

Cognitive Impairment in Atrial Fibrillation Patients: A Literature Review

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Introduction: Atrial fibrillation (AF) has become one of the most significant health problems worldwide, warranting urgent answers to currently pending questions on the effects of AF on brain function. Recent evidence has emerged to show an association between AF and an increased risk of developing dementia and worsening of stroke outcomes. In the last two decades several reports have shown an association between AF and cognitive function, ranging from impairment to dementia.

Purpose: To present data on cognitive impairment in atrial fibrillation patients.

Materials and methods: The study material consisted of reviewed articles on the topic found on the globally accepted electronic databases, PubMed, Medline, Google Scholar; regarding cognitive decline in atrial fibrillation patients. The study material consisted of scientific books, reviews and research papers published online.

Results: In the absence of clinical stroke, people with incident atrial fibrillation are likely to reach thresholds of cognitive impairment or dementia at earlier ages than people with no history of atrial fibrillation. Results in a large sample of patients show that AF may be associated with higher risk for both cognitive impairment and dementia in patients with preexisting stroke, even if there was significant heterogeneity in the analysis for cognitive impairment. Adequate oral anticoagulation and improved management of the overall cardiovascular risk profile in individuals with AF offer the promise of reducing the impact of AF on cognitive decline and dementia.

Conclusion: AF is associated with higher risk of developing AD and dementia. Future studies should examine whether specific treatments, including optimal anticoagulation, can decrease this risk.

Keywords: Atrial Fibrillation, Dementia, Cognitive Decline, Stroke, Cognitive Impairment, Epidemiology**1. Introduction**

Atrial fibrillation (AF) is a common cardiac arrhythmia [1]. There is growing evidence that AF is a risk factor for cognitive decline and dementia [1,2]. Recent studies have suggested possible associations between cognitive decline and atrial fibrillation [3,4]. Atrial fibrillation and cognitive impairment share similar risk factors, such as age, diabetes, hypertension, and heart failure, which could confound the association [2]. Cerebral hypoperfusion, reduced brain volume, microbleeds, white matter hyperintensity, neuroinflammation, and genetic factors have been considered as potential mechanisms involved in the pathogenesis of AF-related cognitive dysfunction [3,5]. Atrial fibrillation was associated with infarctions and lower total grey matter volume [6,7]. A smaller hippocampal volume has been observed in patients with AF than in controls [7]. Flow disturbances as experienced during AF can disrupt the blood brain barrier and leave the brain vulnerable to damage [8]. A

recent study found higher levels of biomarkers of cerebral injury such as microtubule-associated Tau protein and glial fibrillary acidic protein (GFAP) in AF patients, suggesting potential blood-brain barrier disruption, which could lead to cognitive decline or dementia in future [8]. Possible connections have also been reported between AF and Alzheimer dementia, with chronic hypoperfusion secondary to abnormal heart rate and the proinflammatory state in AF both promoting white matter abnormalities and cerebral amyloid deposits [9]. Alzheimer dementia patients with AF or heart failure presented with older ages of dementia onset and death than Alzheimer dementia patients without heart disease [7].

In the absence of clinical stroke, people with incident atrial fibrillation are likely to reach thresholds of cognitive impairment or dementia at earlier ages than people with no history of atrial fibrillation [10]. Our results in a large sample of patients show

that AF may be associated with higher risk for both cognitive impairment and dementia in patients with preexisting stroke, even if there was significant heterogeneity in the analysis for cognitive impairment [11]. Adequate oral anticoagulation and improved management of the overall cardiovascular risk profile in individuals with AF offer the promise of reducing the impact of AF on cognitive decline and dementia [1,4,12]. Multiple observational trials have shown that catheter ablation is also associated with a lower risk of cognitive decline, dementia and improved cognitive testing that can be explained through a variety of pathways [13]. Long-term, adequately powered, randomized trials are required to define the role of catheter ablation in the management of AF as a means to lower the risk of cognitive decline, stroke and dementia [13]. This paper will review the potential mechanisms leading to cognitive dysfunction in AF patients and examine the available data on the impact of a sinus rhythm restoration and maintenance strategy in reducing the risk of cognitive decline.

2. Materials and Methods

The study material consisted of reviewed articles on the topic found on the globally accepted electronic databases, PubMed, Medline, Google Scholar, regarding cognitive decline in atrial fibrillation patients. The key words used were Atrial fibrillation, dementia, cognitive decline, stroke, cognitive impairment, epidemiology. The study material consisted of scientific books, reviews and research papers published online.

2.1. Atrial Fibrillation and Cognitive Function

The most basic evidence supporting an association of AF with worse cognitive function comes from cross-sectional studies

comparing cognition in individuals with and without AF [1]. Moreover, about 25% of patients with AF in the absence of neurological deficits have tomographic signs of one or more silent cerebral infarcts [6,14]. Atrial fibrillation is well recognized as an important and independent risk factor for cerebrovascular disease at all ages [15]. We have previously reported an association between hypertension and diabetes and low cognitive function in the elderly [16]. Cerebrovascular disease is the most important potentially preventable form of dementia and in very elderly people vascular dementia may account for almost half of all cases [15]. The AF patient's risk profile is also dynamic, and many risk factors change over time; many of the reported associations are based on baseline risk and have not tracked temporal changes in risk [17]. The presence of atrial fibrillation was consistently associated with poorer performances on all the subtests of the neuropsychological battery [18]. Atrial fibrillation (AF) is a strong risk factor for Alzheimer's disease (AD) independent of ischemic stroke [19]. One of the causes of low cognitive function in these patients appears to be permanent AF [10,14]. Men with AFIB exhibited lower performance on global cognitive ability and cognitive abilities including Similarities (abstract reasoning), Visual Reproductions-Immediate Recall, Visual Reproductions-Delayed Recall, Visual Organization, Logical Memory-Delayed Recall, and Trail Making A (scanning and tracking) and Trail Making B (scanning, tracking, and executive functioning) [20]. Hospitalized patients aged ≥ 65 years with AF and/or focal neurologic deficits at admission are at increased risk for Impaired Cognitive Function [21]. Elevated B-type natriuretic peptide levels have been associated with the risk of heart failure, AF, and mortality [22].

Assessment of cognitive impairment

| | |
|-------------|---|
| Suspect | Patient history, appearance, changes in behaviour |
| Confirm | Collateral history from family |
| Examine | Full medical examination, brief screening assessment |
| Investigate | Renal/liver/respiratory/thyroid compromise, B ₁₂ , folate; syphilis serology (in high-risk patients) |
| Exclude | Depression, neurological/psychiatric disease, medication/drug use |
| Measure | Psychometric testing using validated battery |
| Image | Multimodal MRI (T1, T2, T2*, DWI) for brain changes |
| Establish | Diagnosis based on clinical + psychometric + imaging |

DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging.

Table: Assessment of Cognitive Impairment [4]

2.2. Atrial Fibrillation and Stroke-Related Cognitive Impairment

The current hypothesis postulates that uncoordinated myocytes activity could explain the impaired/loss of atrial contraction seen in AF patients, and the resulting blood stasis would cause the increased thromboembolic risk [3,18]. Prior stroke is a contributor to CI, but AF is also associated with CI independently from prior stroke [11,23]. There is consistent evidence supporting an association between AF and increased incidence of dementia in patients with stroke whereas there remains considerable

uncertainty about any link in the broader population [24]. Atrial fibrillation is another main risk factor for cerebrovascular disease [11,16,21]. Non-valvular atrial fibrillation (NVAf) is an established risk factor for thromboembolism and stroke [25]. Chronic nonrheumatic atrial fibrillation retained an independent relation to cognitive impairment also after adjusting for those variables associated with mental decline in univariate models [26]

A systematic review including more than 77,000 patients

with normal baseline cognitive function and not suffering an acute stroke, showed that AF significantly increases the risk of incident dementia (HR 1.42, CI 1.17–1.72, $p = 0.002$) [3]. In these community-living elderly men, we found an association between atrial fibrillation and low cognitive function independent of stroke, high blood pressure, and diabetes [3,16]. As populations age, the incidence of AF is expected to increase, and there has been increasing, although inconsistent, evidence that AF may contribute to the development of thinking problems and dementia [27].

2.3. Atrial Fibrillation and Incidence of Dementia

A recent study found higher levels of biomarkers of cerebral injury such as microtubule-associated Tau protein and glial fibrillary acidic protein (GFAP) in AF patients, suggesting potential blood–brain barrier disruption, which could lead to cognitive decline or dementia in future [7,8]. Mini-mental state examination (MMSE), due to its simple application, is a valuable and valid screening tool for measuring cognitive status, and it may be used to classify the severity of CImp, although it does not constitute the sole criterion for diagnosing dementia or for differentiating specific forms of dementia [28]. Dementia was reported to be up to 2-fold more common in patients with AF than in those without it [5,18]. Aging is associated with a large increase in the prevalence and incidence of degenerative (Alzheimer's disease) and vascular dementia, leading to a

devastating loss of autonomy [12,29].

In the past decade, several vascular risk factors have been found to be associated with vascular dementia but also Alzheimer's disease [12,29]. Some longitudinal studies have found significant associations between hypertension, diabetes mellitus, and metabolic syndrome, assessed at middle age, and dementia [12,29]. We have also recently found that symptoms of middle- and late-onset depression in patients with AF may be an early sign of dementia and also contribute to disease mismanagement that can increase dementia risk [28]. AF was present in 132 (4.3%) participants at baseline and was diagnosed in 370 (12.2%) more over a mean of 6.8 years of follow-up; 572 participants (18.8%) developed dementia (449 with AD) [30]. Atrial fibrillation was associated with an increased risk of cognitive decline (hazard ratio [HR] 1.14, 95% confidence interval [CI] 1.03-1.26), new dementia (HR 1.30, 95% CI 1.14-1.49), loss of independence in performing activities of daily living (HR 1.35, 95% CI 1.19-1.54) and admission to long-term care facilities (HR 1.53, 95% CI 1.31-1.79) [31,32]. Atrial fibrillation (AF), in addition to macro embolic complications, may also produce multiple cerebral ischemic areas due to micro embolic phenomena and transient hypoperfusion, eventually leading to a progressive cognitive impairment and even to acclaimed vascular dementia [33].

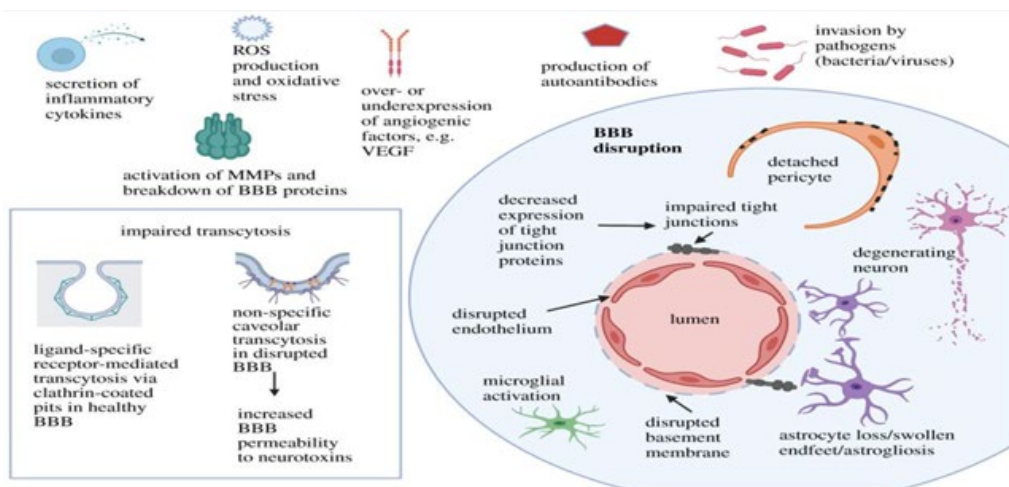


Figure: Blood-Brain Barrier (BBB) Disruption [8]

2.4. Atrial Fibrillation and Brain Abnormalities

There is increasing evidence that atrial fibrillation is associated with an increased risk of asymptomatic or silent cerebral infarction and as a result may confer an increased risk of progressive cognitive impairment on a person [18]. Atrial fibrillation was associated with infarctions and lower total grey matter volume [6,7]. A smaller hippocampal volume has been observed in patients with AF than in controls [7]. Both AF and dementia can be caused by vascular inflammation [7,34]. The inflammatory markers C-reactive protein (CRP) and IL-6 are elevated with AF and dementia [34]. Furthermore, preliminary data are emerging also on the association between AF and reduced mobility in older adults independently of comorbidities and frailty markers [14].

2.5. Prevention of Cognitive Impairment in People with Atrial Fibrillation: Rhythm Maintenance Strategy

Longitudinal studies of AF patients with no cognitive impairment at the time of diagnosis suggest that careful use of appropriate anticoagulant therapy can significantly reduce the incidence of cognitive disorders [13,17,31]. A recent study assessed dementia risk in male and female AF patients with a very low embolic risk (CHA2DS2-VASc 0 or 1); even for this risk profile, patients treated with oral anticoagulants had a lower dementia risk than those from whom treatment was withheld [13,17,31]. Anticoagulation is associated with cognitive benefit in participants with AF independent of stroke and TIA [35]. No definite evidence at present indicated that antiplatelet therapy is inferior to anticoagulant with regard to prevention of dementia

in people with AF [35]. Use of dabigatran and well-managed warfarin therapy were associated with similar risks of stroke, cognitive decline, and dementia at 2 years, suggestive that either strategy is acceptable [17].

Although there are randomized control data that show direct oral anticoagulants (DOAC) lower risk of stroke and intracranial bleeding compared to warfarin therapy, there remains a lack of data to determine if DOAC therapy may lower risk of cognitive decline and dementia in comparison to warfarin therapy [17]. It is unrealistic to aim for a significant mortality reduction among AF patients older than 85 years with moderate to severe dementia, and therefore the main goal in this patient group should be to reduce morbidity [31]. Multiple studies have found that those who undergo ablation for AF have a lower risk for dementia than AF patients not undergoing ablation [36]. After receiving a pacemaker and undergoing atrioventricular nodal ablation, there was a significant improvement in perfusion and cognitive function at 3-month follow-up [36]. Patients in the sinus group had a lower-risk profile and received antithrombotic therapy less frequently than the AF group [14,18]. However, a significant proportion of patients, particularly in the AF group received less than optimal thromboembolic prophylactic treatment with anticoagulants [14]. Outcomes after catheter ablation for AF are favorable and patients experience a better quality of life, arrhythmia-free survival, and lower rates of hospitalization compared to patients treated with antiarrhythmic drugs [28].

Multiple observational trials have shown that catheter ablation is also associated with a lower risk of cognitive decline, dementia and improved cognitive testing that can be explained through a variety of pathways [28]. there was no association between overall cognitive decline and Non-Valvular AF after 3 years' follow-up, nor any apparent effect of anti-thrombotic therapy [17,25]. Independent of etiopathogenetic mechanisms (thromboembolic or hemodynamic hypotheses), prevention of cognitive impairment in older persons should consider the treatment of atrial fibrillation and its consequences [26].

2.6. Limitations

Limited research was available on atrial fibrillation management, specifically on atrial ablation and improvement in cognition. This is a limitation because there are few researches that is written and published. This could be a source of bias. Another limitation is that due to lack of funds, the only articles that were used in this review were open access articles.

3. Conclusion

Atrial fibrillation (AF) is associated with higher risk of developing AD and dementia. Long-term, adequately powered, randomized trials are required to define the role of catheter ablation in the management of AF as a means to lower the risk of cognitive decline, stroke and dementia Future studies should examine whether specific treatments, including optimal anticoagulation, can decrease this risk.

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