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Case Report

Treatment Strategy for a Trial Fibrillation in Elderly Patients

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ABSTRACT

In patient's ≥ 65 years, Atrial Fibrillation (AF) prevalence is high and increases further with age. Now-a-days, it has been estimated that AF affects 5% of ≥ 70-years patients, while approximately 10% of patients aged ≥ 80-years suffers from this arrhythmia. Evidence suggests that elderly people are predisposing to AF, due to aging-related cardiovascular remodelling and modifications. Symptoms due to AF could be directly caused by arrhythmia, such as palpitation, or indirectly by exacerbating other conditions such as angina, heart failure and structural cardiomyopathy. Since 2000's, novel drugs and therapies have become available also for the elderly but, unfortunately, have not been extensively evaluated in this population. Particular interest should be payed to emerging pharmacological and non-pharmacological treatment for AF, such as dronedarone or catheter ablation, and their perspective in the older patients. However, the absence of clear superiority of rate control or rhythm control strategy in the elderly makes particularly difficult the choice of an appropriate treatment. The pathophysiology, diagnosis, and the management of AF in older patients are reviewed in this paper.

Keywords: Antiarrhythmic drug; Atrial Arrhythmias; Catheter ablation; Non-pharmacological treatment; Rate control strategy; Rhythm control strategy

INTRODUCTION

Even if Atrial Fibrillation (AF) is a well-known disease since many years, there are few data about older adults with AF as they were often excluded from major trials, although 70% of AF individuals are aged between 65 and 85 years. Therefore, the best treatment for these patients remains a challenge that should be faced. In patient's ≥ 65 years, AF prevalence is high and increases further with age. Now-a-days, it has been estimated that AF affects 5% of ≥ 70-years patients, while approximately 10% of patients aged ≥ 80 years suffers from AF [1].

In patients acutely admitted to a geriatric ward, the prevalence of AF is 46% [2]. In particular, these patients exhibit increased rate and duration of hospitalizations due to stroke, Heart Failure (HF), arrhythmias and pacemaker implantations. Thus, the morbidity of AF in the elderly patients is of considerable importance and, even if AF cannot be considered directly life threatening, it is undoubtedly related to a huge mortality risk, being the annual mortality rate 8% in patients aged >75 years [1].

Rhythm control consists of using pharmacological and/or electrical means to restore Sinus Rhythm (SR) in the acute setting and to maintain it in the long term. On the contrary, rate control strategy is based on atrioventricular node blocking agents that slow ventricular rate during AF. New perspectives on management and treatment of AF in the elderly have come from studies that actively enrolled this group of patients; breakthroughs in invasive approaches and in pharmacological treatment could change the clinical management. We have reviewed scientific literature in order to perform an up-to-date of the pathophysiology, diagnosis, and the management of AF in older patients with particular interest in evaluating the role of rate or rhythm strategy in this setting.

CASE STUDY

AF occurrence: Causes and clinical diagnosis

Elderly patients have often hypertension, HF, ischemic heart disease, valvular heart disease and other conditions that predispose to AF [3]. In particular, structural heart disease enforces atrial chamber abnormalities that are associated to higher prevalence of AF [4]. Recently, also obstructive sleep apnoea and obesity have been found to be independent risk factors for AF [5,6].

The progression from paroxysmal to persistent and permanent forms occurs because of electrical and structural remodelling. Arrhythmia itself creates electrical adaptations, contractile

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dysfunction, and structural modifications: shortening of effective refractory period of atrial myocytes, slowing of the intra-atrial conduction and reduction of contractile function have been shown [7]. The longer the time before rhythm control treatment, the more difficult SR recovery is [3].

The diagnosis of AF requires a 12-lead Electrocardiogram (ECG) record, showing the arrhythmia. This is often a random finding, because the elderly patients are frequently asymptomatic [8]. When AF is suspected, repeated ECGs, dynamic ECGs, or other monitoring systems are advised. A patient with a first-diagnosis of AF should be evaluated, at least, with echocardiography and blood tests, including thyroid hormones.

Rate control strategy

Rate control could be the first-line therapy, especially for asymptomatic elderly patients [9,10]. To achieve this goal, β-blockers seem to be the most effective drug, according to data from the AFFIRM sub-study [11].

Other drugs are available as alternative. Further than, non-dihydropyridine calcium channel blockers (diltiazem and verapamil) Digoxin could be considered especially in acute HF, while should be avoided in patients without HF, in which has been shown to be an independent risk factor for death [9,12]. Of note, in the elderly patients, in whom renal function is often compromised, digoxin dose had to be cautiously chosen. Finally, amiodarone could be used as a last resort, but due to its multiple side effects, it could not be considered as a standard for rate control [13].

Moreover, strict rate control has been shown to not improve morbidity and mortality more than lenient control; thus, a careful evaluation of these drugs dose is advisable to prevents every bradycardia, pathological pauses and low rate associated symptoms, that could require a pacemaker implantation [14,15].

Rhythm control strategy

Both electrical and pharmacological cardioversion can be related to serious side effects and, for patients aged ≥ 75 years, OAC must be administered even in case of AF episodes shorter than 24-48 hour, due to high thrombotic risk (CHA_2DS_2-VASc score at least 2 because of age) [16]. Usually, amiodarone is considered the safest choice for pharmacological cardioversion in the elderly, even if its efficacy is limited [17]. Particularly, in older people, coexisting heart, renal, or hepatic impairment could discourage the use of most Antiarrhythmic Drugs (AADs) indicated for restoration and maintenance of SR. If the recurrence of AF occurs despite AADs, the number and the frequency of the attempts to restore SR should be limited, especially in the elderly patients.

Almost every AAD has been associated with serious side effects and, among these; the induction of arrhythmias could be the most serious. Pro-arrhythmic effect of class I and III agents is associated to an increased number of ventricular ectopic beats, monomorphic ventricular tachycardia, and prolongation of QT interval, torsade de pointes and severe bradycardia. Quinidine, flecainide, sotalol, and dofetilide have been shown, in previous studies, to be the AADs most prone to provoke ventricular pro-arrhythmias [18].

The CAST study documented that flecainide and other IC drugs are associated to higher mortality than placebo, when used in ischemic heart disease with previous myocardial infarction and severely reduced ejection fraction [19]. Thus, it is advisable to exclude the presence of structural heart disease before treating a patient with propafenone or flecainide. Moreover, in the elderly, further caution is request due to the high probability of underlying coronary artery disease. When a I class antiarrhythmic drug is administrated in an outpatient setting, ECG should be monitored closely: therapy should be stopped if QRS widening is greater than 150% of the baseline [10,20]. To investigate possible myocardial ischemia, exercise-induced arrhythmias and rate dependent QRS widening, an exercise test should be performed after 1 or 2-weeks of treatment [9-16].

Patient known for ischemic heart disease with preserved ejection fraction and no sign or symptom of heart failure could be treated with class III antiarrhythmic agents (amiodarone, dofetilide, dronedarone, and sotalol) [9,10]. According to the PALLAS study, (i) permanent AF patient's ≥ 65 years with coronary artery disease, HF or previous stroke, and (ii) patients ≥ 75 years with diabetes and hypertension, resulted to have an increased risk of cardiovascular events during treatment with dronedarone [21]. Thus, dronedarone should be carefully considered for elderly patients with structural heart disease.

Amiodarone and dofetilide are the only AAD available for HF patients. In case of left ventricular hypertrophy (wall thickness >13 mm) amiodarone is the only recommended treatment, even if this indication is poorly supported by literature [9]. When a class III agent is the drug of choice, QTc interval must be monitored and treatment should be titrated down or stopped in case of QTc ≥ 520 ms.

In any case of AAD use, a regular follow up is mandatory. Follow-up must include clinical evaluation and biochemical measurement (serum creatinine, potassium, thyroid function just in case of amiodarone therapy). Dofetilide and sotalol dosage should be modified in case of renal impairment, due to pro-arrhythmic concerns [9,10].

Role of catheter ablation in the elderly

As previously underlined, lowering heart rate strategy may induce extreme bradycardia, while AADs could have pro-arrhythmic side effects and dangerous interactions. Over the past 20-years, there have been many reports about safety and effectiveness of catheter ablation in patients with symptomatic AF refractory to pharmacological treatment. Therefore, Pulmonary Veins Isolation (PVI) has become a valuable therapeutic option in symptomatic patients, as an alternative approach to AADs [22].

However, the role of catheter ablation has not been well defined in the elderly population with AF [9,10]. Patients older than 75-years were usually excluded from many trials on catheter ablation. So far, the main volume of data regarding the safety and efficacy of this procedure has been derived from studies focused on younger patients mainly without structural heart disease and little co-pathology, and then turned over into the elderly population [23].

Furthermore, data from a worldwide survey had suggested a 4.5% rate of major complications during the AF ablation procedure (death, cardiac tamponade, strokes, and transient ischemic attacks) [24].

More recently, several studies have shown similar results in the elderly and younger patients treated with radiofrequency catheter ablation both for adverse events incidence and percentage of success, even at long follow up [25-29].

According to these data, the opportunity to treat the elderly patients with an invasive strategy could be considered. In any case, the presence of left atrial thrombus or impossibility to receive anticoagulation for at least 6-8 weeks after the procedure contraindicates ablation treatment. Now-a-days, cryobaloon PVI is getting clinical space. This technique has similar results than radiofrequency PVI both for efficacy and safety [30]. Cryobaloon has a lower risk of pulmonary vein stenosis and oesophageal injury, but higher incidence of phrenic nerve palsy, that usually recovers completely [31]. Of note, this method has a main limitation. The setting of atrial lesions is limited to PVI and a second procedure with RF could be required to maintain SR [27].

To date, catheter ablation in octogenarians accounts for 3.7-4.7% of all ablation procedures [25].

Recently, the Catheter Ablation *vs.* Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial have been published. This is the largest multicentre randomized trial to compare PVI vs. standard rhythm and/or rate control drugs. The study enrolled 2204 symptomatic patients, aged ≥ 65 years. Over a median follow-up of 48.5 months, the primary composite end point of death, serious bleeding, stroke or cardiac arrest occurred in 8.0% of patients in the ablation group *vs.* 9.2% of patients in the drug therapy group (Hazard Ratio [HR], 0.86 [95% CI, 0.65-1.15]; *P*=.30). According to the intention-to-treat analysis, the subgroup of patients aged ≥ 75 years did not benefit from catheter ablation considering the primary cumulative end-point [32]. Probably, the results of the CABANA trial should definitively exclude older people from indication of pulmonary vein isolation, unless disturbing symptoms are present.

A further strategy could be considered in the elderly patients, especially if highly symptomatic: Atrioventricular Node (AVN) ablation with pacemaker implantation. However, the PABA-CHF study show that PVI has a better outcome than AVN ablation with biventricular pacing according to quality of life, ejection fraction and walking test results [33]. However, in a study by Hseih et al, elderly patients with refractory paroxysmal AF were treated with AVN ablation plus single-chamber pacing or AF ablation, and the long-term results were compared. AF symptoms were improved in the ablate and pace group more than in the ablation group. Of note, in the very long-term follow-up ablate and pace treatment was associated with higher incidence of HF than pulmonary veins isolation [34].

Which strategy in elderly patients?

Assuming that increasing time in SR reduces AF-related morbidity and mortality, rhythm control strategy (AADs, cardioversion, and catheter ablation) is often used in clinical practice. Anyway, whether rhythm control strategy can improve clinical outcome remains unclear, particular in older adult, for whom the risk of adverse drug events and side effects from catheter ablation are particularly increased.

Since early 2000's, multiple published randomized controlled trials and systematic reviews have compared AF treatment strategies. No benefit in survival was associated to rhythm or rate control, neither in >65 years patients with at least one stroke risk factor, nor in HF patients with severe depressed systolic function [35-40].

Unfortunately, patients >75 years were poorly represented in those trials, therefore data on specific treatment strategy remain weak [39,40]. Almost 90,000 patients were analysed in a meta-analysis on five observational studies focusing on ≥ 75 years patients (range 75-92 years) [41-46]. No differences in cardiovascular mortality (OR 1.09; 95% CI 0.81–1.47; *n*=2292) and all-cause mortality (odds ratio 1.11; 95% CI 0.78-1.59; *n*= 28,526) have been shown in pharmacological therapy for rate *vs.* rhythm control. Thus, even after high volume studies on real-life, no strong recommendation could be advisable about choosing rhythm or rate control as AF first-line therapy in the elderly.

CONCLUSION

Since 2000's, treatment of AF has been implemented with new therapies, demonstrated to be safe even for older patients. Up-to-date, clinical interest for these patients, previously excluded from trials and therefore under treated, is growing up. Patient preference and drug safety profile should drive the better strategy, paying particular attention to the presence of structural heart disease and chronic kidney disease. Evidence in favour of rate or rhythm control are lacking in this population. Randomized controlled trials are needed to focus the best care for the elderly, because AF is particularly prevalent among them.

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