Atrial Fibrillation and Deterioration in Cognitive Function

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Abstract: The link between atrial fibrillation and cognitive decline and dementia has gained interest of the medical community lately. More research is being conducted to prevent and or delay this morbidity as no curative therapy is available for cognitive decline and dementia. The exact mechanism of causation is unclear. Multiple pathophysiological mechanisms have been implicated. Lately, treatment for atrial fibrillation including anticoagulation and catheter ablation therapies have shown to decrease the risk of deterioration of cognitive function. In this review we summarize epidemiologic studies linking the association, potential mechanisms, and impact of various modalities of therapy of atrial fibrillation on cognitive function outcomes. (Curr Probl Cardiol 2019;44:100386.)

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder with rise in its incidence and prevalence as the western population continues to age. According to an epidemiological study conducted in 2010, worldwide prevalence of AF is 596.2 and 373.1 per 100,000 men and women respectively.[1] In the United States, the prevalence is much higher, 925.7 and 520.8 per 100,000 men

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and women respectively.[1] The incidence of AF has increased roughly 350% over the past 50 years. Even though cardiovascular mortality and morbidity has declined in general with advances in prevention and treatment, incidence of AF is expected to rise.[2] The rise of prevalence to epidemic levels is attributed to aging population, concomitant with increase in risk factors such as obesity and hypertension. It is well established that AF is a risk factor for ischemic stroke and heart failure.[3] Recently, new evidence has emerged pointing the correlation between AF and cognitive decline, specifically dementia. Dementia is a disorder of progressive cognitive impairment in the absence of any disturbances in consciousness, with prevalence of greater than 5% in population aged 65 years and above. The prevalence doubles up every 5 years after the age of 65. Every year, approximately 800,000 individuals develop mild cognitive impairment and more than 5000,000 individuals develop dementia in the US alone.[4] The most common form of dementia is Alzheimer's disease (AD) followed by vascular dementia (VaD). Stroke is one of the well-recognized causes of dementia. It is difficult to predict the magnitude of cognitive decline with stroke as size of infarct, location, and number of infarcts influence the consequent cognitive decline. Therapies aimed at improvement of cognition have been disappointing[5] and only actionable strategy is prevention by addressing modifiable risk factors: hypertension, diabetes, diet, hyperlipidemia, obesity, and vascular insults.

Association Between Atrial Fibrillation and Cognitive Decline and/or Dementia

Identifying the relation between AF and onset of dementia with cognitive impairment, as well as assessing if such association exists independent of stroke was of vital importance. Association between AF and cognitive impairment was first reported by Rotterdam study from the Netherlands.[6] Investigators observed more than double the prevalence of dementia in AF patients of age 55 or above in 6584 participants, out of whom women and younger age (<65 years) had stronger association. In patients with AF, history of stroke was not enough to explain this association. Many small studies identified AF as an independent predictor of dementia (both AD-type and VaD) after controlling for potential confounders.[7,8] Atherosclerosis Risk in communities-neurocognitive study (ARIC-NCS) study, a community-based prospective cohort done over 20 years in a population of 12,515 reported greater cognitive decline in AF patients when compared to non AF patients. AF-related cognitive decline was 16% while incident AF was associated with 23% higher risk

of dementia. Although the occurrence of stroke attenuated that association, it still remained significant. This indicates that some other factors in addition to stroke play a role in the causation of cognitive decline in AF patients such as silent cerebral infarcts. The cognitive decline in AF patients ages $>$ 57 years is significant when compared to that of AF patients $\leq$ 57 years of age.[9]

Recently, as a part of ARIC study, 325 patients were administered detailed cognitive tests and monitored for heart rhythm for 14 days. The study demonstrated that patients with persistent AF but not paroxysmal AF have reduced cognitive function, thus suggesting AF burden causes cognitive function deterioration.[10]

A cross-sectional study conducted on 122 AF patients without history of stroke and 546 people without AF in Germany from the same community, aged 35-85 years, reported poor performance of AF patients at tasks of learning, memory, and execution of function as compared to patients without AF after a thorough cognitive assessment.[11] Amnestic mild cognitive impairment and global cognitive function were observed to be decreased in patients with AF in Europe and the United States based on cross-sectional studies.[12,13]

Even though results of cross-sectional studies indicate that AF is associated with decrease in cognition, due to limitation of study design itself, these studies cannot establish temporality of the association.

More convincing evidence was observed in studies with longitudinal follow-up. In multinational ONTARGET and TRANSCEND trials with 31,506 patients for a follow-up of a median of 5 years, it was reported that patients with pre-existing baseline AF or who developed AF during the trial had 13% increased risk of cognitive decline through minimental state examination (MMSE); which was defined as a drop of 3 or more points.[14] Similarly, a community-based cardiovascular health study in the US reported that AF is associated with a faster decline in MMSE after median follow-up of 7 years.[15] In the ARIC study among 935 stroke-free patients, the decline in executive function and verbal fluency was associated with incident AF. Interestingly, this association was only present in patients with subclinical cerebral infarcts highlighting that vascular insult is likely the cause of cognitive deterioration.[16]

Elevated risk of stroke in AF patients logically point toward higher risk for VaD. A meta-analysis based on studies published in the period between 1950 and 2009 reported that 10% of patients had dementia before their first stroke, and another 10% developed dementia immediately after the first episode of stroke. More than a third developed dementia after recurrent episodes of stroke.[17]

However, recent studies suggest that AF patients can have a higher risk of developing Alzheimer's dementia after excluding clinical vascular events. In a US based study with 3045 participants, AF patients had a higher risk of developing Alzheimer's dementia in excess of 50% than in patients without AF.[18] Secondary analysis of the ONTARGET and TRANSCEND trials,[14] the Finnish CAIDE study,[19] and the Rotterdam cohort[20] have suggested an association between AF and the risk of dementia. This result was substantiated with a large scale study with >6,00,000 patients in Taiwan, showing increase in risk of dementia by 42% in AF patients than those without AF.[21] Pooling data from studies provided a hazard ratio 1.42 (1.17-1.72) (95% confidence interval) of dementia in AF patients.[22] In a study done by Miyasaka et al., mortality risk was significantly higher in dementia patients even after adjustment of additional risk factors and hence the diagnosis of dementia remained a significant independent predictor of death.[23]

Atrial Fibrillation and Brain Structural Abnormalities

Recent studies explored the changes in brain phenotype in AF patients. One such study was age, gene and/or environment susceptibility—Reykjavik conducted a study on 4251 patients from Icelandic population. This study reported an association between the presence of AF and lower brain volume and gray matter.[24] Another community-based cross-sectional study in Minnesota, US has also reported lower total gray matter volume and infarctions in AF patients.[25] Supporting this theory, a cross-sectional study of autopsy in 134 patients with AF and 194 without AF has reported increased prevalence of Alzheimer disease's neuropathologic changes (neuritic plaques, neurofibrillatory tangles) in AF patients.[26] Other studies also suggest that AF patients suffer from higher burden of silent cerebral infarctions, cerebral microbleeds, and white matter disease.[27] Rapid cognitive decline and elevation of risk of dementia in AF patients might be explained by these lesions.[16]

Predictors of Cognitive Impairment and Dementia in Patients with Atrial Fibrillation

Studies have reported that higher $CHADS_2$ and CHA_2DS_2-VASc scores can predict dementia in AF patients.[21,28] However, this prediction is not surprising as age, being the strongest predictor of dementia, is included in this score schemes. To date, no well-validated tool has been developed to assess the risk of dementia or cognitive decline in AF

patients. The efficacy of anticoagulant treatment is another predictor of the cognitive impairment in AF patients.

Mechanisms of Causation of Cognitive Decline and Dementia Secondary to Atrial Fibrillation

Although the mechanism linking AF and cognitive decline is not well-established, available evidence supports this association. It was well-established that stroke almost doubles the risk of dementia.[29] The Framingham Study indicated that AF exerts a significant impact on the risk of stroke which was independent of the often-associated cardiovascular abnormalities.[30] Elevated stroke risk in AF patients does not alone explain the increase in rate of progression of cognitive decline and incidence of dementia in AF patients.[29] Other factors, such as oral anticoagulation-associated microbleeds, silent cerebral infarcts, cerebral hypoperfusion, and microembolism are also partners in impacting dementia or cognitive decline.[31] Aside from stroke risk, AF also doubles the risk of silent cerebral infarcts, which in return was a risk factor for dementia.[32,33]

The impact of subclinical cerebrovascular disease mediating cognitive impairment in AF patients has been addressed in ARIC study. In this study, a group of stroke-free AF participants with silent cerebral infarcts had higher risk of cognitive decline. Patients were followed for 12 years and MRI was used to detect silent cerebral infarctions (SCI).[16] The hypercoagulable state due to AF must be responsible for this mechanism, and thus use of anticoagulation must be vital to regulate cognitive outcomes in AF patients.[34] AF also contributes to risk of dementia via its impact on cardiac function, as patients with AF may have reduced cerebral perfusion due to beat to beat variation in stroke volume,[35] and improvement in cerebral blood flow by restoration of sinus rhythm in AF patients through cardioversion or ablation was shown to reduce the deterioration of cognitive function.[36,37] Consequences of AF such as low cardiac index, have an association with dementia according to data reported in some studies.[38,39] AF was a well-established risk factor for heart failure, which in turn can impact cerebral hypoperfusion.[40,41]

Microbleeds were frequent in patients with AF and are linked to lacunar infarcts, degenerative changes in brain, and increased risk of cerebral hemorrhage.[42] Unfortunately, oral anticoagulation therapy increases the chance of development of microbleeds, and in the Rotterdam study, patients using coumarin anticoagulants had increased risk of microbleeds. Among patients with greater variability in anticoagulation control, the

risk of microbleeds was particularly higher.[43] Currently, left atrial cardiopathy, as a predecessor of AF, can be vital in the establishment of cerebrovascular disease as well as in the development of cognitive decline and dementia. Presence of electrocardiographic left atrial abnormalities was associated with increased risk of ischemic stroke; which is predominantly a vascular insult in nature and rarely lacunar infarct.[44,45] The impact of left atrial cardiopathy on dementia risk, independent of AF needs to be further explored.

Impact of Modality of AF Therapy on Dementia

Anticoagulation Therapy Using Vitamin K Antagonists

CHA_2DS_2VASc score is a stroke risk prediction tool that assigns points for congestive heart failure, hypertension, age, diabetes, stroke, vascular disease and female gender. A score of ≥ 2 necessitates oral anticoagulation therapy either with Vitamin K Antagonists (Coumarin or Warfarin derivatives) or with direct oral anticoagulants (DOACs).[46] Prevention of stroke in AF patients by anticoagulants may decrease the risk of dementia, as stroke itself can double the risk of dementia. Jacobs et al. studied the risk of dementia in AF patients who were on Warfarin based on duration of effective anticoagulation by measuring the time in therapeutic range INR. In their study, a linear increase in risk of dementia was observed with decrease in time in therapeutic range only in patients aged <80 years.[47] These results are consistent with increased risk of dementia in AF patients less than 70 years old reported by Bunch et al.[48] The influence of anticoagulation therapy in AF patients with dementia has become the objective of recent studies. Two such studies using data from Intermountain Healthcare Clinical Pharmacist Anticoagulation Service, in Utah, US reported higher risk of dementia in patients whose INR was either subtherapeutic or supratherapeutic compared to AF patients with INR in therapeutic range consistently.[49,50] Failure in assessing the impact of baseline cognitive function on the association of suboptimal oral anticoagulation and future risk of dementia has limited the value of these studies. For example, patients with worse cognitive function during initiation of oral anticoagulation would later on develop dementia inspite of an adequate therapeutic regimen. These types of questions can be addressed via randomized trials only, but it is likely considered unethical to withhold anticoagulation therapy in AF patients to study dementia risk; which makes it more complex. A retrospective study from Sweden conducted on 444,106 AF patients reported 29% lower risk of dementia in patients

on anticoagulant treatment at baseline. Moreover, in their subgroup analysis there was no difference in Warfarin and DOACs subgroups in Dementia risk; which was found in earlier studies.[51]

Direct Oral Anticoagulant Therapies

Several DOACs were compared to warfarin which demonstrated noninferiority for stroke prevention and have similar or improved safety profiles.[6] Although the drugs have not been tested for long-term impact on cognitive decline, a previous study has demonstrated additional benefits via direct thrombin inhibition using combination of hirudin (naturally occurring thrombin inhibitor) and donepezil in AD patients.[52] Washout of hirudin will gradually lower the benefits obtained. Thrombin inhibition in animal model reduces the inflammation of central nervous system, as thrombin is upregulated in AD patients.[53] Many studies on the novel drugs like Factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban), and direct thrombin inhibitor (dabigatran) highlight their safety profile and efficacy. However, studies to more specifically identify the impact of these drugs over dementia are yet to be done. Jacobs et al. reported less dementia in DOAC anticoagulated patients when compared to warfarin anticoagulated patients for AF.[54] A recent meta-analysis of 8 studies and 471,057 individuals concluded DOAC significantly reduced the incidence of dementia compared with warfarin in patients with nonvalvular AF.[55] While this study suggests a beneficial role of DOAC's in decreasing dementia in AF patients, further prospective studies are needed to confirm these findings.

Statin Therapy and Renin-Angiotensin-Aldosterone Axis Modulation

Statins have pleotropic effects via regulation of the vascular inflammation as well as reduced oxidative stress.[56] The role of these mechanisms to impact dementia in AF patients still remains an area of active research. Use of atorvastatin and ezetimibe therapy for AF patients have a positive impact on the measures of cognition and has proven also beneficial to retain medial temporal lobe size.[57] Reduction in inflammatory markers and improved cognition are also noted in similar studies with the usage of combination therapy for 1 year.[58] The seemingly positive effects of statin-based therapy on brain function, volume, and dementia progression, including non VaD, would further support a role of proinflammation and oxidative stress. The ONTARGET and TRANSCEND trials studied

the impact of angiotensin conversion enzyme inhibitor and angiotensin receptor blocker therapy on cardiovascular outcomes.[59] The absence of this therapy in AF patients resulted in nonsignificant rise in dementia, identified by periodic MMSE with a median follow-up of 56 months.

Catheter Ablation of Atrial Fibrillation

Catheter ablation procedures were less invasive procedures with usage of alternate sources of energy compared to classical surgical management. The results of the surgical ablation of AF in patients undergoing cardiac surgery depend on the energy source used and on the site, depth of the lesion produced.[60] Patients with symptoms refractory to pharmacologic therapy are often evaluated for atrial fibrillation catheter ablation (AFCA) therapy to improve the symptoms associated with AF. Although clinical data suggests that AFCA was better compared to the current pharmacologic therapy,[61-63] AFCA was associated with procedural complications which may have an impact on cognitive outcomes. AFCA lesions may create a nidus for embolic periprocedural transient ischemic attack and cerebrovascular accident (TIA and/or CVA). Extensive registry studies have reported 0.5%-1%, incidence of symptomatic periprocedural TIA and/or CVA to be associated with AFCA.[64-67] Irrespective of severity of the periprocedural events, the long-term prognosis of cognitive and functional recovery is excellent among patients with symptomatic TIA and/or CVA associated with AFCA.[67] The prevalence of postoperative cognitive dysfunction in AFCA patients after long-term follow-up was 13%-20%.[68] The prevalence of asymptomatic cerebral events was 7%-38% identified through MRI in AFCA patients[69] which was reduced on long-term follow-up resulting in less chances of chronic cerebral infarcts.[62]

One prospective registry-based study compared outcomes between 4212 patients who underwent AFCA and 16,848 patients with age and gender matched AF. Dementia and stroke were significantly lower in AFCA group.[70] Similarly, a multicenter registry from the United Kingdom and Australia also reported decrease in incidence of stroke during a mean follow-up of 3.1 years.[71] Duration of left atrial access is the main predictor of cognitive impairment.[69] Strategies that reduce the left atrial access time, optimize the anticoagulation approach, and address the timing of direct current reversion may have an effect on the prevalence of postoperative cognitive dysfunction.[68] Keeping in mind the short-term risk of symptomatic and asymptomatic cerebral events associated with AFCA, higher intraprocedural activated clotting time targets and

avoidance of intraprocedural cardioversion were the additional strategies proposed. Sinus rhythm maintenance with conventional radiofrequency ablation was not satisfactory in both paroxysmal and persistent AF patients. Recurrence of AF, catheter as a source of iatrogenic embolism, air embolism, and charring of the catheter are the factors that influence the risk of thromboembolic events and in turn cognitive decline. Still Radio Frequency (RF) ablation management shows lower mortality and cognitive dysfunction rates compared to medical management of AF. Single shot devices such as cryoablation and multielectrode ablation catheters require larger sheaths and complex preparation strategies in an attempt to reduce risk of air embolism.[72]

Even though preclinical studies suggested cryoablation is less thrombotic than radiofrequency ablation, clinical studies have not demonstrated such benefits.[69]

SCI observed in 35% of patients with phased RF ablation while it was 10% with cryoablation. Deneke et al. reported that 94% of the SCI lesions disappear with long-term follow-up.[73] Multielectrode ablation catheters with phased RF technology were promising in safety concern and efficacy with slightly increased risk of thromboembolic events or silent cerebral ischemia. The complications reported in various studies during PVAC/MASC/MAAC were TIA and/or stroke, tamponade, ACS, pericardial effusion.[73]

Contact force sensing catheter use with ACL during AF ablation significantly reduces fluoroscopy times by 77%, radiation dose by 71%, and procedural time by 19% but does not improve overall safety or the risk of cardiac complications. Impact of these recent technologies like multielectrode ablation and CF sensing catheter usage over cognitive decline was to be unraveled yet.[74]

Left Atrial Appendage Closure

Left atrial appendage (LAA) closure is another rapidly developing procedure, as LAA has been identified as a source of cardioembolism in approximately 90% of nonvalvular AF.[75] LAA closure might lead to prevention of decline in stroke-related cognitive impairment. Various devices are now available for LAA closure such as PLAATO (Appriva Medical Inc.),WATCHMAN (Boston Scientific), AMPLATZER CARDIAC PLUG (St. Jude Medical), AMPLATZER AMULET (St. Jude Medical), Occlutech LAA (occlutech), WaveCrest (Coherex Medical) among others. PROTECT-AF trial compared Watchman device with warfarin usage and demonstrated reduction in embolic events, stroke, cardiovascular

mortality with the implant.[76] Another similar confirmatory trial, PREVAIL presented to address the limitations of PROTECT-AF, reported significant reduction in early safety events like pericardial effusion compared to PROTECT-AF along with noninferiority of the device.[77] Similar results obtained by other studies highlighting the reduction in hemorrhagic stroke with follow-up of 2.3[77] and 4 years.[78] Freixa et al. described that cerebrovascular events after LAA occlusion with Amplatzer cardiac plug were infrequent and nondisabling.[79] Amplatzer AMULET was under clinical trials for comparison with WATCHMAN device. Impact of LAA closure on dementia is the potential concept for future research as the long-term outcomes of novel LAA closure device usage can be addressed.

Conclusion

Available data clearly indicates association between AF and cognitive decline. There can be several potential mechanisms. CVA is a major cause of cognitive impairment in AF patients. Silent cerebral infarction, altered cerebral perfusion either due to lack of left atrial kick or due to beat to beat variability of blood pressure and resultant deleterious effects on cerebral perfusion and autoregulation, vascular inflammation, increased oxidative stress, medial temporal lobe atrophy associated with AF have been implicated to be the potential causes of cognitive decline in the absence of clinical stroke.

Benefits from oral anticoagulation therapy have also been observed, including reduction in risk of stroke and nonstroke-related dementia. Warfarin increase in time in therapeutic range was associated with decreased incidence of dementia. While some studies suggest that DOAC's may be superior to warfarin in prevention of dementia, further long-term prospective studies are needed. Atrial fibrillation catheter ablation (AFCA) is associated with increased risk of cognitive impairment through periprocedural cerebral embolism, but mid-and long-term outcomes are thought to be very favorable. Registry data supports that a durable sinus rhythm established with ablation improves cognitive function, although the much needed data from randomized controlled trials is lacking.

Statin therapy appears to help improving cognitive outcomes in AF patients, however impact of other forms of therapy is unclear. Dementia is one of the prominent problems associated with patients of AF, thus affecting their quality of life and the financial stress for healthcare. Clinicians treating AF should be aware of the association with cognitive

decline to deliver appropriate care including counseling, monitoring, and therapy to reduce risk.

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There have been studies linking atrial fibrillation and cognitive decline and dementia. The authors summarize clearly different aspects of this association.

Several perspectives can be drawn from this interesting manuscript.

First, the association between atrial fibrillation and the decline of cognitive function is evident.

Second, there are several underlying mechanisms that can account for this association. Cerebral vascular accidents are a major cause of cognitive impairment in patients with atrial fibrillation. Silent cerebral infractions are present in patients with atrial fibrillation and are associated with a decrease of cerebral perfusion either due to lack of left atrial kick or due to beat to beat variability of blood pressure. In addition, vascular inflammation, increased oxidative stress and medial temporal lobe atrophy are other factor in the development of cognitive decline even in the absence of clinical stroke. Third, several therapies have been associated with significant improvement in cognitive function in atrial fibrillation. Oral anticoagulation is known to improve the risk of stroke and non-stroke related dementia. Atrial Fibrillation Catheter Ablation is associated with increased risk of cognitive impairment through peri-procedural cerebral embolism, however, mid and long-term outcomes are favorable on cognitive function. Registry data supports that a durable sinus rhythm established with ablation improves cognitive function. Statin therapy appears to help improving cognitive outcomes in atrial fibrillation patients. The effect on quality of life associated with dementia and cognitive decline in patients with should be emphasized. Finally, clinicians treating atrial fibrillation should be aware of the association with cognitive decline and thus, they should deliver appropriate care including counseling, monitoring and therapy to reduce risk.

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