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Arrhythmia (R Kabra, Section Editor)

Role of Catheter Ablation as a First-Line Treatment for Atrial Fibrillation

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Abstract

Purpose of review Catheter ablation has emerged as the most effective long-term rhythm controlling strategy in patients with symptomatic atrial fibrillation (AF). Over the last few years, the role of ablation has shifted from a last-resort strategy toward a first-line approach in AF management. The purpose of this review is to highlight the rationale behind an early ablation strategy and to summarize recent data regarding its effectiveness.

Recent findings Pulmonary vein isolation (PVI), the cornerstone of catheter ablation of AF, is superior to antiarrhythmic drugs (AADs) in preventing recurrence of AF. PVI is most effective when performed early in the disease process. Recent studies have shown significant long-term benefit in patients treated with PVI early after AF diagnosis and/or prior to use of AADs.

Summary PVI is emerging as a highly appropriate first-line therapy for patients with symptomatic AF. As ablation technologies continue to improve, offering PVI to patients with recently diagnosed atrial fibrillation may become standard of care.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia in the USA, with an estimated 2.7 to 6.1 million Americans suffering from this disease. These numbers will likely increase as life expectancy prolongs [1]. It has been estimated that the prevalence of AF in developed countries is as high as one in four middle-aged adults. Treatment of AF is aimed at reducing symptoms and preventing risk of cardioembolic events and arrhythmia-related cardiomyopathy.

For many years, pharmacological therapy remained the mainstay of AF management, either with the use of drugs that slow conduction through the atrioventricular (AV) node or with the use of antiarrhythmic drugs (AADs) for rhythm control. The pendulum has shifted toward a rhythm controlling strategy in symptomatic patients with paroxysmal and persistent AF [2]. Rhythm control is also preferred in patients with congestive heart failure and left ventricular systolic dysfunction thought to be secondary to atrial fibrillation in an attempt to halt irreversible cardiac electrical and structural remodeling [3].

Many patients managed with a rhythm controlling strategy are optimal candidates for percutaneous catheter ablation, an alternative to AAD therapy. The cornerstone of AF ablation is achieved by pulmonary vein isolation (PVI), whereby electrically active myocardial tissue surrounding the pulmonary veins in the left atrium is isolated through different techniques. These include point-by-point ablation using radiofrequency energy, circumferential balloon ablation using cryothermic or other ablative energy sources, or a recent promising method using pulsed field ablation by employing rapid high voltage pulse to myocardial tissue [4].

Catheter ablation is highly effective in reducing the burden of AF and preventing adverse long-term outcomes. PVI in particular is known to be superior to AADs in terms of composite endpoints such as death in select patient populations as well as symptom control [3, 5]. Even in studies that did not show a statistically significant difference between PVI and medical therapy, patients that underwent PVI experienced lower-than-expected event rates and treatment crossovers [6].

PVI has emerged as an important first-line therapeutic option for patients with AF for a number of reasons that we will summarize in this review: (1) Ablation is most effective when performed earlier in the course of the disease; (2) ablation is more effective than AADs in reducing long-term burden of AF; and (3) PVI technologies are progressing to the extent that the procedure is extremely safe and can be performed expeditiously.

Overall effectiveness of catheter ablation and predictors of recurrence

The effectiveness of catheter ablation has been defined both clinically and electrophysiologically. AF ablation results in improvement in symptoms from AF [7], betterment of quality of life in patients with AF [7], and possibly reduction in risk of death or cardiovascular hospitalization [3, 6, 7]. In the randomized catheter ablation vs antiarrhythmic drug therapy for atrial fibrillation (CABANA) trial, patients with paroxysmal and persistent AF treated with catheter ablation had a 51.7% risk of death or cardiovascular hospitalization, compared with a 58.1% risk of these outcomes in patients treated drug therapy (HR 0.83; $p = 0.001$).

Electrophysiologically, AF ablation is more likely to result in lower recurrence rates of AF as documented by ECG monitoring following ablation [8–10]. In the literature, success following ablation is commonly assessed by time to recurrence of AF [11–13]. Time to recurrence can strongly determine response to therapy and post-ablative outcome [14]. A newer and perhaps more clinically predictive electrophysiologic endpoint—AF burden—has been linked with improvement in symptoms and quality of life in patients with AF [15]. Multiple trials have shown superiority of catheter ablation to AADs in time to recurrence of AF in patients with paroxysmal and persistent AF [8–10, 16].

The chronicity and pattern of AF play a significant role in current management strategies. Current guidelines focus on symptomatic drug-refractory AF and identify success rates based on whether the AF are paroxysmal, persistent, or long-standing persistent (Table 1) [17]. Patients with paroxysmal AF have the lowest recurrences of AF after ablation [5]. Patients with paroxysmal AF who develop recurrence are commonly found to have pulmonary vein (PV) reconnection upon re-ablation, and PV re-isolation can improve outcomes in this population [18, 19].

Patients with persistent AF have higher risk of AF recurrence than patients with paroxysmal AF. PVI is less effective in patients with nonparoxysmal AF [20] as these patients tend to have non-PV AF triggers such as the left atrial myocardium [21, 22] or focal areas such as the superior vena cava [23], coronary sinus [24], or vein of Marshall [25, 26]. In patients with persistent AF, PVI alone may result in maintenance of sinus rhythm in approximately 50% of patients [5, 27]; often, these patients require additional ablation or substrate modification [28, 29]. Non-PV triggers become more prevalent in patients as AF progresses from paroxysmal to persistent to long-standing persistent [30, 31].

In addition to the AF pattern, multiple clinical factors predict response to ablation. These include hypertension, older age, and appropriate sleep apnea treatment [32], among other factors [33]. Left atrial dilatation and strain likely result in atriopathic changes that promote maintenance of AF [34]. Indeed, B-type natriuretic levels have been found to correlate with AF burden and strongly predict arrhythmia recurrence following ablation [35]. Furthermore, left atrial

Table 1. Current atrial fibrillation treatment guidelines [5, 38]

Clinical scenario	Recommendation	Level of evidence
Catheter ablation for paroxysmal atrial fibrillation* in symptomatic patients who have failed at least one class I or class III antiarrhythmic drug when a rhythm control strategy is needed	Class I	A
Catheter ablation for paroxysmal atrial fibrillation* in symptomatic patients for initial rhythm control	Class IIa	B
Catheter ablation for persistent atrial fibrillation$^{\Delta}$ in symptomatic patients who have failed at least one class I or class III antiarrhythmic drug when a rhythm control strategy is needed	Class IIa	A
Catheter ablation for persistent atrial fibrillation$^{\Delta}$ in symptomatic patients for initial rhythm control strategy	Class IIb	C
Catheter ablation for long-standing persistent atrial fibrillation♦ in symptomatic patients who have failed at least one class I or class III antiarrhythmic drug when rhythm control is needed	Class IIb	B
Catheter ablation for atrial fibrillation in symptomatic patients with reduced left ventricular ejection fraction to decrease hospitalization for heart failure and possibly lower mortality rates	Class IIb	B-R

*Paroxysmal atrial fibrillation: atrial fibrillation that terminates within 7 days of onset
$^{\Delta}$Persistent atrial fibrillation: atrial fibrillation that fails to terminate within 7 days of onset
♦Long-standing persistent atrial fibrillation: atrial fibrillation that lasts more than 12 months

volume on 3-dimensional echocardiography is an established risk factor for AF recurrence [36]. Recent studies have also shown pre-ablation prognostication success using cardiac MRI, and that pre-procedural LA functional assessment is superior to LA volume in predicting AF recurrence following ablation [37].

Atrial fibrillation progression and effectiveness of early intervention

AF is a temporal disease that progresses electrophysiologically with changes in atrial substrate [39–41]. It is well-known that AF begets AF [42] as a result of electrical and structural remodeling in the atrium over time [43]. One of the studies that best illustrated electrical remodeling was performed by using a fibrillation pacemaker to maintain AF in a goat which ultimately resulted in reduction of its atrial refractory period by decrease in depolarizing current through $I_{Ca,L}$. Initially, this rapid atrial pacing resulted in only short episodes of AF; however, after multiple days, AF lasted more than 4 h. After 2–3 weeks of pacing, 90% of goats had persistent AF [42]. This high AF burden ultimately leads to structural remodeling [44], which has been described histologically in explanted hearts that had increased interstitial collagen in patients with persistent as compared with paroxysmal AF [45].

Moreover, atrial fibrosis plays a key role in sustaining the reentry that drives AF maintenance and has also been linked to AF recurrence and therapy failure [46]. Progression of paroxysmal AF to persistent and long-standing persistent AF is attributed to the changes in substrate [47]. Comorbidities such as heart failure, hypertension, and advanced age promote structural and electrical remodeling that can perpetuate AF [48–51]. Paroxysmal AF has been described as a window of opportunity to modify disease progression [52].

Given the "vicious cycle" of AF progression, the clinical paradigm is shifting toward early intervention in patients with AF. Currently, the guidelines recommend ablation as a class I indication in patients with drug-refractory paroxysmal AF and as a class IIA indication for paroxysmal AF without prior AAD use [5]. However, the clinical standard is evolving away from a drugs-first strategy. In a meta-analysis of 4950 patients who underwent ablation for symptomatic AF, diagnosis-to-ablation times (DTAT) of 1 year or less were associated with lower rates of AF recurrence as compared with diagnosis-to-ablation times of greater than 1 year (relative risk, 0.73 [95% CI, 0.65–0.82]; $P < 0.001$) [53]. Additionally, previous studies have shown that more remodeling correlates with lower ablation success rates, likely due to resistant substrate [54, 55]. These findings provide insight regarding potential benefits of earlier ablation in AF management which can slow the atrial remodeling process and disrupt the vicious cycle of AF progression [53].

Catheter ablation compared with anti-arrhythmic drugs

A rhythm controlling strategy with AAD therapy results in high rates of AF recurrence. Early analyses from the AFFIRM experience have found that roughly 50% of patients treated with AADs remain in sinus rhythm at 1 year [56, 2].

In contrast, PVI ablation results higher chances of maintaining sinus rhythm during clinical follow-up. The STOP AF investigators studied symptomatic patients with drug-refractory AF (78% paroxysmal, 22% early persistent) and randomized them to treatment with another AAD or PVI using the cryoballoon. At 12 months, treatment success was 69.9% in patients treated with PVI as compared with 7.3% in patients treated with AAD. Importantly, 79% of the patients in the AAD arm during those 12 months crossed over to the PVI arm due to recurrent symptomatic AF [57]. In a recent meta-analysis of patients with AF and heart failure, Khan et al. found that catheter ablation was more likely than AAD therapy to reduce the risk of all-cause mortality [58].

In the largest study to date comparing ablation to AAD therapy for patients with symptomatic AF, the CABANA investigators randomized 2204 patients with symptomatic AF (42.9% paroxysmal, 57.1% persistent) to PVI ablation, with additional ablative procedures at the discretion of the site investigators, versus standard rhythm and/or rate control drug therapy guided by contemporaneous guidelines [6]. Notably, of the patients assigned to drug therapy, 27.5% ultimately received PVI ablation. Although the primary endpoint of this study (mortality, cerebrovascular accident, or serious bleeding) occurred with similar frequency in patients in both groups, the secondary end point of postblanking AF (time to first recurrence) was reduced by 48% with catheter ablation compared with drug therapy. Furthermore, the composite secondary end point of death from any cause of cardiovascular hospitalization occurred in 51.7% of patients in the PVI group, as compared with 58.1% of patients in the drug therapy group (HR 0.83, log-rank $P = 0.001$) [6]. A notable limitation of STOP AF and CABANA is the high level of crossover from the AAD to the ablation group and vice versa.

CABANA results complemented previous, smaller studies comparing ablation to drug therapy for patients with symptomatic AF. A recent meta-analysis of 3500 patients with AF concluded that catheter ablation was associated with a statistically significant reduction in AF recurrence as compared with AADs (RR, 0.42; 95% CI, 0.33–0.53; $P < 0.00001$). With respect to all-cause mortality, there was a statistically significant reduction for patients with both AF and heart failure with reduced ejection fraction who underwent ablation as compared with similar patients treated with AADs (RR, 0.52; CI, 0.35–0.76; $P = 0.0009$). Patients treated with ablation compared with patients treated with AADs had statistically lower rates of cardiovascular hospitalizations as well [7].

Safety data of catheter ablation

Despite overwhelming evidence supporting the efficacy of catheter ablation, only approximately 4 to 10% of patients with drug-refractory paroxysmal AF actually undergo ablative therapy [5, 59–65]. In patients with heart failure with reduced ejection fraction in whom the long-term benefit of ablation may extend beyond symptom relief, less than 10% of patients received ablation [66]. The reason for this is, in part, due to the fact that AF ablation has historically been perceived as an arduous and technically difficult procedure [67] performed only in tertiary care academic medical centers [68] and offered to only those patients with limited other management options [69]. Nowadays, this perception cannot be further from the truth.

In addition to efficacy data, numerous large studies have demonstrated that ablation is a safe procedure, especially over the last 5–10 years [6]. Over the last decade, operator experience has significantly increased, and electrophysiologic technology has advanced [5, 60]. In a meta-analysis including 83,236 patients with symptomatic AF who underwent ablation over a 12-year period, the overall complication rate was low at 2.9% and significantly decreased during the last 6 years of the study (2007–2012) in contrast to the preceding 6 years (2000–2006; 2.6% versus 4% rate of complications, respectively; $P = 0.003$) [70].

Furthermore, in a recent single-center study which analyzed 2750 consecutive RF ablations for AF, the overall rate of major complications was 0.84%. Rates of cardiac tamponade (0.18%), phrenic nerve palsy (0.04%), and major vascular complications (0.18%) were also low in this population [71]. In another study including 10,378 ablations over 16 years, less than 1% of patients had major complications, and no patients died during the procedure. Highlighting the importance of institutional experience, the risk of pericardial effusion requiring pericardiocentesis decreased to 0.1% in the last 2 years of the study period [72]. Other institutions have similarly reported zero deaths with AF ablation [6, 3, 73].

It is important to note that procedural safety is closely linked with operator and hospital experience. Low volume ablation centers (less than 21 PVI ablations per year) statistically have greater odds of developing procedural complications (adjusted odds ratio [OR], 2.06; $P < .001$) [74]. In a major analysis of 93,801 ablations performed over the course of a 10-year period, Deshmukh et al. reported a 6.29% rate of complications, 81% of which occurred in patients whose ablations were performed by operators with less than 25 ablations per year and in hospitals with less than 50 ablations per year. This study ultimately demonstrated a statistically significant association between adverse outcomes and operator and hospital volume ($P < 0.001$) [68].

Overall, catheter ablation is a safe procedure and, when performed by experienced operators and in hospitals with high ablation volumes, results in very low complication rates and minimal mortality [6, 72, 3, 73].

Catheter ablation as first-line therapy

As discussed above, a rhythm controlling strategy is most effective early on in the AF disease process, and catheter ablation is more effective than drug therapy in rhythm control. As such, it would make sense that ablation be considered an important first-line strategy for patients with symptomatic AF, soon after the diagnosis of AF is established. Indeed, a resurgence of data regarding use of ablation in drug-naïve patients has appeared as PVI technology has advanced over the last few years [75].

In the early days of PVI, Wazni et al. randomized 70 patients with symptomatic AF who had never been treated with an AAD to PVI using radiofrequency ablation or drug therapy. In this study, after 1 year of follow-up, 13% of patients who underwent PVI had recurrent symptomatic AF, compared with 63% of patients who received AAD group [76]. The AAD group also had a significantly higher rate of hospitalization compared with PVI group (54% vs 9%, respectively). Afterwards, the RAAFT-2 trial randomized 127 treatment-naïve patients with paroxysmal AF to either RF ablation or AADs. These investigators demonstrated superiority of RF ablation to AAD therapy in both symptomatic recurrence (47% for ablation group vs 59% for AAD group) and atrial tachyarrhythmia recurrence (54.5% for ablation group vs 72.1% for AAD group) at 2-year follow-up [77]. Findings by Cosedis-Nielsen et al. also support the role for PVI in patients with symptomatic AF not previously treated with AADs [78]. A meta-analysis summarized these studies and found that radiofrequency catheter ablation was associated with significantly higher freedom from AF recurrence compared with AAD therapy in patients with symptomatic AF treated with PVI as a first-line strategy [79]. Notably, these patients were relatively young with CHADS2 scores on the lower side.

As PVI technologies have advanced over the last 5 years, catheter ablation has become even more effective due to a number of factors including lesion durability and expeditious ablative technology [80, 81]. The EFFICAS II investigators used a radiofrequency ablation catheter with an integrated force sensor that provided contact force feedback, an important recent development of RF technology. Conduction gaps in the PVs were assessed at least 3 months after the index PVI, and patients treated with contact force technology were more likely to have chronically isolated PVs [80]. Indeed, a recent meta-analysis comparing ablation with and without contact force showed that the use of contact force resulted in greater success and less fluoroscopy times [82].

The advent of balloon-based PVI approaches, most notably the cryoballoon (CB), has been paradigm-shifting in the introduction of technology specifically tailored to the 3-dimensional PVs [83, 84]. CB and RF ablation are similar with regard to risk of AF recurrence [85–90]. FIRE AND ICE demonstrated CB ablation to be non-inferior to RF ablation in 762 patients with drug-refractory paroxysmal AF (1-year Kaplan–Meier event-rate estimates, 34.6% and 35.9%, respectively; hazard ratio, 0.96; 95% confidence interval [CI], 0.76 to 1.22; $P < 0.001$) [73]. Patients treated with PVI with the CB had a statistically significant lower rate of repeat ablation [HR = 0.65 (95% CI: 0.45–0.95); $P = 0.03$], all-cause rehospitalizations [HR = 0.72 (95% CI: 0.57–0.91); $P = 0.01$), and post-ablative cardioversion [HR = 0.49 (95% CI: 0.25–0.98); $P = 0.04$] as compared with RF ablation [91]. In terms of safety, maintenance of tissue architecture in CB-treated PVs may provide an even more forgiving window of reversibility that results in a lower risk of complications [92].

The predictability and favorable safety profile of CB PVI have bolstered the case for catheter ablation as first-line therapy for patients with symptomatic AF [75]. In the recent FREEZE cohort study, Straube et al. identified 373 patients with AAD-naïve paroxysmal AF treated with RF (180 patients) or CB (193 patients) and found that both approaches were safe and effective. The authors did identify a non-statistically significant trend for more AF recurrences and complications in the RF group. Notably, during follow-up at 12 months, there were fewer cardioversions (1.2 vs 11% $P < 0.01$) and rehospitalizations (28.2 vs 50%, $P < 0.01$) in patients who underwent CB ablation as compared with patients who underwent RF ablation. Overall procedure times and left atrial catheter dwell times were also shorter in the CB cohort [75]. Importantly, in the FIRE AND ICE study, phrenic nerve injury at discharge was reported more often in CB than in the RFC treatment cohort (2.7% vs 0%; $P = 0.001$), and there was a trend for more groin site complications in the RFC cohort rather than in the CB cohort (4.3% versus 1.9%; $P = 0.09$). Additionally, mean total procedure and left atrial dwell time were significantly shorter for the CB cohort, whereas mean fluoroscopy time was significantly shorter in the RFC cohort [91].

Encouraging data are emerging with regard to patients with persistent AF, as well. The recently published PRECEPT study prospectively investigated the outcomes of contact-force sensing RFA catheters in symptomatic patients with persistent AF; in 348 patients who underwent PVI, freedom from AF at 15 months was 61.7% with a primary adverse event rate of 3.8% [93]. Some patients also underwent additive ablation of the posterior left atrium and other non-PV triggers. The STOP persistent AF trial assessed the safety and efficacy of PVI in patients with drug-refractory persistent AF using the CB and identified a 54.8% rate of atrial tachyarrhythmia freedom at 12 months, with a primary adverse event rate of 0.6% (95% CI; 0.1%–4.4%) [94]. The higher rate of AF freedom in the PRECEPT trial could be attributed to additional non-PV trigger ablations performed; however, baseline patient characteristic of AF duration was limited to 1 year in PRECEPT as compared with 6 months in the STOP persistent AF trial.

The recently described randomized Cryo-FIRST trial was designed to compare AAD treatment against CB PVI as first-line therapy in treatment-naïve patients with AF; this study is currently underway [95].

Diagnosis to ablation time

In efforts to further understand the clinical benefit of early ablative therapy in patients with symptomatic AF, recent investigators have proposed the diagnosis-to-ablation time as a predictor for AF recurrence. Bunch et al. showed that as DTAT increased, there was a direct increase in 1-year AF recurrence. These authors also showed that increase in DTAT resulted in higher rates of heart failure hospitalization and mortality at 1 year [96]. Moreover, Kawaji et al. also demonstrated greater arrhythmia freedom and reduced incidence of both cardiovascular hospitalizations and repeat ablations in patients with shorter DTAT as compared with longer, especially among those with congestive heart failure [97].

In a meta-analysis of 6 studies encompassing 3548 patients with both paroxysmal and persistent AF who underwent PVI ablation, Pranata et al. found that DTAT had a hazard ratio of 1.19 for AF recurrence. Importantly, DTAT times of > 1 year were associated with HR 1.60, and DTAT times of > 3 years were associated with HR 1.73. Upon subgroup analysis of data that compared > 6 years to < 1 year, the HR was 1.93. The authors termed DTAT as a "modifiable" risk factor for recurrence [98].

In summary, diagnosis-to-ablation time reflects the importance of early intervention in patients with AF and has also become an evolving method for predicting AF recurrence after PVI. Further studies are required to determine the extent to which DTAT predicts long-term clinical outcomes after ablation.

Areas of investigation

As described previously, PVI is both a safe and effective tool as a first-line therapy for appropriately selected patients. Although traditional AF classification phenotypes (paroxysmal, persistent, long-standing persistent) are still considered when determining appropriate candidates for ablation [5], advancements in cardiac rhythm monitoring have challenged the clinical significance of this classification scheme [99]. Charitos et al. demonstrated a discordance between clinically classified AF and measured AF burden as recorded by patients' implantable continuous monitoring devices. In this study, only 46.7% of clinically paroxysmal and 32.7% of clinically persistent AF patients met their objectively measured AF classifications [100]. Modifying the AF substrate with an early ablation strategy should be considered even in select patients traditionally classified as having persistent AF.

An early ablation strategy may benefit specific subpopulations—such as patients with diabetes mellitus (DM) who develop electromechanical atrial remodeling and relatively higher rates of AF as compared with the general population [101–104]. Previous studies have evaluated AF recurrence rates following ablation in this population; some studies [105–110] but not all [111, 112] found higher recurrence rates in diabetic patients. In the diabetic population, patients treated with ablation had lower rates of AF recurrence and hospitalization as compared with patients treated with AADs [113]. Indeed, an early ablation strategy may be particularly beneficial in patients with diabetes, who have accelerated rates of AF progression. Further studies are required to determine if this is the case.

PVI as a first-line strategy is even more tempting with up-to-date ablation technologies. Over the last few years, pulsed field ablation (PFA) has emerged a safe and highly effective PVI tool. By increasing cell membrane permeability via electroporation, PFA delivers highly targeted and rapid cell death via nonthermal energy [114, 115]. The IMPULSE investigators recently achieved complete pulmonary vein isolation in all 81 patients in the study, who had an 87.4% AF freedom rate at 1-year follow-up. Time for energy delivery was no longer than 3 min per patient, total procedure times were just over 90 min, and complications rates were extremely low [116]. Overall, PFA is promising and capable of advancing PVI with its high tissue specificity, shorter procedure times, and even higher efficacy by achieving PVI.

Conclusion

PVI ablation has become an important first-line therapy for patients with AF. Ablation is extremely safe and highly effective, especially when performed early on in the disease process.

Compliance with Ethical Standards

Conflict of Interest

Ibrahim El Masri, Sharif M Kayali, Theodore Manolukas, and Yehoshua C. Levine 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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