and may eventually contribute to neuritic injury and neuronal death [66]. It has been suggested that brain hypoperfusion may be caused by the continuous loss of cholinergic innervation of intracerebral blood vessels [67].

#### CBF and HF

In the presence of HF as well as older age, the mechanisms that regulate changes in CBF become compromised [68]. Reduced CBF was observed in patients with HF, and a correlation with an increasing prevalence (of up to 25%) of cognitive dysfunction was found [69]. Improvement in heart

function following transplantation or resynchronization increased levels of CBF and cognitive function [45, 70, 71].

There is growing evidence that reduced CBF due to HF has a role in both pathological hallmarks of AD: amyloid beta (A $\beta$ ) deposition and tau protein aggregation [72].

#### A $\beta$ and tau protein in HF

Reduced CBF compromises the oxygenation of neurons. In HF, neurons are chronically exposed to an insufficient blood supply. Therefore, HF does not result in sudden neuronal death; instead, neurons undergo a metabolic energy crisis. The lack of energy results in acidosis and oxidative stress followed by a cascade of pathological consequences such as dysfunction of enzymes and protein synthesis. It has been shown that brain acidosis is associated with aggregation of both the altered tau and A $\beta$  [73]. Furthermore, an acidic environment stimulates autoactivation of the lysosomal enzyme asparaginyl endopeptidase, which cleaves inhibitor 2 of protein phosphatase 2A [74]. Phosphatase 2A accounts for most of the tau protein phosphatase activity; therefore, its disinhibition results in hyperphosphorylation of tau [75]. Abnormal hyperphosphorylated tau protein loses the ability to bind to tubulin to promote its assembly into microtubules. Instead, it binds to normal tau protein, which leads to formation of tau oligomers and their aggregation into neurofibrillary tangles [76, 77].

Lack of energy has also been shown to upregulate beta secretase 1, a protease responsible for cleavage of the amyloid precursor protein [78]. This results in accumulation of A $\beta$  protein and formation of amyloid plaques. However, the increased processing of amyloid precursor protein is not the only mechanism involved in AD pathology. It has been suggested that a more important mechanism in HF is impaired A $\beta$  clearance across the blood-brain barrier (BBB) [66].

#### BBB and impaired A $\beta$ clearance

The BBB consists of endothelial cells connected by tight junctions and a thick basement membrane which is supported by astrocytic end feet. The BBB represents an important part of a functional cellular structure known as the neurovascular unit, which also includes pericytes and microglia [79].

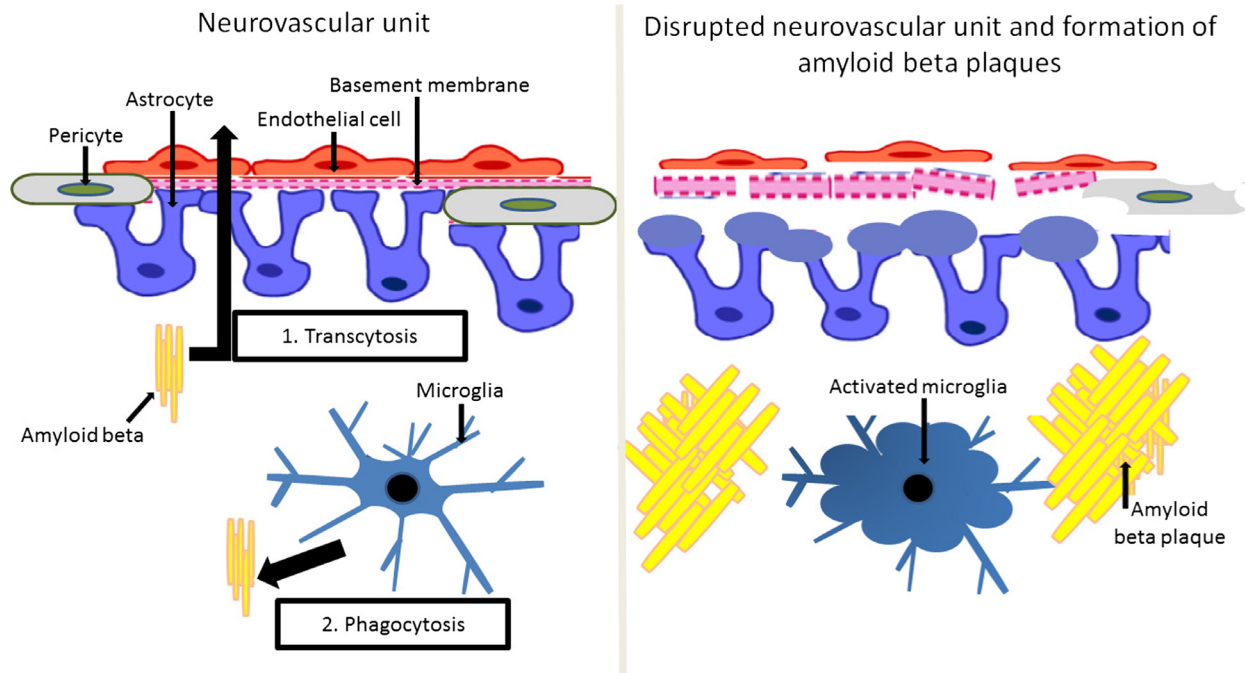
Dynamic communication between the cells of the neurovascular unit is required to enable efficient clearing of A $\beta$  to prevent it from accumulating in plaques [80]. Impaired cerebral blood supply can lead to failure in maintaining adequate oxygenation of the cells [58]. Hypoxia results in regressive changes and can cause the breakdown of the BBB which impairs the clearance of A $\beta$ .

There are several ways in which A $\beta$  is cleared across the BBB from brain parenchyma into the blood [66]; two of these are discussed here (Fig. 1). The first mechanism involves transcytosis through the cells of the BBB, and the second represents phagocytosis by microglia [81]. Microglia play a major role in scavenging A $\beta$  and their accumulation and activation is a typical feature of AD pathology [82]. Thus, it is beneficial to clear A $\beta$  in the early stages of the disease [83]. However, during progression of the disease, activated microglia are further involved in inflammatory processes [84] and lose their ability to phagocytose A $\beta$  [85].

The disruption of the neurovascular unit is characterized by many pathological events, as shown in Fig. 1. Endothelial dysfunction seems to play a crucial role, as degeneration of endothelial cells is part of the disease process of AD [86]. Activation of endothelial cells and abnormal communication between these cells and pericytes is followed by the disruption of the basement membrane and swelling of the astrocytic end feet. Dysfunction of the BBB leads to infiltration of inflammatory cells, which increases oxidative stress [87]. Pericytes seem to contribute to destructive inflammatory responses [88]. Inflammation and oxidative stress compromise neuronal repair mechanisms [89, 90] and further impair the phagocytic function of microglia.

Breakdown of the BBB results in the impaired clearance of A $\beta$  via transcytosis, which leads to amyloid accumulation in the brain parenchyma and in and around capillaries; this is known as cerebral amyloid angiopathy (CAA). CAA, a major pathological insult to the neurovascular unit [91], is associated with cognitive impairment [92] and is present in more than 80% of patients with AD [93]. Okamoto *et al.* [93] found that cerebral hypoperfusion accelerates CAA, which is consistent with the hypothesis that a reduction in CBF precedes AD pathology.

Heart failure gives rise to compensatory neurohormonal activation which is adaptive and restores



**Fig. 1** The neurovascular unit, amyloid beta clearance and formation of amyloid beta plaques. The blood–brain barrier is composed of endothelial cells supported by a basement membrane and astrocytic feet. The blood–brain barrier represents an important part of a functional structure known as the neurovascular unit, which also includes pericytes and microglia. Amyloid beta is cleared by transcytosis through the cells of the blood–brain barrier and by phagocytosis by microglia. Disruption of the neurovascular unit is characterized by dysfunctional endothelial cells with abnormal intercellular connections, thickening and rupture of the basement membrane, swelling of astrocytic end feet and activated pericytes and microglial cells. The breakdown of the blood–brain barrier inhibits amyloid beta clearance via transcytosis. Activated microglia are not able to phagocytose its excess which results in accumulation of amyloid beta plaques.

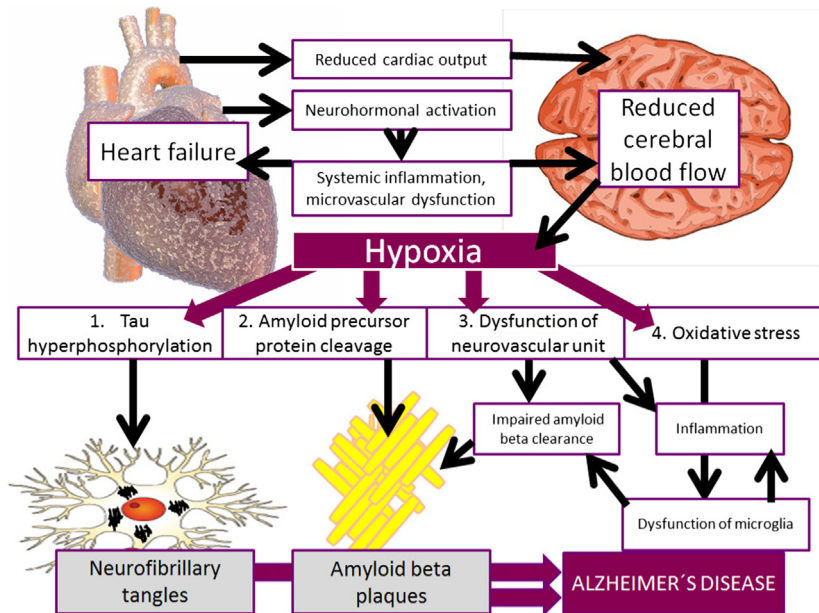
cardiac output in the short term, but leads to a vicious circle of progressive remodelling and further neurohormonal activation which is maladaptive in the long term. Major components of the progressive pathophysiology of HF are systemic inflammation, oxidative stress and impaired endothelial function [94]. Despite a lack of sufficient evidence, it seems likely that the systemic inflammatory state in HF has an impact on the neurovascular unit and contributes to its dysfunction (Fig. 2).

#### Animal models

A suitable animal model of AD is one that can be used for the analysis of vascular morphology, blood flow and memory impairment [95, 96]. In a critical review of mouse models that are used to demonstrate effects of cardiovascular diseases on cognition, Bink and colleagues concluded that the

most promising model is based on hypoperfusion caused by bilateral common carotid artery stenosis [97]. This animal model represents a chronic hypoperfusion of the brain caused by placing microcoils around the carotid arteries [98]. The dissection revealed activated microglial cells and astrocytes, white and grey matter changes, hippocampal atrophy and micro-infarcts [99–101]. These findings support a link between brain hypoperfusion and the development of AD [102, 103].

In a second mouse model, ligation of the aortic arch between the carotid arteries demonstrated chronic HF leading to a reduced ejection fraction. This model showed increased permeability of the BBB and decreased CBF [104]. Using both mouse models, A $\beta$  deposits were observed [105, 106] supporting the association between cardiac dysfunction and AD pathology.



**Fig. 2** Model of the relationship between heart failure and Alzheimer's disease. This model shows the possible direct and indirect pathways of the contribution of heart failure to the development of Alzheimer's disease. Low cardiac output may directly lead to reduced cerebral blood flow. Neurohormonal activation, inflammation and microvascular dysfunction may indirectly contribute to impaired perfusion and therefore insufficient oxygenation of the brain. Hypoxia induces hyperphosphorylation of tau protein and expression of beta secretase which cleaves amyloid precursor protein. In addition, insufficient blood supply causes disruption of cells comprising the neurovascular unit and induces oxidative stress.

In experimental studies on rats, acute cessation of blood flow induced expression of diffuse A $\beta$  peptide and amyloid precursor protein in the hippocampus, entorhinal cortex and neocortex [107]. This further supports the above-mentioned theory that cerebral hypoperfusion places the brain at risk of amyloid deposition. Neurohormonal maladaptive changes and systemic inflammation have not been discussed in these articles.

### Blood pressure

Arterial hypertension is the most common comorbidity of and a critical risk factor for HF as well as an important contributor to the development of AD, independent of HF [108, 109]. As HF increases in severity, patients often experience low or fluctuating blood pressure [110] that can impair cognition both acutely and in the long term. Hypotension in HF is associated with poor outcome [111] and predicts cognitive impairment amongst patients with HF [112]. A decline in blood pressure is observed several years prior to the diagnosis of AD which can be attributed to impaired cerebral

autoregulation and vasomotor reactivity [113]. Therefore, it has been speculated that low blood pressure accelerates neurodegeneration [114, 115]. Fluctuating blood pressure may be a result of systolic pump failure, treatment or nonadherence to dietary recommendations or medication [110, 116]. In addition, it has been related to poor performance in cognitive tests, structural brain changes and white matter hyperintensities [117, 118].

However, hypotension is a marker of advanced stage HF [119], where renal function and response to diuretics deteriorate, uraemia and systemic inflammation increase, and numerous neurohormonal and metabolic pathways are progressively and abnormally activated. Furthermore, increasing doses of neurohormonal antagonists are beneficial even in patients with low blood pressure [120], suggesting that whereas hypotension may contribute to dementia, neurohormonal antagonists may retard the progression of HF. Typically, up-titration of drugs is initially associated with lower blood pressure and increasing symptoms of fatigue,

dizziness and possibly impaired cognition, but the long-term effects are protective and may retard dementia. Thus, balancing the use of HF drugs with aspects of frailty in patients with dementia becomes difficult.

Hypertension often precedes HF and contributes to the progression of this disorder [121]. Furthermore, hypertension is a major risk factor for the development of left ventricular hypertrophy and myocardial infarction which may result in HF [110]. In addition, midlife hypertension in particular is a risk factor for AD [4, 122]. Correct management of blood pressure may therefore affect the emergence of AD in HF patients in a complex manner. However, the findings from studies of the relationship between hypertension and dementia in older age are not consistent [123]. Results from clinical trials that examined the preventive effect of antihypertensive therapy on dementia were not conclusive: whilst some studies proved a protective effect of some antihypertensive drugs on the prevention of dementia [123], this was not confirmed in other trials [124, 125].

Furthermore, hypertension may produce additive vascular pathology through disruptions of both the BBB and CBF homeostasis. The effect of hypertension can be related to increased vascular stiffness and acceleration of atherosclerosis [108, 126].

### Atherosclerosis

Atherosclerosis is an important mechanism underlying conditions resulting in HF, such as coronary heart disease. Even in the absence of preceding myocardial infarction or macrovascular coronary disease, atherosclerosis, inflammation, endothelial dysfunction and microvascular remodelling are thought to be critical features of the pathophysiology of HF, in particular HF with preserved ejection fraction [127]. Furthermore, atherosclerosis is associated with a risk of developing dementia in the elderly [128]. Although atherosclerosis used to be attributed particularly to vascular dementia, it is now becoming increasingly evident that it contributes to the pathogenesis of AD [129].

However, it is not completely clear whether the observed effect of atherosclerosis on AD is due to direct vascular changes or whether there is an effect of common risk factors and underlying diseases. This relationship may be explained by the presence of ischaemia caused by disturbances

in CBF due to progressive vascular narrowing [130]. However, atherosclerosis is a complex disease that involves several biochemical, immunological and inflammatory mechanisms that lead to damage of the vascular wall, and accumulation of cholesterol crystals and inflammatory cells [131]. This leads to progressive compensatory and adaptive vascular morphological changes and disruption of the neurovascular unit [132]. Atherosclerosis is also related to the formation of small intracerebral aneurysms that can underlay micro-bleedings observed in the brain of patients with AD [133].

Furthermore, atherosclerosis and AD share common risk factors, such as age [134], *ApoE4* polymorphisms [135], homocysteine [136], smoking [137], obesity [138] and chronic inflammation [139]. In addition, both atherosclerosis and AD are strongly associated with several underlying conditions, such as hypertension [4], diabetes mellitus [140] and hypercholesterolaemia [4]. The latter may explain the association between AD and extensive peripheral atherosclerosis [141, 142].

A number of post-mortem studies have been conducted to investigate intracerebral atherosclerotic changes in patients with AD, as shown in Table 1. According to Yarchoan and colleagues, 77% of individuals with AD had apparent atherosclerosis in the circle of Willis, compared with only 47% of control subjects. The association between atherosclerosis of the circle of Willis and AD pathology was more significant for women than men [143].

Beach and co-workers demonstrated that the grade of atherosclerosis of the circle of Willis was more severe in cases with AD and vascular dementia compared with nondemented individuals [144]. The severity of cerebrovascular atherosclerosis of the circle of Willis was associated with an increased number of A $\beta$  plaques and neurofibrillary tangles in two studies [144, 145]. Honig *et al.* [146] also established a strong link between cerebral atherosclerosis and the density of A $\beta$  plaques, but did not find any association with neurofibrillary tangles.

However, this evidence is inconsistent with the findings of several other studies in which a relation between atherosclerosis and AD was not confirmed. In a post-mortem study, Kosunen *et al.* [147] found no relationship between atherosclerotic changes and AD pathology. Similarly, in an autopsy study by Zheng and colleagues, there was

**Table 1** Association between intracranial atherosclerosis and Alzheimer's disease pathology: overview of autopsy studies

Reference	Number of participants (patients with AD; control subjects)	Mean age at death $\pm$ SD, years (patients with AD; control subjects)	Results
Beach <i>et al.</i> 2007 [144]	215; 92	82.6 $\pm$ 8.2; 84.3 $\pm$ 6.8	Relation to both A $\beta$ plaques and neurofibrillary tangles
Dolan <i>et al.</i> 2010 [149]	200;/	87.6 $\pm$ 7.1;/	No relation to AD pathology
Honig <i>et al.</i> 2005 [146]	676; 226	78.8 $\pm$ 8.8; 82.9 $\pm$ 10.0	Relation to A $\beta$ plaques, but not to neurofibrillary tangles
Kosunen <i>et al.</i> 1995 [147]	32; 6	84.0 $\pm$ 9.0; 82.0 $\pm$ 16.0	No relation to AD pathology
Roher <i>et al.</i> 2003 [145]	32; 22	85.2; 85.5	Relation to both A $\beta$ plaques and neurofibrillary tangles
Luoto <i>et al.</i> 2009 [237]	466;/	70.8 $\pm$ 46.9;/	No relation to AD pathology
Roher <i>et al.</i> 2011 [129]	61; 36	85.1 $\pm$ 7.3; 84.9 $\pm$ 6.1	Relation to both A $\beta$ plaques and neurofibrillary tangles
Yarchoan <i>et al.</i> 2012 [143]	410; 59	77.1 $\pm$ 10.5; 69.6 $\pm$ 15.9	Relation to A $\beta$ plaques, neurofibrillary tangles and CAA, particularly in women
Zheng <i>et al.</i> 2013 [238]	81; 23	84.9 $\pm$ 7.1; 84.6 $\pm$ 5.9	No relation to AD pathology

SD, standard deviation; AD, Alzheimer's disease; A $\beta$ , amyloid beta; CAA, cerebral amyloid angiopathy.

no significant correlation between atherosclerosis and A $\beta$  plaques or neurofibrillary tangles. By contrast, the authors showed that atherosclerosis was associated with micro-infarcts, which have previously been correlated with the grade of cognitive decline [148].

In the Baltimore Longitudinal Study of Aging, a prospective longitudinal study in which a complete autopsy was conducted in 170 participants, it was confirmed that the presence of atherosclerosis in intracranial vessels increases the risk of dementia independently from cerebral infarction, but no association was found between the degree of atherosclerosis and AD pathology [149].

#### Coronary artery disease and myocardial infarction

Several studies have confirmed that coronary artery disease is associated with cognitive impairment [150, 151], reduced hippocampal volume [152] and dementia [153]. Recently, Graban and colleagues showed that coronary artery disease

was more common in patients diagnosed with vascular dementia compared with controls [154]. The results from the Rotterdam study demonstrated that unrecognized myocardial infarction was associated with a higher risk of dementia, increased white matter lesions and brain infarctions in men [155].

The Bronx Aging Study provided evidence that women with a history of myocardial infarction had a fivefold increase in the risk of dementia [156]. However, in some studies, such as the Honolulu-Asia Aging Study and the Rochester Epidemiology Project, no such associations with later cognitive impairment [157] or dementia [158] were found. Therefore, further studies are needed to investigate the link between AD and prior myocardial infarction.

#### Atrial fibrillation

Atrial fibrillation (AF) is the most common type of arrhythmia. Its prevalence in HF ranges between



13% and 40% [159, 160] and is even higher in HF with preserved ejection fraction [161]. It has been suggested that AF can precipitate HF, but a causative relationship has not been established [162]. In a large number of studies, scores in cognitive tests were reduced and learning, memory, attention and executive functions were impaired in individuals with AF [163–165]. Furthermore, neuroimaging studies have demonstrated a reduced hippocampal volume in AF patients [166]. It has been found that AF increases the risk of dementia [167, 168] and predicts its development in subjects with cognitive impairment [169, 170]. Surprisingly, in the Rotterdam study, AF was related more strongly to AD than vascular dementia [171], whilst Bunch *et al.* [172] found that it was associated with all types of dementia disorders. However, in other studies, no correlation between AF and dementia or cognitive decline was found [173, 174]. Studies of the role of AF in dementia disorders are shown in Table 2.

A recently published meta-analysis of 21 studies confirmed that AF is associated with an increased risk of cognitive impairment and dementia [175]. However, the estimated relative risk of dementia was high (2.7) only amongst AF patients who experienced a stroke. In a wider population, AF was shown to increase slightly the risk of cognitive impairment (relative risk of 1.4).

Cerebral emboli have been reported in at least one-third of HF patients [176], and the risk of embolism increases in the presence of AF. Progressive asymptomatic embolism may persist for many years and can cause cerebral damage. This condition is a possible contributor to cognitive impairment [177] and has been found to be associated with AD [178]. Another cause of cognitive decline may be irregular and rapid ventricular rates which could lead to fluctuating and reduced CBF due to low cardiac output [179]. This may be especially common in the setting of acute HF secondary to rapid AF, where a combination of pulmonary oedema, hypoxia, renal failure and hospitalization may contribute to confusion in susceptible patients.

Treatment with a vitamin K antagonist or novel oral anticoagulants is recommended in patients with AF, except in rare cases in which there are no risk factors for stroke [180]. Despite national and international recommendations, almost half of patients with AD and AF do not receive anticoag-

ulation, which may cause microemboli and further worsen cognition. The most common reason for undertreatment of AF with anticoagulants is old age [181, 182]. However, there is evidence that patients with AD have an increased risk of intracranial bleeding [66], which is a serious adverse effect of vitamin K antagonists. Therefore, new ways to treat AF in patients with AD are of considerable interest [183].

#### Heart valve disease

It has been suggested that aortic and mitral valve damage may contribute to AD by causing hypoperfusion of the brain [184]. In autopsy studies, valve damage was a common finding amongst patients with AD [185]. In an echocardiographic study, patients with AD were more likely to have aortic valve thickening and regurgitation compared with control subjects, patients with vascular dementia and nondemented individuals that experienced stroke [186]. Another echocardiographic examination of patients with AD showed impaired transmitral flow efficiency of diastolic filling compared with control subjects. The authors of this initial study [187], which was conducted in age-matched groups of patients with and without AD, found that the value of vortex formation time (an emerging quantitative index of cardiac health) is out of the optimal range in patients with AD. Vortex formation time is an emerging quantitative index of cardiac health. If this parameter is within optimal range it suggests efficient intraventricular blood transport.

#### Sleep-disordered breathing

Sleep-disordered breathing (SDB) is common in the elderly and presents as obstructive, central or mixed sleep apnoeas characterized by pauses in breathing or shallow breaths during sleep [188, 189]. Obstructive sleep apnoea is the most common type of this condition and is associated with cardiovascular morbidity and mortality [190].

The prevalence of SDB is higher in HF patients compared with the general population and affects HF patients with preserved and reduced ejection fraction to a similar extent [191, 192]. It is estimated that 18% of HF patients have obstructive sleep apnoea and <1% suffer from the central form [193], although these two types of SDB may coexist in HF [194]. It seems likely that sleep apnoea syndrome leads to several pathophysiological

**Table 2** Atrial fibrillation as a risk factor for dementia disorders in a stroke-free population: overview of studies

Reference	Study design	Results			Conclusion
		AF and dementia	AF and AD	AF and vascular dementia	
Bunch <i>et al.</i> 2010 [172] Intermountain Heart Collaborative Study	Longitudinal study Follow-up for 5 years	–	OR = 1.06; P = 0.59	OR = 1.73; P = 0.001	AF is associated more strongly with vascular dementia than with AD
Dublin <i>et al.</i> 2011 [167]	Longitudinal study Follow-up for 6.8 years	HR = 1.38; 95% CI 1.10–1.73	HR = 1.50; 95% CI 1.16–1.94	–	AF is associated more strongly with AD than with all-cause dementia
Forti <i>et al.</i> 2006 [239]	Longitudinal study Follow-up for 4 years	HR = 1.10; 95% CI 0.40–3.03	–	–	AF is not associated with dementia in a cognitively normal population
Marengoni <i>et al.</i> 2011 [173] Kungsholmen project	Longitudinal study Follow-up for 6 years	HR = 0.90; 95% CI 0.50–1.70	HR = 0.80; 95% CI 0.4–1.5	–	AF is not associated with dementia or with AD
Ott <i>et al.</i> 1997 [171] Rotterdam study	Cross-sectional population-based	<75 years OR = 2.6; 95% CI 0.60–11.40 >75 years OR = 2.2; 95% CI 1.30–3.80	OR = 1.8; 95% CI 0.9–3.5	OR = 1.5; 95% CI 0.4–4.9	AF is associated more strongly with AD than with vascular dementia
Peters <i>et al.</i> 2009 [240] Hypertension in the Very Elderly	Double-blinded randomized controlled trial	HR = 1.031; 95% CI 0.619–1.718	–	–	AF is not associated with dementia
Rastas <i>et al.</i> 2007 [241] Vantaa Study	Longitudinal study Follow-up for 3.5 years	HR not available	–	–	AF is not associated with dementia

OR, odds ratio; HR, hazard ratio; CI, confidence interval; AD, Alzheimer's disease; AF, atrial fibrillation.

conditions, such as tachycardia, hypertension and arrhythmia, that contribute to the development or exacerbation of HF [195]. In the presence of HF, the sensitivity of central chemoreceptors is enhanced which results in unstable ventilator control systems leading to the development of sleep apnoea [196, 197]. Therefore, the relationship between HF and SDB is complex, with both conditions influencing each other.

Increasing evidence shows that SDB is also associated with cognitive decline and abnormalities of the hippocampus and synaptic plasticity, and occurs more frequently in patients with AD than in nondemented individuals [198, 199]. It is debated whether SDB is involved in the aetiology of AD; it is possible that it could contribute to the development of AD through cerebral hypoxaemia, inflammation and/or oxidative stress [200–202]. Treatment with continuous positive airway pressure has been shown to slow cognitive deterioration in patients with mild and moderate AD [203] and seems to be well tolerated [204].

Although not yet supported by research, it seems likely that SDB may be a common comorbidity in patients with HF and AD and have a role in the pathogenesis of both conditions.

#### Effects of medication

In HF with reduced ejection fraction, neurohormonal antagonists reduce symptoms, morbidity and mortality [17]. These drugs include renin–angiotensinogen–aldosterone system (RAAS) antagonists, beta-blockers and mineralocorticoid receptor antagonists [205]. Diuretics are often required in HF to reduce congestion and symptoms, but do not improve outcomes and may contribute to dehydration, hypotension and neurohormonal activation [17]. Overuse of diuretics in the elderly can lead to or worsen cognitive problems due to electrolyte disturbances, especially hyponatraemia [182]. Blocking the RAAS improves cognition in a manner that does not depend on blood pressure [206, 207]. Angiotensin II receptor antagonists may have a neuroprotective effect on focal cerebral ischaemia [208]. Treatment with these agents may prevent cognitive decline by reducing the likelihood of vasoconstriction and thrombogenesis and, at the same time, potentiating vasodilatation and endothelial modulation [209]. However, although HF with preserved ejection fraction also involves neurohormonal activation,

randomized controlled trials have not been able to demonstrate improved outcomes with neurohormonal antagonists. This may be due to underpowering of these studies or the fact that multiple age-related comorbidities may be relatively more dominant in HF with preserved ejection fraction than in HF with reduced ejection fraction. In a large registry-based study, RAAS antagonists do appear to be associated with improved outcomes [210].

In AD, cholinesterase inhibitors, which are the most commonly prescribed antedementia drugs [211], may have cardioprotective functions [212]. It has been reported that donepezil decreases cardiovascular mortality [213]. In patients with subclinical HF, a decrease in the level of brain natriuretic peptide has been observed as a consequence of donepezil treatment. This suggests that cholinesterase inhibitors could have a beneficial therapeutic effect in HF [214]. Similar results have been found in an observational study in which the use of cholinesterase inhibitors was associated with a 35% reduced risk of myocardial infarction in patients with AD [215].

This relationship may be explained by the fact that cholinesterase inhibitors have anti-inflammatory properties which positively impact the inflammation underlying atherosclerosis [216]. It has also been suggested that these agents have a negative chronotropic effect on the heart and increase vagal tone by augmenting acetylcholine [217, 218]. This is in line with an experiment performed on animal models, where vagal nerve stimulation improved the survival after HF [219]. Furthermore, this finding is supported by beneficial effects on reducing heart rate observed with beta-blockers and ivabradine, which reduce heart rate by direct action on the sinus node and improve outcomes in HF [220] and coronary disease [221]. These findings are in contrast with current clinical practice as donepezil is not always prescribed for patients with both AD and cardiovascular disease [214]. On the other hand, excessive cholinergic stimulation, which may be caused by cholinesterase inhibitors, has been reported to cause arrhythmias, such as bradycardia, sick sinus syndrome and torsades de pointes [222].

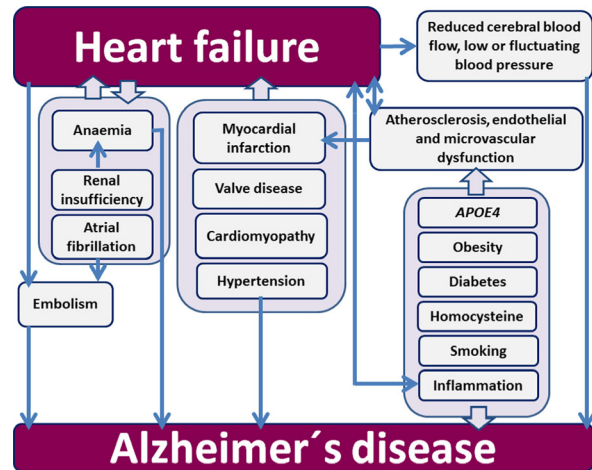
#### Discussion

Interest in 'cardiogenic dementia' has been renewed by evidence of cognitive decline in patients with HF. In this review, we have attempted to

explain how HF contributes to the development of AD. However, not all studies included here examined patients who were diagnosed with AD, thus much evidence relates to dementia in general. The results of several studies are limited by the fact that AD often overlaps with other dementia types, such as vascular dementia. Epidemiological studies have shown that both AD and vascular dementia share similar risk factors [223], and vascular pathology has been observed in autopsy investigations in patients with AD more frequently than expected [224]. There has been a lack of consensus on integrating vascular changes into diagnostic criteria of dementia [224]; therefore, the diagnosis of AD may vary in different studies.

Reduced CBF is a well-established factor associated with cognitive impairment in HF patients, and microscopical findings support this relationship. However, the progressive pathophysiology of HF involves maladaptive neurohormonal activation, systemic inflammation, oxidative stress and impaired endothelial function [94]. It is likely that the relationship between HF and dementia is much more complex than initially thought and may reflect neurohormonal activation and systemic remodelling, rather than perfusion alone. Both HF and AD are strongly associated with advanced age. Elderly individuals usually suffer from many comorbidities that have a dual effect on AD: both affecting it directly and causing cardiovascular diseases. It has been suggested that underlying and concomitant conditions may be more important in the development of AD than reduced CBF [225]. However, the direct role of hypoperfusion versus the indirect role of neurohormonal activation or comorbidities remains unclear, and specific causes are difficult to isolate.

Atherosclerosis is strongly involved in the pathogenesis of HF and has been suggested to contribute to AD. Its risk factors such as hypertension, hypercholesterolaemia, *ApoE4* polymorphisms, obesity, smoking, homocysteine and chronic inflammation have been demonstrated to increase the risk of AD and may play a role in microvascular dysfunction in HF even in the absence of macrovascular coronary disease. Furthermore, AF and anaemia are involved in the pathogenesis of HF and AD in several ways: they may both precipitate and be caused by HF, as well as contribute to the onset of AD [226–228]. HF may lead to renal insufficiency and vice versa [229] and additionally kidney insufficiency



**Fig. 3** Schematic diagram of the complex relationship between heart failure and Alzheimer's disease.

contributes substantially to the development of anaemia [230]. Fig. 3 shows the various ways in which these conditions are involved in the emergence of AD in HF patients.

Evidence suggests that treatment of HF may improve cognition and delay the onset of dementia. However, the therapeutic management of HF is complicated by side effects and their interaction with ageing, frailty and perhaps dementia itself. Furthermore, there is no treatment proven to retard the development of or improve outcomes in HF with preserved ejection fraction, which is the type of HF that is particularly common in the elderly and those with comorbidities such as AF.

As the relationship between HF and AD becomes increasingly important with the ageing worldwide population, more attention should be focused on the field of neurocardiology, a subspecialty concerned with associations between the heart and brain [231, 232]. Awareness of cognitive impairment should challenge clinicians in primary care units as well as cardiologists, and cognition should be evaluated in patients with HF. An interdisciplinary approach towards elderly patients is recommended [233–235]. The future of neurocardiology may depend on integrating medical knowledge of interactions between chronic degenerative and cardiovascular diseases and applying this knowledge in clinical practice [236]. Better understanding of such relationships may result in benefit for elderly patients from appropriate evidence-based treatment.

**Conflict of interest statement**

No conflicts of interest to declare.

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