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Should Ablation Be First-Line Therapy for Patients with Paroxysmal AF?

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Opinion statement

Atrial fibrillation is the most common cardiac arrhythmia and the number of patients is expected to continuously increase in the next years. Catheter ablation is an effective, safe, and well-established treatment for patient with symptomatic and drug-resistant paroxysmal atrial fibrillation (PAF). Over the last decade, there was an increasing body of evidence demonstrating superiority of catheter ablation over antiarrhythmic drugs (AADs) in maintaining sinus rhythm. However, randomized clinical trials have not been conclusive to consider catheter ablation as a first-line therapy for PAF. The encouraging results of RAAFT Trial were not confirmed in the MANTRA-PAF Trial and in the RAAFT-2 Trial. Recent meta-analyses showed that catheter ablation is more effective than AAD therapy as a first-line treatment for PAF. In particular, relatively young patients and patients with no or minimal cardiovascular disease are the subpopulation that benefitted more from catheter ablation. On the other hand, the meta-analysis showed that catheter ablation causes more severe side effects than AAD therapy, underling the importance of patient selection and operator experience. To date, there are no univocal evidences to consider catheter ablation as a first-line therapy for PAF. Apart from patients' preference and avoidance of toxicity of AADs, the published data are supportive to consider a first-line catheter ablation in a peculiar subpopulation of patients. In particular, younger patients, patients with sinus node dysfunction related to AF, and patients with tachycardiomyopathy are the subgroups that seem to be good candidates for catheter ablation as a first-line therapy for PAF.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, and it has a significant impact on morbidity and mortality. Although AF itself is not a life-threatening arrhythmia, it increases the risk of incidence of stroke, systemic embolism, heart failure, and death. Moreover, AF significantly decreases quality of life, mainly in relation to symptoms and socioeconomic problems. Worldwide, more than 30 million patients in 2010 had been diagnosed with AF and the number is expected to continuously increase in the next years. For these reasons, AF has become one of the most important public health problems and a significant cause of increasing health care costs in Western countries [1–7].

In the late 1990s, catheter ablation emerged as a promising treatment strategy for patients with AF. Initially, catheter ablation was prudently reserved as a "last-line" strategy for highly symptomatic patients who were refractory to multiple antiarrhythmic drugs (AADs). However, considering the ineffectiveness of AADs for rhythm control and the significant risks associated with AAD therapy [8–13], catheter ablation of AF has rapidly spread worldwide. In a meta-analysis, Calkins et al. reported an increased cumulative complication rate for AAD treatment compared to that of catheter ablation [14]. Therefore, AF ablation has been well accepted in patients with drug-refractory AF. Over time, as the success of catheter ablation has improved and the complication rate declined, the threshold for proceeding with ablation has fallen. According to the last HRS/EHRA/ECAS Expert Consensus Statement on catheter and surgical ablation of AF [15], catheter ablation is now recommended with a class I level of evidence A for patients with symptomatic paroxysmal AF (PAF) refractory or intolerant to just one or more AAD. For selected patients, the guidelines even propose catheter ablation as a first-line therapy [16–18]. The basis for considering catheter ablation as a first-line therapy in PAF was derived from an increasing body of research demonstrating superiority of ablation over AADs in maintaining sinus rhythm. Several clinical trials reported arrhythmia-free-survival ranging from 50 to 75% at 1 year after catheter ablation compared to only 10–30% with AADs [19–24].

The first evidence for catheter ablation as a first-line treatment in patients with PAF came from the Radiofrequency Ablation vs. Antiarrhythmic drugs as First-line Treatment of symptomatic atrial fibrillation (RAAFT) Trial published in 2005. Subsequently, two multicenter randomized trials and two consecutive case series have assessed the benefit of catheter ablation as a first-line treatment for PAF.

Randomized clinical trials

RAAFT Trial

The RAAFT Trial was the first randomized study comparing AADs and catheter ablation as a first-line treatment in patients with AF [24]. It was a somewhat small study including only 70 patients with symptomatic AF for at least 3 months (96% PAF) randomized in three different centers. The primary endpoint was any recurrence of symptomatic AF or asymptomatic AF lasting longer than 15 s documented at Holter or event recorder during a 1-year follow-up. Secondary endpoints were hospitalization and quality of life evaluation. The technique adopted for catheter ablation was a standardized pulmonary vein antrum isolation (PVAI) guided by intracardiac echocardiography and confirmation of isolation using a circular mapping catheter. In this early study, all procedures were performed using the 8-mm tip nonirrigated ablation catheter because the irrigated-tip catheters were not yet approved for AF ablation. At 1 year of follow-up, both treatments reduced the frequency of AF episodes; however, a greater proportion of patients assigned to the AAD arm experienced at least one recurrence of symptomatic AF, compared with those assigned to the PVAI (63 vs. 13%, $p < 0.001$) accounting for 80% relative risk reduction with catheter ablation ($p < 0.001$). PVAI was associated with a superior control of AF

in terms of fewer hospitalizations (9 vs. 54% of patients, $p < 0.001$) and a statistically significant improvement in the patients' quality of life at 6 months. Regarding complications, there were no differences between the two arms (12.5 vs. 11.5%). In addition, there was a high rate of crossover from the AAD group to the PVAI group (51%) and it is likely that the actual benefit of ablation in the RAAFT Trial was underestimated. Thus, RAAFT, for the first time, showed the feasibility, safety, and efficacy of catheter ablation as a first-line treatment in patients with PAF.

Khaykin et al. published a cost comparison analysis on the RAAFT study [25]. Briefly, the cost of catheter ablation included an overnight hospital stay, a pre-procedure transesophageal echocardiogram, cost of the catheters including the use of intracardiac echocardiography, physician fees, cost of two CT scans, a loop recorder, a 24-h Holter, and cost associated with various procedural complications. The cost related to the medical treatment included oral anticoagulation therapy, monthly INR monitoring, office visits, risks associated with anticoagulation, and AAD costs. In addition, costs of follow-up were also calculated including two family physician visits, one specialist visit, two ECGs, and an echocardiogram. Patients who experienced recurrences had additional costs related to hospitalization, cardioversion, diagnostic tests, and additional visits. After the first year of follow-up, catheter ablation was more expensive than AAD with a total cost per patient of US$12,823 compared to US$6053. Interestingly, at the end of the second year, the total costs per patient were US$15,303 for catheter ablation and US$14,392 for AADs. The higher initial costs of catheter ablation compared to those of medical therapy were balanced after 2 years of follow-up mainly because of arrhythmia recurrences and crossover to the ablation arm after failing AADs.

MANTRA-PAF Trial

After the encouraging results of RAAFT, a larger multicenter randomized trial, the Medical ANtiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) compared catheter ablation with AAD therapy as a first-line therapy for symptomatic PAF [26]. Ten centers in Scandinavia and Germany participated in the study. Overall, a total of 294 patients were enrolled and randomized to catheter ablation ($n = 146$) and AADs ($n = 148$). The primary endpoint of the study was the pre-visit and cumulative burden of symptomatic and asymptomatic AF on 7-day Holter recordings. Freedom from any AF after 24 months of follow-up, cumulative burden of symptomatic AF, time to first recurrence, and quality of life were among the secondary endpoints. There was no significant difference in terms of total cumulative AF burden between the two arms. At 24 months, catheter ablation was associated with a significantly lower AF burden compared to that of AAD ($p = .007$), improved quality of life, higher freedom from symptomatic AF (93 vs. 84%, $p = 0.01$), and higher freedom from any AF (85 vs. 71%, $p = 0.004$), accounting for a 48% relative risk reduction ($p = 0.004$). Complications were similar between the two arms (17 vs. 15%).

Both RAAFT and MANTRA-PAF showed similar findings; even though in the MANTRA-PAF, there is nearly a two-fold lower effectiveness of ablation in terms of relative risk reductions compared to that of the RAAFT study. This finding can be explained by considering the differences between the two studies. Of interest, the ablation techniques adopted in the MANTRA-PAF were heterogeneous according

to the discretion of the enrolling center. These techniques included pulmonary vein isolation (PVI) guided by circular mapping catheter or circumferential PVI guided by a 3D electroanatomic mapping system without confirmation of isolation using a circular mapping catheter. Several randomized trials demonstrated that PVI without confirmation using a circular mapping catheter is inferior to PVI guided by circular mapping catheter in terms of long-term outcomes [27, 28]. Finally, the rate of crossover from AAD arm to ablation was considerable (36%), and again, the real benefit of ablation over AAD in the MANTRA-PAF may have been underestimated as that with the RAAFT Trial.

Recently, at the 2015 European Society of Cardiology Congress, Nielsen presented the 5-year AF recurrence data of the MANTRA-PAF. Two hundred and forty-five patients completed this follow-up period, 125 belonging to the catheter ablation group and 120 to the AAD group. The superiority of catheter ablation reported at 2 years was sustained at 5 years. AF burden was lower in the ablation group ($p = .003$) as well as the burden of symptomatic AF ($p = .02$). Freedom from any AF and freedom from symptomatic AF were higher in the ablation group compared to that from the AAD group (86 vs. 71%, $p = 0.001$ and 94 vs. 85%, $p = 0.015$ respectively). In addition, at 5 years, 61 patients in the medical group were still taking AADs vs. 13 patients in the ablation group ($p = 0.001$). Walfridsson et al. published the quality of life and symptom burden data in the MANTRA-PAF population [29]. The Short Form-36 and the EuroQol-five dimensions questionnaires were used to assess the health-related quality of life, whereas the Arrhythmia-Specific questionnaire in Tachycardia and Arrhythmia was used to assess the symptom burden. This analysis showed that both arms had a significant improvement in the health-related quality of life as well as in symptom burden. At 24 months follow-up, patients in the catheter ablation group had better physical scales scores and fewer arrhythmia episodes. A cost-effectiveness analysis was also performed in the MANTRA-PAF population [30]. The authors found that the 24-month average cost to treat PAF with catheter ablation as a first-line therapy was approximately doubled compared to that with AADs. The difference was mainly driven by the cost of the procedure and cardioversions. However, a subgroup analysis comparing younger (<50 years) and older (>50 years) patients showed that catheter ablation was cost effective as a first-line treatment in the younger population. The main reason for this finding is that younger patients have an earlier stage of AF which may be much more responsive to pulmonary vein isolation compared to older patients. This subgroup of patients also have fewer comorbidities than older patients such as hypertension, valve disease, diabetes, and sleep apnea, the absence of which may also improve the outcome of ablation.

RAAFT-2 Trial

The RAAFT-2 Trial was a multicenter randomized clinical trial involving 16 centers in Europe and North America [31••]. One hundred and twenty-seven antiarrhythmic drugs- ($n = 61$) and ablation-naive ($n = 66$) patients with paroxysmal AF were randomly assigned 1:1 to either treatment. Inclusion criteria were symptomatic recurrent paroxysmal AF, one AF episode documented in a 12-lead ECG, and ≤4 episodes in the previous 6 months. Patients were followed at 1, 3, 6, 12, and 24 months. The primary outcome was the time to first documented, either symptomatic or asymptomatic, atrial arrhythmia ≥30 s detected by ECG, Holter, transtelephonic monitoring (TTM), or rhythm strip. Secondary outcomes were

symptomatic recurrences of any atrial arrhythmia and quality of life assessment. Different from the RAAFT Trial, ablation was performed using an irrigated-tip ablation catheter in RAAFT 2. After randomization, patients entered in a 90-day blanking period in which AADs were titrated or ablation was performed. Patients in the AAD group were able to crossover to the catheter ablation group after the 90-day treatment period if AADs had failed due to intolerance, adverse events, or inefficacy. Different from the MANTRA-PAF study, the RAAFT-2 ablation technique was standardized and involved PVI with confirmation of entrance block. Forty-four patients (72.1%) in the AAD group and 36 patients (54.5%) in the ablation group experienced the primary outcome in the 2 years of follow-up (hazard ratio [HR], 0.56; [95% CI, 0.35–0.90]; $p = 0.02$). Regarding the secondary outcomes, 59% in the AAD group and 47% in the ablation group experienced recurrence of any symptomatic atrial arrhythmia (HR, 0.56 [95% CI, 0.33–0.95]; $p = 0.03$), whereas recurrence of AF occurred in 57.4% of patients in the AAD group and in 40.9% in the ablation group (HR, 0.52 [95% CI, 0.28–0.40]; $p = 0.02$). Quality of life improved in both groups compared to the baseline, but there was no statistical difference between the two arms. In the ablation group, PVI was achieved only in 87% of the cases and in 21.3% of the procedures ablations in non-PV regions was performed. Complication rate of catheter ablation was surprisingly higher than previously reported with a 9% rate of overall complications and 6% rate of pericardial effusion with cardiac tamponade [32, 33]. In the AAD group, 16.4% of patients received more than one type of medication, 59% of patients had to discontinue at least one AAD, and 47.5% of patients underwent ablation after 1-year follow-up. This study demonstrated that catheter ablation was modestly superior to AADs for the prevention of atrial arrhythmias over 2 years of follow-up. However, ablation carries risks even in experienced hands. In addition, the rate of any atrial arrhythmias recurrence was higher when compared to that of previous studies, probably due to the more intensive follow-up with the biweekly TTM, which demonstrates that atrial arrhythmia recurrences are common with both therapeutic treatments.

Single-center experiences

In addition to the randomized clinical trials previously discussed, there are two single-center experiences in the literature that evaluate catheter ablation as a first-line therapy. Tanner et al. reported their experience in a consecutive series of patients who underwent AF ablation at their center between 2001 and 2009 [34]. A total of 72 out of 434 (17%) patients were selected for first-line ablation of AF, mainly because of patient preference or medical reason. After a follow-up of 12 months, the success reached 78% in the first-line ablation group, compared with 64% in patients undergoing ablation after failing AADs ($p = 0.03$). The decision to perform catheter ablation in the early stage of AF was associated with a significantly higher success rate and a reduced need for a redo procedure.

Namdar et al. evaluated the benefit of first-line ablation of PAF using the cryoballoon technology [35]. It was a small study including 18 patients who preferred to avoid AAD therapy. The study showed effective PVI in 100% of the cases, and 89% of the patients were free from recurrent AF after a mean follow-up of 14 ± 9 months. Follow-up was performed with a 24-h Holter recording at 1, 2, 3, and 12 months and a 5-day Holter at 6 months. Although the result of

this study was encouraging, the relatively high success rate might be influenced by the absence of prolonged monitoring during the follow-up. Recently, cryoballoon ablation has been shown to be noninferior to radiofrequency ablation in patients with PAF [36]. In addition, the FIRE and ICE randomized clinical trial showed no significant difference between the two technologies in terms of safety. Thus, if a first-line treatment is the choice it might be reasonable to consider cryoballoon ablation as well as standard radiofrequency ablation.

Meta-analysis

In a recent meta-analysis published by Hakalahti et al., catheter ablation appears to be more effective than AAD therapy as a first-line treatment for PAF [37••]. The risk of AF recurrence was significantly higher among patients treated with AADs (risk ratio [RR] 0.63; 95% CI, 0.44–0.92; $p = 0.02$). In particular, patients that benefitted more from catheter ablation were relatively young and with no or minimal cardiovascular disease. The meta-analysis showed that catheter ablation causes more severe side effects than AAD therapy, underlying the importance of patient selection and operator experience.

A meta-analysis on catheter ablation and AAD therapy as a first- and second-line therapy by Khan et al. indicated that catheter ablation was associated with significant risk reduction of AF recurrence both as a first- and second-line treatment compared to AADs [38]. Considering together as first- and second-line therapy, catheter ablation demonstrated a 60% reduction in the risk of recurrence (relative risk [RR], 0.40; 95% CI, 0.31–0.52; $p = <0.001$). In the subgroup of patients who underwent first-line ablation, the analysis revealed a 48% reduction in the risk of recurrence (RR, 0.52; 95% CI 0.30–0.91; $p = 0.02$).

In which patients is it reasonable to consider ablation as a first-line therapy?

Young patients

As it turned out from the randomized trials and from the meta-analysis, patients that mainly benefit from catheter ablation are relatively young and overall healthy. Younger patients tend to be more symptomatic and less willing to take long-term medications due to potential side effects and pro-arrhythmia. In addition, the German Ablation registry [39] reported a trend toward a reduced complication rate in the young patient undergoing AF ablation. Not surprisingly, the authors demonstrated that age ≤45 years was typically associated with a lower prevalence of relevant co-morbidity and a greater rate of early stages of AF (PAF) compared with the control group with >45 years resulting in lower $CHADS_2$ and CHA_2DS_2VASc scores. Leong-Sit et al. found similar findings that may support ablation as a first-line therapy in this age group [40]. The authors found no major complications among 309 ablations performed in patients younger than 45 years. Additionally, these patients had smaller atria and most of them were paroxysmal. There was also a greater freedom-from-AF without AAD therapy in this subpopulation. The natural history of AF is characterized by a gradual worsening over time [41, 42]. Initially AF is trigger driven, typically from the pulmonary veins. Over time, diverse mechanisms in isolation and combination result in an atrial myopathy with electrical,

structural, and contractile changes [43, 44]. The natural progression of PAF to persistent AF reaches up to 24.7% over 5 years and is related to age and co-morbidities. Based on the concept that AF begets AF [45], it might be justified for an early AF ablation in young patients in order to be more effective instead of waiting until AF has progressed to persistent [46].

Patients with sinus node dysfunction related to AF

Another subgroup of patients who may benefit from a first-line catheter ablation is the category of patients with sinus node dysfunction [47]. Prolonged sinus pauses on termination of AF are an accepted indication for permanent pacemaker implantation. However, these frequently occur in patients on AADs or rate-controlling drugs. Hocini et al. demonstrated that after catheter ablation of AF, there is progressive improvement of sinus node function, suggesting that tachycardia-mediated remodeling of the sinus node occurring in these patients is responsible for sinus node pauses. In these patients, an early AF ablation might avoid the need for a permanent pacemaker.

Patients with tachycardiomyopathy

A small subset of patients with AF experience dilated cardiomyopathy also called tachycardiomyopathy. Various cellular mechanisms have been implicated as causes of tachycardiomyopathy, including the depletion of myocardial energy stores by chronic tachycardia, which causes oxidative stress and injury and leads to abnormal calcium handling and β-adrenergic responsiveness [48]. Typically, these patients have rapid ventricular rates and relatively persistent AF. Calvo et al. [49] demonstrated that patients with tachycardiomyopathy secondary to AF benefit from catheter ablation, with a significant improvement in the left ventricular systolic function as well as a reduction in the left ventricular end-diastolic diameter and left atrial diameter. The outcome of patients with tachycardiomyopathy after ablation did not differ from that of patients with no structural heart disease.

Avoid toxicity of AADs

Although AAD therapy is perceived as safer than catheter ablation, it still carries the possibility of debilitating side effects. In the CTAF Trial, 18% of the patients receiving amiodarone and 11% of the patients receiving sotalol or propafenone had to discontinue treatment because of side effects of medications [11]. In particular, amiodarone, which is the most effective AAD, is associated with the most dangerous side effects. After 5 years of therapy, ≥30% of the patients will discontinue the amiodarone because of side effects [50]. Finally, AADs may also increase mortality as shown by the CAST and SWORD trials [12, 13]. An increased risk of mortality was also reported in an analysis of the AFFIRM Trial (HR 1.49, $p = 0.0005$). On the other hand, pooling together two of the latest and largest trials, STAR AF II and ADVICE, catheter ablation-related adverse effects are about 3% and fatal complications were 0.3% [51, 52]. In particular, one death due to atrioesophageal fistula and one death related to a massive stroke happened 24 days after the ablation. Six patients had a transient ischemic attack/stroke, five patients experienced cardiac tamponade, and 15 patients had vascular adverse events (hematoma or arteriovenous fistula or pseudoaneurysm). Cappato et al. described the risk of fatal complications during AF ablation with an observed incidence of 0.98 deaths per 1000 patients after studying >45,000 procedures [53].

Ongoing trials

The data to date is supportive of first-line catheter ablation of AF but is far from definitive. Currently, there are a few clinical trials which are further evaluating the first-line strategy. The EAST Trial is examining whether early aggressive intervention of AF can prevent AF progression and result in improvements in mortality, hospitalization, and morbidity associated with AF over 8 years of follow-up [54]. The EARLY AF Trial will also evaluate the benefit of early ablative intervention of AF using the cryoballoon compared to that of medical therapy [55]. The primary endpoint will be recurrence of AF using an implantable loop monitor.

Conclusions

AF has a significant impact on morbidity and mortality. Catheter ablation is an effective, safe, and well-established treatment for patients with PAF. Although the current guidelines recommend catheter ablation after AAD failure, there is limited evidence to consider catheter ablation as a first-line therapy for PAF. Apart from patients' preference and avoidance of toxicity of AADs, younger patients, patients with sinus node dysfunction related to AF, and patients with tachycardiomyopathy are the subgroups that seem to be good candidates for catheter ablation as a first-line therapy for PAF.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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