ATRIAL FIBRILLATION

RESEARCH ARTICLE

Expanding the Evaluation and Treatment of Patients with Atrial Fibrillation to Minimize the Risk of Dementia

T. JARED BUNCH, MD, BRIAN G. CRANDALL, MD, J. PETER WEISS, MD, JEFFREY S. OSBORN, MD, DAVID L. JOHNSON, MPAS, PA-C and JOHN D. DAY, MD

Intermountain Heart Institute, Intermountain Medical Center, Murray, Utah

KEYWORDS. atrial fibrillation, alzheimers disease.

Introduction

As clinicians we are facing an ever-increasing aging population. By the year 2030, one in five Americans will be 65 or older (an estimated 71.5 million).1 Compounding age-based changes are that these patients are presenting with enhanced longevity with coexistent cardiovascular diseases.2 Cardiovascular diseases impact multiple organ systems, and medications required to improve outcomes in one organ system may be detrimental to another. As such, a multisystem understanding and therapeutic approach to disease states will be essential to manage these patients.

Epidemiology of atrial fibrillation and dementia

Atrial fibrillation (AF) remains the most common cardiac arrhythmia in clinical practice. The incidence and prevalence of the arrhythmia is on the rise. Similar to many disease states, the prevalence of AF increases markedly with age. Approximately 5% of the population over the age of 65 years, and 10% of people aged over 80 years, will develop AF,3–5 however, the prevalence of AF is increasing beyond what is explained by age alone. AF risk factors (Table 1) such as hypertension, congestive heart failure, left ventricular hypertrophy, coronary artery disease and diabetes mellitus, and obstructive sleep apnea are also on the rise.6 As such, the number of affected individuals with AF is expected to increase two to three times over the next three decades in Western populations.2,7 Furthermore, the often multiple comorbid disease states that increase risk of AF produce challenges in therapy decisions and efficacy.

Dementia is a disorder that is a disease state characterized by impairment of memory and at least one additional cognitive domain.8 Dementia leads to a decline from previous levels of function and impacts quality of life and daily function.9 Similar to AF, age is a significant risk factor for dementia, in particular Alzheimer’s disease.10 For example, the estimated annual incidence of Alzheimer’s disease is 0.6–1.0% (65–74 years), 2.0–3.3% (75–84 years), and 8.4% (>85 years).10 Furthermore, dementia is estimated to be present in up to two-thirds of nursing home residents.11

Risk factors (Table 2) for dementia include genetic factors such as apolipoprotein E, vascular disease states such as hypertension, diabetes, atherosclerosis, metabolic syndrome, chronic kidney disease, and lower function status across social, mental, and physical activity domains.12–19

Atrial fibrillation and dementia disease associations

There have been many studies that have identified a potential association between AF and dementia (Table 2).
The majority of these studies have shown a significant association when large populations are studied over time. In a large meta-analysis of 15 studies (14 used in pooled analysis), Kwok et al.20 examined whether the association of AF and dementia persisted across multiple study protocols and diverse populations. In 46,637 participants (mean age 71.7 years) they found that AF was associated with a significant increase in total or overall dementia (odds ratio (OR) 2.0, 95% CI 1.4–2.7, p<0.0001). The association of AF and dementia persisted in general populations and those that focused primarily on stroke patients (OR 2.4, 95% CI 1.7–3.5, p<0.001).

We examined the question regarding the association of AF and dementia and if there was an association across all potential dementia subtypes. We studied 37,025 patients with a mean age of 60.6 ± 17.9 years who had a minimum of 5 years of follow-up. Within this population, 10,161 (27%) developed AF and 1,535 (4.1%) dementia. The dementia subtypes identified were vascular dementia (VD; n=179), senile dementia (n=321), Alzheimer’s dementia (n=347), and non-specific dementia (n=688). We found an increased incidence of dementia in general and all dementia subtypes in those patients with AF (non-specific, 1.3% (355) versus 3.3% (333), p<0.0001; Alzheimer’s, 0.7% (199) versus 1.5% (160), p<0.0001; and vascular, 0.3% (89) versus 0.9% (90), p<0.0001). In addition, in all types of dementia, the cognitive decline occurred earlier in patients with AF versus patients with no AF. Surprisingly, we found that the strongest association of AF and dementia was in the youngest cohort studied (patients ≤70 years). For example, for vascular dementia the OR was 2.20 (p=0.004), for senile dementia the OR was 3.34 (p=0.0001), for Alzheimer’s dementia the OR was 2.3 (p=0.001), and for non-specific dementia the OR was 2.87 (p<0.0001).

### Table 1: Risks factors for the development of atrial fibrillation and dementia

<table>
<thead>
<tr>
<th>Disease state</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>Age, Hypertension, Heart failure, Diabetes mellitus, Coronary artery disease, Left ventricular hypertrophy, Diastolic dysfunction, Sleep apnea, Chronic kidney disease, Alcohol consumption, Genetic factors/familial</td>
</tr>
<tr>
<td>Dementia</td>
<td>Age, Vascular atherosclerosis, Stroke, Hypertension, Diabetes mellitus, Chronic kidney disease, Sleep apnea, Alcohol consumption (excessive), Smoking, Genetic factors/familial, Chromosomal defect (Down Syndrome), Low functional status</td>
</tr>
</tbody>
</table>

The majority of these studies have shown a significant association when large populations are studied over time. In a large meta-analysis of 15 studies (14 used in pooled analysis), Kwok et al.20 examined whether the association of AF and dementia persisted across multiple study protocols and diverse populations. In 46,637 participants (mean age 71.7 years) they found that AF was associated with a significant increase in total or overall dementia (odds ratio (OR) 2.0, 95% CI 1.4–2.7, p<0.0001). The association of AF and dementia persisted in general populations and those that focused primarily on stroke patients (OR 2.4, 95% CI 1.7–3.5, p<0.001).

We examined the question regarding the association of AF and dementia and if there was an association across all potential dementia subtypes. We studied 37,025 patients with a mean age of 60.6 ± 17.9 years who had a minimum of 5 years of follow-up. Within this population, 10,161 (27%) developed AF and 1,535 (4.1%) dementia. The dementia subtypes identified were vascular dementia (VD; n=179), senile dementia (n=321), Alzheimer’s dementia (n=347), and non-specific dementia (n=688). We found an increased incidence of dementia in general and all dementia subtypes in those patients with AF (non-specific, 1.3% (355) versus 3.3% (333), p<0.0001; Alzheimer’s, 0.7% (199) versus 1.5% (160), p<0.0001; and vascular, 0.3% (89) versus 0.9% (90), p<0.0001). In addition, in all types of dementia, the cognitive decline occurred earlier in patients with AF versus patients with no AF. Surprisingly, we found that the strongest association of AF and dementia was in the youngest cohort studied (patients ≤70 years). For example, for vascular dementia the OR was 2.20 (p=0.004), for senile dementia the OR was 3.34 (p=0.0001), for Alzheimer’s dementia the OR was 2.3 (p=0.001), and for non-specific dementia the OR was 2.87 (p<0.0001).

### Table 2: Population-based and longitudinal studies that examine the association of incident dementia and atrial fibrillation

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Population</th>
<th>Follow-up</th>
<th>Dementia diagnosis</th>
<th>Dementia risk association</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piguet 200322</td>
<td>Mean age 80.4</td>
<td>6 years</td>
<td>Clinical and neuropsychological examination</td>
<td>TD: 35% (AF) vs 30% (no AF)</td>
</tr>
<tr>
<td></td>
<td>n=377</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tilvis 200458</td>
<td>Mean age 79.7</td>
<td>1, 5, 10 years</td>
<td>Clinical Dementia Rating</td>
<td>AD: 13% (AF) vs 11% (no AF)</td>
</tr>
<tr>
<td></td>
<td>n=650</td>
<td></td>
<td>Mini Mental Status Exam</td>
<td>TD: HR 2.9 (95% CI 1.3–6.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Association only at 5-year follow-up</td>
</tr>
<tr>
<td>Rastas 200759</td>
<td>Mean age 88</td>
<td>3.5 years (mean)</td>
<td>Clinical Dementia Rating</td>
<td>AD: 16.4% (AF) vs 18.6% (no AF)</td>
</tr>
<tr>
<td></td>
<td>n=553</td>
<td></td>
<td>Mini Mental Status Exam</td>
<td>TD: HR 0.9 (95% CI 0.5–1.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marengoni 200960</td>
<td>&gt;78 Years</td>
<td>4.0 years (mean)</td>
<td>Cognitive test battery</td>
<td>TD: HR 0.8 (95% CI 0.4–1.5)</td>
</tr>
<tr>
<td>Peters 200961</td>
<td>Mean age 83.5</td>
<td>2.2 years (mean)</td>
<td>Clinical Examination</td>
<td>TD: HR 1.03 (95% CI 0.62–1.72)</td>
</tr>
<tr>
<td></td>
<td>n=3336</td>
<td></td>
<td>Mini Mental Status Exam</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bunch 201062</td>
<td>Mean age 60.6</td>
<td>5 years</td>
<td>Clinical Examination if MMSE abnormal</td>
<td>TD: HR 1.44 (95% CI 1.23–1.69)</td>
</tr>
<tr>
<td></td>
<td>n=37,025</td>
<td></td>
<td>ICD-9 Codes</td>
<td>AD: HR 1.06 (95% CI 0.85–1.33)</td>
</tr>
<tr>
<td>Dublin 20111</td>
<td>Median age</td>
<td>6.8 years (mean)</td>
<td>Cognitive Abilities Screening</td>
<td>AD: HR 1.38 (95% CI 1.10–1.73)</td>
</tr>
<tr>
<td></td>
<td>74.3</td>
<td></td>
<td>Instrument</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=3,045</td>
<td></td>
<td>Neuropsychological and clinical assessment</td>
<td></td>
</tr>
<tr>
<td>Marzona 201263</td>
<td>Mean age 66.5</td>
<td>56 months (mean)</td>
<td>Mini Mental Status Exam</td>
<td>TD: HR 1.14 (95% CI 1.03–1.26)</td>
</tr>
<tr>
<td></td>
<td>n=31,506</td>
<td></td>
<td></td>
<td>ND: HR 1.30, 95% CI 1.14–1.49</td>
</tr>
</tbody>
</table>

TD: total dementia; AD: Alzheimer’s dementia; ND: new dementia; HR: hazard ratio.
The risk associations across all dementia subtypes declined with advancing age. Of the progressive dementias, Alzheimer’s disease is the most common. In addition to our data, other studies have found a risk trend or association between AF and Alzheimer’s disease. Piguet et al., in a study of 377 patients studied over 6 years, found that 13% of those with AF compared with 11% without AF developed Alzheimer’s dementia. In addition, Dublin et al., in a study of 3,045 patients, studied for a mean of 6.8 years, found a significant risk for the development of Alzheimer’s disease in those with AF compared with those without (hazard ratio (HR) 1.50; 95% CI 1.16–1.94)).

Mechanisms underlying atrial fibrillation and dementia associations

For senile and Alzheimer’s dementia, the mechanisms underlying the association with AF are unknown. There are several biologic mechanisms that have been proposed. The most common proposed is the role of chronic system embolization (Figure 1). This hypothesis arises from the well-established role of left atrial appendage thrombus and systemic macroembolization and stroke (Figure 1a). In patients with senile, vascular, or Alzheimer’s dementia, often there is diffuse cerebral atrophy and white matter changes. In this regard, it is plausible that microemboli from the left atrial appendage results in chronic small ischemic insults, and once a critical mass of neuron loss has occurred clinical cognitive decline is manifest. In this sense, stroke and dementia are manifestations of the spectrum of left atrial appendage and left atrial mechanical dysfunction stemming from AF and subsequent blood stasis and embolization. This hypothesis is supported by the observation the cerebral microinfarcts are a predictor of clinical dementia.

Another potential aspect to consider in the association of dementia and AF is the treatment to prevent thromboembolism. Since age is a component of the CHADS2 score, many elderly patients with AF are treated with systemic anticoagulation with a vitamin K antagonist. Cerebral microbleeds can occur and tend to increase with age. Microbleeds have been shown to be associated with hippocampus atrophy. Patients with cerebral microbleeds are also high risk of long-term cognitive decline. Hypertension is often seen in patients with microbleeds, which as discussed previously is also a common mechanism underlying both AF and dementia. Unfortunately, the risk factors for cerebral microbleeds with age have not been clearly defined. Although long-term anticoagulation and/or antplatelet use are obvious targets of study, the role of these agents and the extent and presence of microbleeds with exposure has not been clearly defined.

Another possible mechanism is that AF unmasks dementia in patients with underlying cerebral microvascular dysfunction. In sinus rhythm, the vascular dynamics/pulse pressure is relatively uniform and consistent (Figure 2). With onset of AF, there can be broad fluctuations in peaks and valleys of pulse pressure. Abnormal pulse wave velocities are associated with subcortical cerebral lesions and dementia. In general, the autoregulatory mechanisms result in microcirculation compensation in the setting of AF. However, all organs have various sensitivities to vascular dysfunction, and in these organs long-term exposure to abnormal flow pulsatility may lead to organ dysfunction. The hippocampus is very sensitive to hypoxia and vascular disease. This regional cerebral sensitivity may provide insight into the atrophy seen in this brain location in patients with AF and why AF patients are more likely to experience cognitive decline.

Another possibility is the long-term end-organ effects of systemic inflammation may result in microvascular cerebral injury and subsequent cognitive dysfunction. We have previously reported that AF independently increases systemic inflammation beyond other cardiac risk factors. Risk of dementia increases in patients with elevated markers of systemic inflammation. Adding to the intrigue of the role of systemic inflammation in patients with AF who develop dementia is that there is a significant association of elevated blood inflammatory markers and risk of cerebral microbleeds.

The many different mechanisms presented (Figure 3) may work in isolation or in combination, and likely evolve over time with disease state progression. There certainly will be new discoveries of risk factors and insights gleaned through genetic exploration. Finally, there is always the possibility that the association is an epiphenomenon, in that both diseases increase significantly with age and have similar risk factors and as such track together. We observed data contrary to this possibility: the highest risk of all types of dementia we observed was in the youngest cohort studied, opposite of what we initially predicted. Also, multiple studies with multivariate analysis methods and distinct comparative cohorts have noted the association. Nonetheless, this possibility reinforces the need to elucidate the mechanisms underlying the association of AF and dementia to assure that the observational study data are correct.

Reducing risk of cognitive decline in patients with atrial fibrillation

Treatment of dementia typically involves a trial of a cholinesterase inhibitor for patients with mild to moderate dementia, vitamin E, and the addition of memantine to a cholinesterase inhibitor to those patients with more advanced disease. In addition, rehabilitation to maintain a high functional status can also provide benefit. Treatment of obstructive sleep apnea appears to slow cognitive decline and impact structural brain changes over time. Although high blood pressure is a risk factor for dementia, antihypertensive agents have only a very modest impact in reducing the risk of cognitive decline.

In regards to this review, the more important question is what can be done to prevent onset of dementia all together. There are intriguing observational data regard-
The role of vitamins, antioxidants, anti-inflammatory drugs, diet, and estrogen replacement therapies to suggest a potential role in dementia prevention.44–49 Most data on therapies for preventing dementia come from observational studies. Unfortunately, for the most part, prospective randomized studies of these therapies have not substantiated the observational study results.

With the correlation observed of AF and dementia, arrhythmia treatment is an intriguing target to explore as a preventative strategy. We examined the question of whether the most aggressive rhythm control strategy, and all that goes along with it, would impact risk of dementia long term. We studied 4,212 consecutive patients who underwent AF ablation and compared them (1:4) with 16,848 age/gender-matched controls with AF (no ablation) and 16,848 age- and gender-matched controls without AF. Patients were enrolled if they had at least 3 years of follow-up. We found that patients who underwent an AF ablation had long-term rates of dementia (all types) similar to patients with no history of AF, and not surprisingly significantly lower rates than those with AF and no ablation. Specifically, Alzheimer’s dementia occurred in 0.2% of the AF ablation patients compared with 0.9% of the AF (no ablation) patients versus 0.5% of the no AF patients (p<0.0001). All other forms of dementia in a combined endpoint occurred in 0.4% of the AF ablation patients compared with 1.9% of the AF no ablation patients and 0.7% of the no AF patients (p<0.0001).50

Figure 1: The figure shows the proposed spectrum of cerebral ischemic from atrial thromboembolism. (a) A left atrial appendage with a thrombus (arrow). Under this image, is a correlative axial T2-weighted MRI image of a patient with an acute large right middle cerebral artery stroke (yellow arrows) with atrial fibrillation. (b) The left atrial appendage emptying velocities that are severely reduced (normal referenced) in a patient with moderate left atrial enlargement and diastolic dysfunction. The reduced mechanical function of the left atrial appendage leads to blood stasis a precursor for thrombus formation. (c) A dilated left atrial appendage and atrium. Arrows highlight the presence of spontaneous echo contrast within the left atrium consistent with blood stasis. In patients with stasis in the left atrium and left atrial appendage, both macro- and microembolism may occur. One postulate in the association of atrial fibrillation and dementia is chronic injury from microembolism. The axial T2-weighted MRI image on the right is in a patient with Alzheimer’s dementia that shows cerebral atrophy, ventricle enlargement, and periventricular white matter changes (yellow arrows).
There are many potential explanations for the results we observed. First, we selected a healthier group of patients to undergo ablation. This is likely correct and explains the differences noted between the two AF groups (ablation versus no ablation). However, there was essentially normalization of dementia outcomes with patients who had no history of AF. Also, we included consecutive patients throughout the state of Utah with ablations performed by various operators, with the requisite of known long-term outcomes to minimize, but not completely eliminate, the inherent selection bias. Next, rhythm control with preserved vascular flow pulsatility improved outcomes in organs that are sensitive to the broad fluctuations which occur in AF. Next, these patients were carefully followed after their ablation with attention devoted to their blood pressure control, sleep apnea, and anticoagulation, and as such it was a multifactorial approach that influenced outcomes. Finally, perhaps the results reflect stopping system anticoagulation in a subset of patients where this is possible (CHADS2 ≤1), that minimized their risk to cerebral microbleeds over time. Regardless of the mechanism(s), the observational findings require confirmation in a large prospective randomized trial.

Antiarrhythmic drugs have not been shown to impact risk of dementia. Recent data involving dronedarone suggest that cerebral ischemic events can be favorably influenced. Dronedarone was studied in the ATHENA trial and reduced the primary endpoint of cardiovascular hospitalization or death by 24%, and the risk of first hospitalization due to cardiovascular events (primarily for AF) by 26%.\textsuperscript{51} In an interesting post hoc analysis of ATHENA a significant reduction in the risk of stroke was shown with dronedarone compared with placebo (HR 0.66 (95% CI 0.46–0.96, p=0.027)).\textsuperscript{52} Unfortunately, use of dronedarone for safety reasons is confined to those with paroxysmal AF and no significant heart failure or left ventricular dysfunction. Nonetheless, the data suggest...
that with safe antiarrhythmic drugs cerebral ischemic events can be influenced in a positive manner.

One disease that is correlated with the onset, progression, and adverse response to treatment strategies with both AF and dementia is the presence of obstructive sleep apnea. The question of whether continuous positive airway pressure can be used as a preventive strategy for the onset of dementia in those patients with AF requires further prospective study.

Examining the cognitive domain after catheter ablation

We have previously discussed the observational data regarding catheter ablation and long-term risk of dementia. However, periprocedural stroke is a known complication of catheter ablation estimated at 0.1–0.8%. More importantly is the role of silent cerebral thromboembolism during and after ablation (Figure 4).

Figure 3: The figure displays potential mechanisms behind the observed association of dementia onset in patients with atrial fibrillation.

Figure 4: Diffusion weighted axial magnetic resonance images of a patient referred to our center with lethargy 3 weeks after a catheter ablation. The imaging performed in the emergency room shows multiple small punctuate lesions (circled). The patient had no focal neurologic deficits on neurologic examination.
Silent cerebral thromboembolism by nature is likely underappreciated and has not been an area of extensive investigation in prior studies. Of the available data, these cerebral ischemic episodes are device and technology dependent, with reported event rates between 8% and 18%. In our practice we have not routinely screened for silent cerebral ischemia. In patients with neurologic symptoms, the magnetic resonance imaging studies that have been performed have typically been normal. The low incidence observed in our population may reflect that we do not cross the septum until the patient is fully anticoagulated; many of our operators do ablation procedures without interrupting warfarin anticoagulation and/or maintain the sheaths outside of the left atrium, and we truly have not looked at all patients to determine the actual incidence. At minimum, understanding the true incidence of silent cerebral thromboembolic events and the potential compounding of events with repeat ablations may help understand if there is a threshold in which ablation transitions from reducing cognitive dysfunction to increasing it.

Conclusion

Mounting evidence continues to support that AF is independently associated with dementia. This association extends across the dementia spectrum and includes Alzheimer’s dementia. The mechanisms underlying these associations are incompletely understood, but with discovery will provide insight into preventative and treatment strategies. These mechanisms underlying AF and dementia may also help in further understanding other disease progressions in patients with AF, such as chronic renal dysfunction. The observational findings with catheter ablation suggest the need to include long-term comprehensive neurocognitive assessment in future therapies, both pharmacologic and non-pharmacologic, to continue to examine the role of rhythm control strategies to prevent dementia.

References


