Artículo de revisión
Rev Urug Cardiol 2015; 30:39-44

ESPECIAL
FIBRILACIÓN AURICULAR

Atrial fibrillation and its association with cognitive decline, cognitive impairment, and dementia in the absence of clinical stroke: a review of the evidence and possible mechanisms

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Abstract

Atrial fibrillation (AF) is the most common arrhythmia in the adult population. AF is widely known to be associated with an increased risk of many adverse outcomes including stroke, heart failure, all-cause death, as well as sudden cardiac death. More recently, there has also been growing interest in the association of AF with cognitive impairment and dementia. In this narrative review, we describe the current evidence that supports the relationship of AF to cognitive decline, cognitive impairment, or dementia in patients without a history of stroke. The exact mechanisms underlying the association of AF with cognitive decline are unclear; however, proposed mechanisms include silent ischemia, pro-inflammatory state, cerebral microbleeds, and cerebral hypoperfusion. Further research is needed to elucidate the underlying mechanisms to facilitate discovery of prevention strategies.

Key words:
ATRIAL FIBRILLATION
ATRIAL FIBRILLATION / prevention & control
DEMENTIA
DEMENTIA, MULTI-INFARCT
MILD COGNITIVE IMPAIRMENT
SILENT CEREBRAL ISCHEMIA

Introduction

AF (AF) is the most common arrhythmia in the United States of America. Nearly 2.7 million individuals have AF and it is a major cause of stroke. It is estimated that 25% of the population aged 40 or older will develop AF during some point in their lifetime(1,2). AF is widely known to be associated with an increased risk of many adverse outcomes including, heart failure, all-cause death, as well as sudden cardiac death[3-6]. Several studies have now established a clear association between AF and cognitive impairment or dementia[7-9].

Mild cognitive impairment (MCI) is defined as impairment in long-term memory that does not adversely affect activities of daily living whereas dementia is defined as memory impairment along with impairment in other cognitive domains that interfere with activities of daily living[10]. MCI is a harbinger of dementia and there is growing interest in identifying risk factors that lead to progression from MCI to dementia. Dementia affects 5-7% of the population globally; in the United States nearly 5 million people are affected. According to some estimates this number may increase dramatically in the near future[11,12].

Numerous studies have reported a significant association between AF and an increased risk of MCI or dementia. Many of these studies included patients with a history of clinical stroke[8,13,14]. Most studies diagnosed AF from physical examination, medical history, International Statistical Classification of Diseases (ICD) codes or a single ECG whereas cognitive impairment was diagnosed with Mini Mental State Examination (MMSE), and de-

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mentia was classified by DSM-IV criteria[15]. However some studies found no association between AF and MCI[16-18]. Similar negative studies for AF and dementia exist as well[19,20].

In contrast to previous reviews that addressed the association of AF with lower cognitive function in patients with clinical stroke[21], this narrative review summarizes current evidence which supports an independent association of AF with cognitive decline, MCI, and dementia in individuals without clinical stroke. We will also postulate potential mechanisms that may underlie this association.

Observational studies that adjusted for clinical stroke

Ott et al. in a landmark study reported odds ratio of 2.3 (95% confidence interval, 1.4 to 3.7) and 1.7 (95% confidence interval, 1.2 to 2.5) for dementia and MCI, respectively, in patients with AF[22]. When the authors adjusted for stroke there was no attenuation in the association between AF and dementia. The study adjusted for other cardiovascular risk factors for decreased cognition including, ischemic heart disease, hypertension and thyrotoxicosis. Interestingly, the risk was higher for Alzheimer's disease than vascular dementia (dementia in association with vascular disease). The study also characterized a slightly stronger AF-dementia association in women. One reason for this difference was a lower prescription rate of anticoagulation for women. Similar difference of higher incidence of stroke among women with AF was observed in the Framingham study[4].

Observational studies that excluded individuals with clinical stroke

Miyasaka et al. in 2007 investigated the association of AF with dementia in the absence of clinical stroke. Adult residents in Olmsted Country Minnesota who were diagnosed with AF in 1986-2000 were included in the study. A total of 2837 patients were studied and patients with prior history of stroke of dementia were excluded. Dementia was the primary outcome. The study found that the cumulative rates of dementia were 2.7% at 1 year and 10.5% at 5 years. Post AF dementia was associated with higher mortality[23].

Knecht et al. in a cross-sectional study defined the association of AF with MCI and structural brain changes in patients without history of clinical stroke. A total of 122 patients were evaluated. Neuropsychological testing and brain imaging were compared in patients with and without AF. Patients with AF were found to have poor performance in learning, memory, attention and executive functions. Hippocampal volume was also reduced in these patients on imaging[24]. The strength of the study is the combination of both clinical and imaging evidence to support the association of AF with MCI and dementia.

Another study recruited 5,888 participants aged >65 years with no AF or clinical stroke at baseline and followed them longitudinally. Participants were excluded when they experienced stroke. The primary outcome in this study was modified MMSE score that was administered throughout the follow-up of 7 years. The study found that the mean modified MMSE score declined faster in patients with AF compared to those without AF. One limitation of this study was that patients who experienced stroke but never sought medical care were not excluded[25].

Chen et al. in 2013 analyzed data from 935 participants who were part of the Atherosclerosis Risk in Communities Study, a community based prospective cohort study. These participants had cognitive testing and brain MRI scans in 1993-95 and 2004-06. Participants with a diagnosis of AF during follow-up had a greater rate of decline in Digit Symbol Substitution and Word Fluency tests. Of note, only participants with AF who had subclinical cerebral infarcts (SCIs) on brain MRI scans experienced greater cognitive decline; participants with AF but without SCIs on brain MRI scans did not have greater cognitive decline than those without AF. Therefore, the association of AF with cognitive decline in stroke-free individuals can be explained by the presence or development of SCIs, raising the possibility of anticoagulation as a strategy to prevent cognitive decline in AF[26].

Marzona et al. analyzed two randomized controlled trials (ONTARGET AND TRANSCEND) with a total population of 32,000 patients and found that the presence of AF increased the risk of MCI by 14% and new dementia by 30%. Subgroup analysis showed consistent results in patients with and without a history of stroke. The authors concluded that AF is an important risk factor for MCI even in the absence of clinical stroke. One of the limitations of the study is the absence of neuroimaging to take into account silent stroke[27].

Possible mechanisms

The development of cognitive decline and or dementia in patients with AF is a complex and multifactorial process. The following is a summary of possible mechanisms (Figure 1) that underlie the

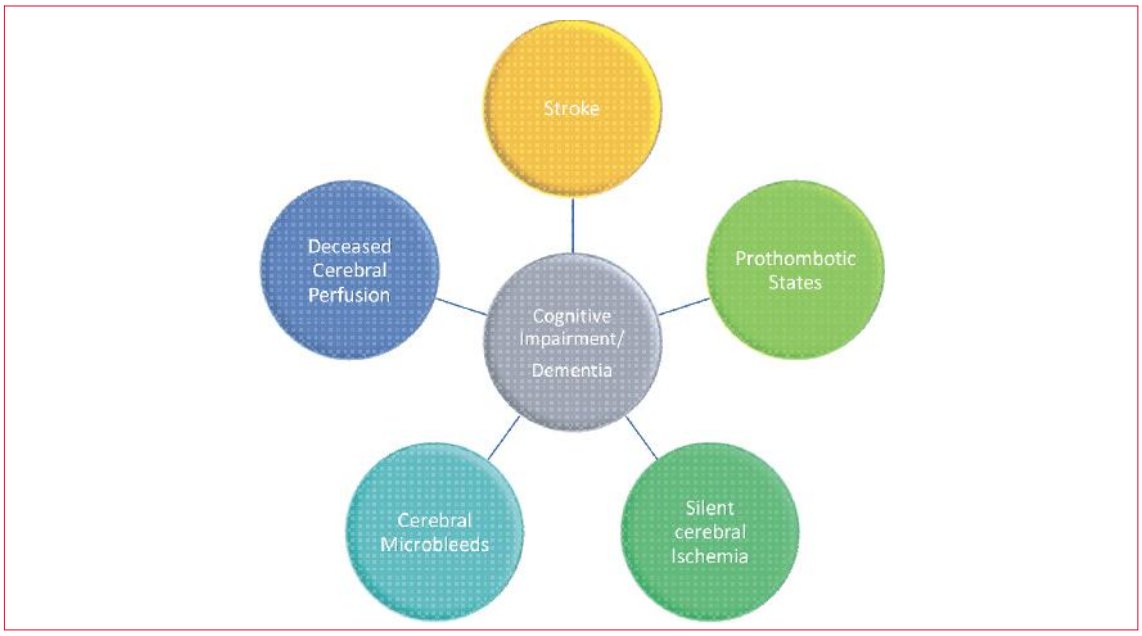

Figure 1. Possible mechanisms underlying the association of atrial fibrillation with cognitive impairment and dementia in patients with atrial fibrillation

association of AF with cognitive decline, MCI, and dementia in the absence of clinical stroke.

Embolic phenomenon and pro-thrombotic states

Stroke is a well-established consequence of AF[4]. Stroke is also an independent risk factor for cognitive decline including MCI and dementia[28]. A possible mechanism for the association of AF with cognitive decline in patients without a history of clinical stroke is silent cerebral ischemia. SCI has been associated with cognitive decline even in the absence of AF[26]. Imaging studies have revealed SCI to be more common in patients with AF than in normal sinus rhythm[26,29,30]. Gaita et al. reported a very high prevalence of SCI in AF patients: 89% in paroxysmal AF, 92% in persistent AF, and 46 % in sinus rhythm. Also the number SCIs was higher in patients with persistent AF when compared to paroxysmal. Cognitive function was worse in patients with any AF in this cohort[30].

Cerebral microbleeds

Classically, AF has been associated with thromboembolic phenomenon; however; a strong association between AF and cerebral micro-bleeds has also been established[31]. The cerebral micro-bleeds occur as a result of microangiopathy and can be identified as small hypointense lesions on T2-weighted MRI[32-34]. The incidence of cerebral micro bleeds increases with age and they are linked to lacunar infarcts and interventricular hemorrhages[32,35]. Cerebral micro-bleeds are also strongly associated with cognitive decline[31]. AF has been associated with a two-fold increased risk of CMB in patients with stroke/TIA[32,35].

Decreased cerebral perfusion

AF leads to a decrease in cardiac stroke volume due to loss of atrioventricular synchrony and impaired ventricle filling[36]. This may lead to a significant decrease in cerebral perfusion especially in elderly patients who have compromised vascular auto-regulation as demonstrated by de la Torre in 2012[37]. Numerous studies have also highlighted regional differences in cerebral blood flow in patients with AF[38-41]. The mean flow velocity decreased significantly in the middle cerebral artery in patients with AF as demonstrated by transcranial Doppler[39,40]. This decrease is more significant for younger patients with AF as demonstrated by Lavy et al[38]. Furthermore, the blood flow is decreased even more in acute stroke among patients with AF compared to sinus rhythm. This may compound the effect of cerebral ischemia in these patients. One study demonstrated significantly increased risk of dementia in patients with higher ventricular rate in AF, supporting the mechanism of cerebral hypoperfusion[42]. Research shows improvement in cerebral blood velocity with cardioversion[36,43].

Other mechanisms

Various inflammatory markers are elevated in AF including CRP, IL-6, and tumor necrosis fac-

tor[44-46]. These inflammatory markers are also linked to cognitive decline[47]. CRP has been shown to be elevated in AF even when adjusted for other cardiovascular risk factors[44,45]. Similarly CD40 L, von Willebrand factor, D-Dimer and prothrombin fragment 1 + 2, have also been shown to be elevated in AF[48-50]. The exact mechanism for the increase in inflammatory markers in AF and their impact on cognitive decline is unclear. Some studies indicated that the elevated pro-inflammatory markers increase the risk of thromboembolism which may be the underlying cause of cognitive decline[49,51]. Both TNF alpha and von Willebrand factor are established predictors of ischemic stroke which support this hypothesis[51,52]. Another possible mechanism includes damage to cerebral vasculature which results in a prothrombotic state and may also lead to the deposition of amyloid resulting in higher chance of developing vascular dementia and Alzheimer's disease[53,54].

AF has been associated with low hippocampal volumes, and both AF and hypertension are associated with small amygdalas[24,55]. Other studies have shown smaller brain volumes in patients with AF[56]. These low cortical volumes may directly result in MCI and increase the chance of developing MCI after stroke[57]. Similar age-related low cortical volumes and predisposition to dementia in AF population may also explain this association.

Possible prevention strategies for cognitive decline and dementia

There is conflicting evidence that warfarin delays the progression of cognitive decline among patients[27]. One study provides evidence in favor of warfarin[58]. The potential problem with warfarin is fluctuating INR values that either predisposes patients to thrombotic or bleeding events. Since cerebral microbleeds is also a possible mechanism for cognitive decline among these patients, a high INR will predispose patients to more microbleeds and hence a higher chance of damage to neural tissue. Data regarding the use of novel anticoagulants are limited and future research will need to be undertaken to study their effect on preventing cognitive decline.

Similarly, no difference was seen in the AFFIRM study subgroup analysis among patients with rate versus rhythm control strategy with antiarrhythmic agents. The AFFIRM trial randomized 4060 patients and found that management of AF with rhythm control strategy had no survival advantage. The risk of stroke was primarily related to the discontinuation of anticoagulation[59]. Subsequently, the AFFIRM investigators compared the results of MMSE in 245 patients and found no difference in the rhythm control arm versus the rate control arm[60].

Conclusions

We found strong evidence for AF as a risk factor for cognitive impairment and dementia even in the absence of clinical stroke. The underlying mechanisms are unclear and may include subclinical cerebral infarcts and cerebral microbleeds. More research is needed to elucidate the underlying mechanisms to facilitate discovery of prevention strategies for AF-related cognitive decline.

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