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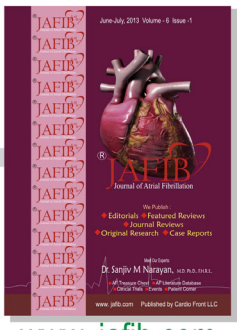

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Effect of Age on Outcomes of Catheter Ablation of Atrial Fibrillation

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Abstract

Age has a great impact in the development of atrial fibrillation, which is the most common arrhythmia found in the elderly. The higher risk of stroke, heart failure and mortality associated with atrial fibrillation highlights the need for successful therapeutic interventions that can translate in better outcomes in this population.

The introduction of catheter ablation has revolutionized the management of atrial fibrillation over the past decades with an undeniable impact in morbidity, mortality and quality of life. This benefit has not been fully extended to the older patients due to the lack of definitive data from randomized control trials assessing the impact of rhythm control strategies such as catheter ablation in this population, in whom a rate-control strategy has been suggested as a better therapeutic option.

In this review, we summarize the pathogenesis of atrial fibrillation in the elderly, the benefits and complications of catheter ablation reported in the literature and the impact of age in the outcomes of ablation compared to younger populations.

Introduction

Epidemiology of Aging and Atrial Fibrillation

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, accounting for more than 2 million adults in the United States[1] and becoming an emerging epidemic of cardiovascular disease. Its prevalence is not only related to the presence of heart disease, as demonstrated in the Framingham Heart Study,[2] where the lifetime risk of developing AF in the absence of conditions such as chronic heart failure or coronary artery disease was 16.5% in men and 15.9% in women.

Besides its deleterious effect in morbidity and mortality, AF has a direct impact in quality of life and health economics, as patients are three and eight times more likely to be hospitalized for non-cardiac and cardiac causes respectively, with an estimated national incremental AF cost from $6.0 to $26.0 billion in the United States.[3]

The elderly group imposes a new challenge in the treatment of this condition, especially because this is the age group that is mostly affected, with an estimated lifetime total risk of 24.3% in men and 23% in women by the age 70.[2] Data from Medicare beneficiaries[4] has shown that the prevalence of AF has doubled from 41.1 per 1000 beneficiaries in 1993 to 85.8 per 1000 beneficiaries in 2007, with a mean annual increase in prevalence of 5.0%. The magnitude of the increase is greater in the elderly group with a mean annual increment of 5.4% among patients 90 years or older compared to 4.3% in patients 66 to 69 years of age.

Key Words:
Atrial fibrillation, elderly, catheter ablation

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Age-related Pathogenesis of AF

The higher prevalence of AF in the elderly is a consequence of multiple insults that will eventually determine the pathologic substrate responsible for the perpetuation of the arrhythmia over time. Conditions such as hypertension, sleep apnea and coronary artery disease are all potential risk factors and its association is well established in the current literature. Specifically, diastolic left ventricular dysfunction, a condition that is well-linked with aging, leads to increased atrial filling pressures and wall stretch, ultimately associated with atrial fibrosis and remodeling, which make AF more likely to develop and to persist.[5]

Data has also shown the association of kidney disease with an increased incidence of AF, even in the group with a mild decrease in glomerular filtration rate.[6] Specifically, in patients with advanced renal disease requiring dialysis, the incident rate is calculated as 148 events per 1000 person-years according to data in older Medicare beneficiaries, and it is associated with a very high mortality rate of 59% one year after the diagnosis of AF.[7]

From the mechanistic standpoint, the effects of aging on conduction of the electrical impulse are well known. Spach et al showed 4 decades ago how aging-induced fibrosis leads to so-called nonuniform anisotropy, and dramatic conduction velocity slowing (zig-zag conduction) in the transverse direction, enabling reentrant circuits in very small regions.[8,9] This concept was later confirmed by optical mapping studies.[10]

AF Progression and Stroke Risk

Despite the challenges in the treatment of AF, the elderly group is the most vulnerable of all to develop short and long term complications such as stroke and progression of AF. A higher risk of stroke is well established with advanced age, with an annual risk attributable to AF of 1.5% in patients aged 50 to 59 years and 23.5% in those aged 80 to 89 years according to the Framingham study.[11] In terms of progression from paroxysmal to persistent AF, age above 75 years has been found to be an independent risk factor in a multivariate analysis along with congestive heart failure, hypertension, COPD and stroke, which are all more prevalent in the elderly.[12]

Aging and AF Treatment Options

Age not only increases the prevalence of AF but imposes significant limitations in its treatment; the higher prevalence of conduction abnormalities limit the use of rate control agents, which in some occasions, make device therapy necessary to overcome the risk of bradycardia and chronotropic incompetence. The use of antiarrhythmic therapy is also limited by multiple comorbidities and there is an increased risk of bleeding complications secondary to antithrombotic therapy, which is especially problematic given the higher susceptibility for disabling stroke in this population.

A higher degree of atrial myopathy in older individuals leads to a more complex substrate, which may affect the success of the procedure and the probability of remaining in sinus rhythm. Studies using substrate mapping in patients with drug-refractory AF undergoing pulmonary vein isolation (PVI) have shown a larger left atrium diameter in older patients (36.21 ± 5.85 mm in < 50 years, 39.03 ± 5.89 mm in 50-65 years and 40.41 ± 5.41 mm in > 65 years, p=0.002) and a lower mean peak-to peak bipolar left atrial voltage compared to younger patients (< 50 years: 2.07 ± 0.84 mV in < 50 years, 1.75 ± 0.72 mV in 50-65 years and 1.86 ± 0.67 mV in ≥65 years, p=0.024).[13]

In terms of catheter ablation of AF, there is extensive evidence of its efficacy in restoring and maintaining sinus rhythm over antiarrhythmic therapy. According to the current guidelines,[14,15] catheter ablation is indicated in symptomatic patients after failing or if intolerant to antiarrhythmic therapy, with electrical isolation of the pulmonary veins as main target. However, despite a common name, AF encompasses several disease stages, and as the disease progresses and persistent AF ensues, a more complex procedure with additional lesions is required to achieve success. These additional lesions include the left atrial roof line connecting the superior aspects of the left and right PVI lesions, the mitral isthmus line between the left inferior pulmonary vein and the mitral isthmus and an anterior line between the roof line and the mitral isthmus. Other interventions include coronary sinus[16,17,18] and superior vena cava[19,20] ablation, alcohol ablation of the vein of Marshall,[21] ablation of complex fractionated electrograms[18,22,23] and isolation of the left atrial appendage.[24]

The efficacy of catheter ablation of AF was described in a metanalysis[25] that included eight randomized controlled trials in patients 51 to 62 years and with paroxysmal AF as the predominant presentation, where catheter ablation reduced arrhythmia recurrence by 71% (RR 0.29, 95% CI 0.20-0.41, p< 0.00001) when it was compared to antiarrhythmic therapy. These data suggest that catheter ablation could also have a potential role in the elderly, in an attempt to improve outcomes in the population most affected by AF; however, the lack of randomized controlled trials assessing the efficacy and safety of catheter ablation in the elderly has been one of the major limitations to expand its use in this age group.

There is a tendency to have a more conservative approach when treating elderly patients, focusing on rate control strategies. One of the trials addressing this issue was the AFFIRM trial,[26] which randomized patients older than 60 years of age to rate vs. rhythm control, demonstrating no clear survival advantage of restoring and maintaining the normal sinus rhythm vs. controlling the ventricular rate; more deaths occurred in the rhythm-control group likely related to pro-arrhythmic effects of antiarrhythmic therapy but the difference was not statistically significant (p=0.08; HR 1.15, 95% CI, 0.99 to 1.34). Despite no differences in the two groups, antiarrhythmics and electrical cardioversion were the primary strategies in the rhythm control group, with only 62.6% of the patients remaining in sinus rhythm after 5 years, which could obfuscate any possible difference when the two groups were compared.

The real question is the impact of sinus rhythm in morbidity and mortality since it is possible that the unfavorable effects of antiarrhythmic therapy counteracted any possible benefit obtained from restoration of normal sinus rhythm. The on-treatment analysis of the AFFIRM trial[27] demonstrated that maintenance of normal sinus rhythm was significantly associated with survival (HR 0.53, 95% CI 0.39-0.72, p < 0.001), which is consistent with the results of the DIAMOND trial,[28] where mortality was similar in patients receiving dofetilide or placebo but there was a significantly lower mortality rate associated to the presence of sinus rhythm regardless of the method used for conversion (spontaneous, pharmacologic or electrical cardioversion) (RR, 0.44; 95% CI, 0.30 to 0.64; P<0.0001).

Despite the lack of randomized controlled trials in the elderly, few studies have shown the efficacy and safety of catheter ablation in this group (Figures 1 and 2).

Corrado et al.[29] reported data in a retrospective study that included 174 patients over 75 years with symptomatic AF (55% paroxysmal) refractory to antiarrhythmic therapy, in which catheter ablation was performed. The procedure consisted of pulmonary vein antrum isolation and isolation of superior vena cava. The success rate after a single procedure was 73% (n=127) over a mean follow-up of 20±14 months while 47 patients had recurrence. Sinus rhythm was obtained after a second procedure in 80% of the recurrent patients. Major acute complications were reported in 1% of the patients and consisted of one stroke and one hemothorax. Minor vascular complications included three groin hematomas (1.5%).

In a prospective analysis of a single center study[30] of 752 patients undergoing catheter ablation for drug-refractory AF, the characteristics of AF and outcomes of catheter ablation were analyzed in two different groups: ≥ 80 years (35 patients) and < 80 years. The rates of paroxysmal, persistent and permanent AF were similar in the two groups. Older patients were more likely to have congestive heart failure (20% vs. 10%, P = 0.06), coronary artery disease (31% vs. 9%, P < 0.0001), and –by definition- a higher CHADS2 score. Eighty percent of the patients in the elderly group and 78% of patients less than 80 years old required additional lesions besides pulmonary vein isolation. The procedure was successful in both groups, with 1-year survival free of AF or flutter without the use of anti-arrhythmic medications of 78% in patients ≥ 80 years and 75% in < 80 years (p = 0.78). Hospital stay was longer in the elderly group (2.9 ± 7.7 vs 2.1 ± 1.1 days, p = 0.001) but there were no differences in the rate of peri-procedural complications or death at one year. The authors pointed out that probably this was a healthier cohort of elderly patients, but the benefit and safety of ablation were evident on these results.

Zado et al.[31] demonstrated the efficacy and safety of catheter ablation in an experienced single center study that enrolled 1165 patients. The protocol included pulmonary vein isolation and focal ablation of non-PV AF triggers and analysis was done comparing three different age groups (< 65 years (n=948), 65-74 years (n=185) and ≥ 75 years (n=32). There was no significant difference in AF control (89%, 84% and 86% respectively, p=NS) during a mean follow-up of 27 months. However, more patients ≥ 75 years were maintained in antiarrhythmic therapy to achieve AF control (20%, 29% and 37% respectively, p = 0.024) and more elderly patients remained on antiarrhythmic therapy even in the absence of AF recurrence. There were no significant differences in the percentage of major complications or repeat ablation; however, older patients were less likely to have redo procedures.

In a retrospective study by Bhargava et al,[32] the impact of age on the outcome of PVI using a cooled-tip catheter was evaluated in three different age groups of patients with drug-refractory symptomatic AF (< 50, 51-60 and > 60 years, which included patients up to 79 years of age). The rate of complications was similar between the groups, except for the risk of stroke, which was higher in patients above 60 years. The recurrence rates at one year of AF were similar (15.1%, 16.7% and 18.4%, respectively; p > 0.05) demonstrating the benefits of ablation across all groups.

Traub et al.[33] compared the outcomes after PVI in 15 patients ≥ 70 years and 45 patients < 70 years. The presence of normal sinus rhythm was established as the primary outcome, with no difference between the two groups at 12 months of follow-up (60% elderly group vs. 80%; p = 0.17). The need for redo ablation was similar in the two groups (20% elderly vs. 24%) as well as the complications rate.

In the search of additional procedures that can be beneficial for elderly patients, AV node ablation has retained clinical utility given its lower complexity and the lower complication rate. However, small studies in the elderly comparing the two techniques suggest that in the appropriate patient, catheter ablation targeting the pulmonary veins is still a better option. In a multicenter, randomized, controlled trial comparing PVI vs. AV node ablation and biventricular pacing (AVN+BiV) in 71 patients from 52-68 years old with symptomatic AF and LV dysfunction (LV EF ≤ 40%), the benefit of PVI was demonstrated in terms of quality of life, 6-minute walk distance and higher ejection fractions long term, with a higher rate of progression in AF and use of antiarrhythmic medications in the AVN+BiV group.[34]

Hsieh et al.[35] compared catheter ablation vs. AV node ablation plus pacing either VVI or VVIR (AVN+pacing) in a small study of 71 elderly patients with medically refractory paroxysmal AF. In this study, catheter ablation included isolation of the arrhythmogenic

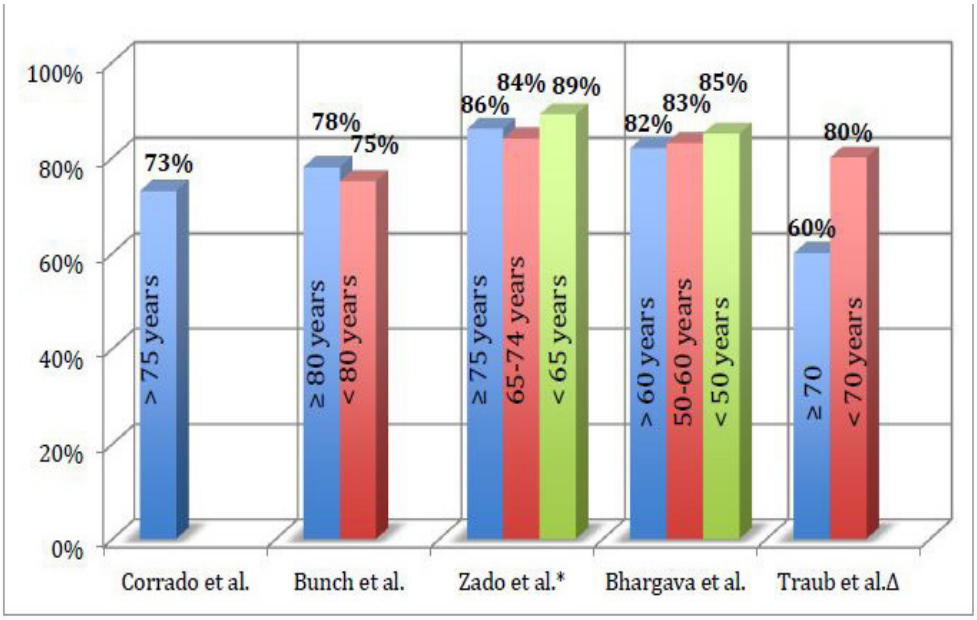

Figure 1: **Catheter ablation procedural success in different age groups.**

* Long-term AF control at one year included patients with no AF off antiarrhythmics (AAD) or on ADD, no AF on AAD restarted after AF recurrence and rare AF on or off ADD. Percentage includes a redo procedure on 9% of patients ≥ 75 years, 27% of patients 65-74 years and 26% of patients < 65 years.
Δ p = 0.17

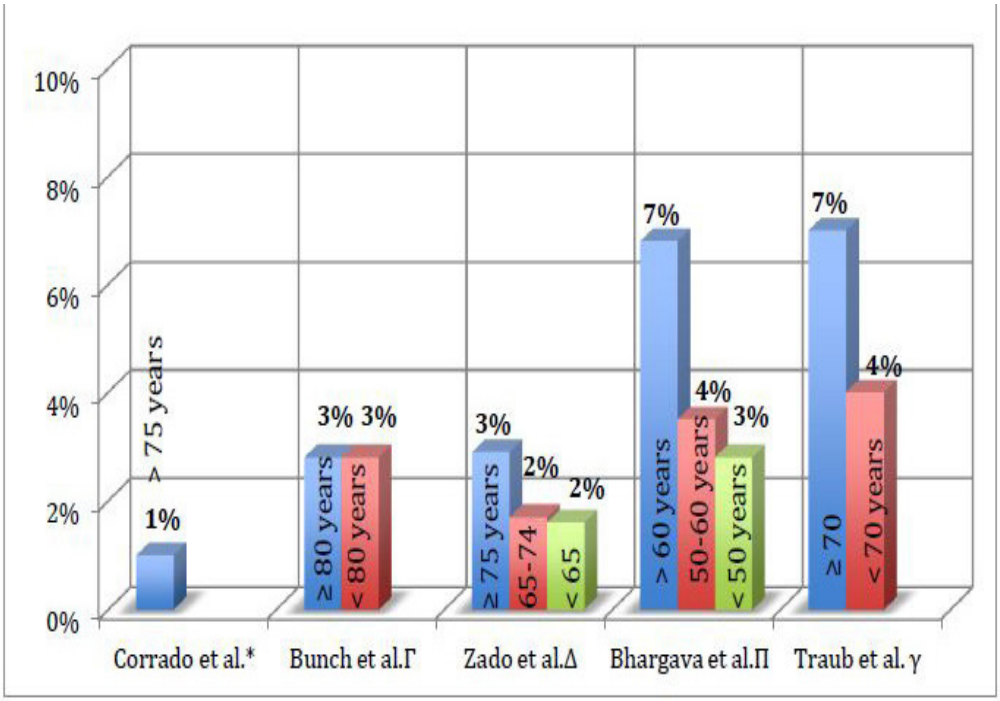

Figure 2: **Procedural complications**

* Stroke and hemothorax
Γ Death (all causes), MI, CVA, perforation with tamponade
Δ Tamponade or effusion requiring drainage, CVA/TIA, atrioesophageal fistula, pulmonary vein stenosis requiring intervention, phrenic nerve injury, anaphylaxis and retroperitoneal bleed. p=NS
Π Tamponade/perforation of left atrium, TIA, stroke and severe PV stenosis. No significant differences between groups except for stroke (3% in > 60 years vs. 0% in < 50 and 50-60 years old, p < 0.05)
γ Three cardiac tamponades, one in < 70 years group and two in ≥ 70 years old. p=1.0

pulmonary veins with a mean of 1.3 pulmonary veins isolated as well as non-PV vein areas with triggered activity in 27% of the patients in the ablation group. The authors reported freedom from symptomatic AF in 100% of the patients in the AVN+pacing group vs. 81% of the patients in the AF ablation group, but there was a higher incidence of heart failure in the AVN+pacing group (53% vs. 24%, p=0.001) as well as worsening left ventricular function from initial evaluation to end of follow-up period (44 ± 8% vs. 51 ± 10%, p = 0.01) compared to the catheter ablation group (46 ± 10% vs. 49 ± 10%, p = 0.37), likely secondary to right ventricular pacing. The progression to persistent AF after about 4 years of follow-up was higher in the AVN+pacing group compared to the ones that underwent ablation of pulmonary veins (69% vs. 8%, p < 0.001). There were no differences in ischemic strokes and cardiac deaths between the two groups.

There is still a need of randomized controlled trials focusing on the elderly group to measure the outcomes of catheter ablation. One of the ongoing studies is the CABANA trial,[36] a randomized controlled trial currently enrolling patients from 18 to 90 years old with documented AF, which will further elucidate the role of catheter ablation vs. antiarrhythmic therapy. While more data is available, we consider that catheter ablation is still the best choice in the elderly as a rhythm control option, along with long-term anticoagulation for stroke reduction making the greatest impact in the population affected most by this condition.

Conclusions:

AF is for the most part, a disease of the elderly and there is still a need to find the best therapy that can lead to tangible results in these patients. The outcomes of catheter ablation of AF in the elderly are similar to the ones obtained in younger populations, and age has become an important reason to establish normal sinus rhythm as a primary goal. In the appropriate patient, catheter ablation is the most effective therapy and with the most impact in morbidity, mortality and quality of life in the elderly group.

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