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Atrial Fibrillation Ablation: First-Line Therapy?

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Abstract

Background: Ablation for atrial fibrillation (AF) is a widely-accepted treatment for this arrhythmia. Ablation is traditionally reserved for second-line therapy in patients who have failed drug therapy, but it may be ready for first-line treatment.
Objective: This article outlines the rationale for using ablation as first-line therapy for AF.
Findings: AF increases both morbidity and mortality. Unfortunately, drug-based therapy for AF is very ineffective and may contribute adversely to both patient morbidity and mortality. Ablation addresses the root causes of AF and thus may be curative. The technique for ablation has become quite consistent and the outcomes better than those with drug therapy. The complication risk is also acceptably low. There is even preliminary evidence to suggest that AF ablation is superior as first-line treatment compared to drugs.
Conclusion: AF ablation is rapidly evolving towards becoming first-line therapy for some patients with this debilitating arrhythmia.

Key words: Atrial fibrillation, Pulmonary veins, Catheter ablation, Review.

Introduction

Atrial fibrillation (AF) is an increasingly common disease, affecting both patient morbidity and mortality. Drug and device-based treatments for AF are palliative, but not curative. AF ablation has emerged as a promising new treatment strategy offering the possibility of a cure. However, by guidelines, ablation is only considered "second-line" therapy for highly symptomatic patients who fail antiarrhythmic medications. As AF ablation achieves more consistency with higher success rates and fewer complications, the procedure may be getting closer to "prime-time" and may eventually be considered as first-line therapy for selected patients in experienced centers. [1]

Importance of Maintaining Sinus Rhythm

Clinical trials such as AFFIRM (AF Follow-up Investigation of Rhythm Management), [2] RACE (Rate Control versus Electrical Cardioversion for AF), [3] and STAF (Strategies for Treatment of AF) ,[4] have compared a strategy of rate control versus rhythm control using antiarrhythmic drugs. All of these trials reached the same conclusion: there is no mortality difference between the two approaches and that rate control may suffice for most patients with AF. Although these conclusions suggest that sinus rhythm may confer no benefit to AF patients, this is not the case. These trials were not comparisons of sinus rhythm versus AF, but a comparison of a rate control strategy

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to a rhythm control strategy that tried to maintain sinus rhythm. However, the success rates of the rhythm control arms were only 20-40%. Additionally, 10-35% of patients in the rate control arms were spontaneously in sinus rhythm. Thus, it is not fair to look at these studies as true evaluations of the benefit of sinus rhythm.

When the data from these trials is analyzed according to the patient's actual rhythm (as opposed to their treatment strategy), the benefit of sinus rhythm over AF becomes clear. An "ontreatment" analysis from the AFFIRM investigators [5] demonstrates that the presence of sinus rhythm was one of the most powerful, independent predictors of survival even after adjustment for all other risk factors. The survival benefit was offset in the trial by the increased mortality conferred by antiarrhythmic drugs. Reduced mortality attributable to sinus rhythm has been shown in other studies .[6,7] These findings are also consistent with large population-based studies that have long shown the negative independent prognostic impact of AF on survival. [8,9]

Finally, AFFIRM and the other trials largely excluded patients who were very symptomatic with their AF. This is an important group that clearly benefits from sinus rhythm and represents more than one-third of all AF patients. [10]

Drug and Device-Based Rhythm Control Works Poorly

Unfortunately, drug and device-based treatments for AF are poor in maintaining sinus rhythm. In the device realm, burst atrial pacing often fails to terminate or minimize AF.[11] Atrial defibrillators acutely terminate AF, but the need for repeated shocks is hard for patients to tolerate. [12] Multisite atrial pacing has also failed to demo strate any consistent reduction in AF burden. [13]

Antiarrhythmic medications (AAM) are the most widely used treatments for rhythm control but their efficacy is borderline. Amiodarone is the most effective AAM, with a 65% 1-year efficacy rate in comparison to sotalol or propafenone in the CTAF study. [14] However, the actual success of amiodarone is likely lower than this reported result. First, CTAF did not include a placebo arm, so we do not know how many patients would have maintained sinus rhythm spontaneously. In a recent meta-analysis of randomized trials on AAM, the incremental treatment effects over placebo were only 21.5%, 33.1%, and 17.4% for class IA, IC and III agents respectively. [15] An AFFIRM trial substudy showed that the success rate of amiodarone was only 60%, compared with 23-38% for other AAMs and 35% for placebo .[5] Thus, AAM are at best a palliative measure to reduce AF. Although reduction of AF burden may be considered a treatment success for some patients, it may not be enough. Small AF burdens can still increase morbidity and mortality and the cutoff for defining a "low-risk" AF burden has not been defined. Furthermore, even brief recurrences may be too much in severely symptomatic patients.

AAM are also associated with debilitating side effects. Discontinuation rates for AAM range from 11-40% in most trials .[14] Amiodarone is the most effective AAM, but also has the most dangerous side effect profile. Within five years, more than 30% of patients on amiodarone will discontinue therapy because of intolerance.[16] Skin discoloration, pulmonary fibrosis, symptomatic thyroidm problems, and neurological/ophthalmic side effects will occur in 2-4% of patients each .[16]

Even worse, AAM treatment can increase patient mortality. This paradigm has been long known, given the results of the CAST and SWORD trials where class I agents and d-sotalol increased mortality when given post-myocardial infarction.[17,18] Both cardiac mortality and arrhythmic death significantly increased in patients on AAM in the Stroke Prevention in AF study .[19] Analysisof the AFFIRM trial reveals a similar disturbing trend. When adjusted for other variables, use of AAM was associated with an increased risk of mortality in spite of the presence of sinus rhythm (hazard ratio 1.49, p=0.0005).[5] Interestingly, noncardiac death increased in the AAM group, which revealed higher rates of both pulmonary and cancer- related mortality. While the direct relationship is not clear, the AFFIRM investigators point out that amiodarone, in particular, has been previously associated with higher non-cardiac mortality in both the EMIAT and AVID trials. [20,21]

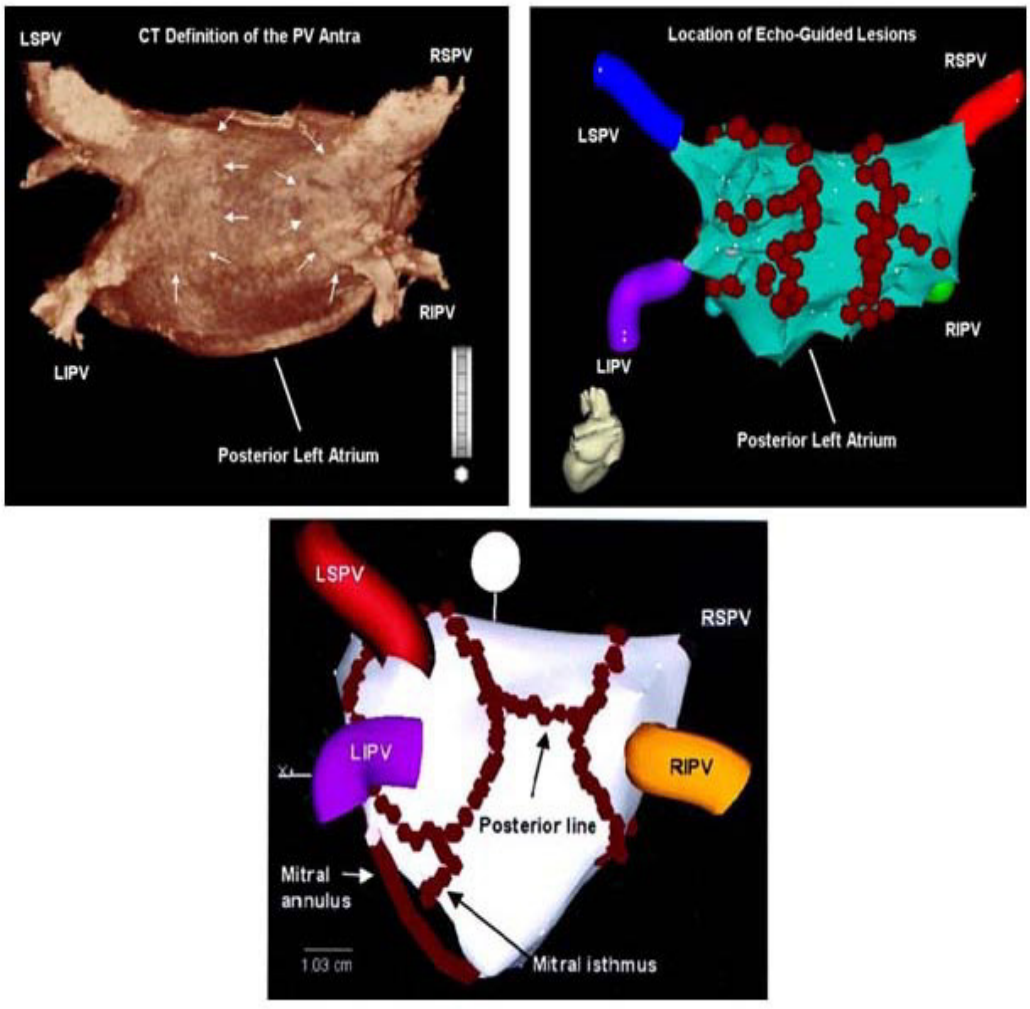
Newer drug therapies are currently in development, but as of yet, none are clinically available. It is also unclear that any of these agents, including

dronaderone, will have an efficacy that is equal to, let alone better than, amiodarone. Finally, these agents may have their own limitations, especially in patients with congestive heart failure or other structural heart disease.

AF Ablation Offers a Curative Option

In contrast to AAM, catheter ablation offers the possibility of curative therapy. Most agree that the endpoint of current AF ablation is to electrically "disconnect" the pulmonary veins (PVs) from the rest of the atrium by ablating around the origin of the veins. That is because the PVs play a major role in both triggering and maintaining AF.[22] Rapid discharges from the PVs initiate fibrillatory conduction [23] with non-PV triggers occurring in no more than 10% of patients .[24] AF is also sustained by pe-

Figure 1: Panels depicting the similarity in location of the radiofrequency lesions produced by various groups' approaches to atrial fibrillation ablation. The upper left panel shows an outer view of a patient's left atrium as seen from the posterior aspect using three-dimensional, multislice computed tomography. Seen clearly are the tubular portions of each of the four pulmonary veins (individually labeled). The borders between the antra of the pulmonary veins and the posterior wall of the left atrium are indicated by the small white arrows. The upper right panel shows a three-dimensional electroanatomical map (CARTO, Biosense Webster Inc.) of the left atrium (same patient as panel above) acquired during atrial fibrillation ablation guided by intracardiac echocardiography (ICE). Using ICE, the borders of the pulmonary venous antra can be accurately defined and lesions can be placed to completely surround and electrically isolate the antra. The red dots represent the anatomical locations of these lesions produced by ICE-guided ablation. The lower panel shows the location of lesions produced using a CARTO-guided approach described by Morady and colleagues. In both cases, the location of the lesion sets is similar, encompassing the anterior and posterior borders of all four pulmonary venous antra. LSPV=left superior pulmonary vein, LIPV=left inferior pulmonary vein, RSPV=right superior pulmonary vein, RIPV=right inferior pulmonary vein. (Reproduced from Verma et al, Circulation 2005, 112:1214-22 with permission from publisher Lippincott Williams & Wilkins).



riodic micro-reentrant circuits, or "rotors," which are localized primarily in the left atrial (LA)-pulmonary vein junction .[25,26] Autonomic inputs may also be very important in triggering and maintaining AF, and appear to be clustered around the PV-LA junctions. [27]

Having understood how AF ablation works, the technique has become much more consistent. Ini tially, there existed a multitude of methods for ablating AF. [24] Some targeted triggered activity in "culprit" PVs only, while others circumferentially ablated around one or more of the PVs. Others attempted to mimic the surgical Maze procedure by creating linear lesions. Today, most centers are empirically isolating all four PVs, since any one may become a triggering focus over time .[28] Furthermore, most groups now ablate outside of the tubular portion of the PV to avoid PV stenosis and improve efficacy. This makes sense given that the PV is funnel-shaped with a large proximal end, referred to as the "antrum," which blends into the posterior wall of the LA. Therefore, to encompass as much of the PV structure as possible, ablation needs to be performed around the entire antrum, along the posterior left atrium. [29] Although ablation in this region is referred to by different names, such as "circumferential PV antrum ablation," or "extraostial isolation," the lesion sets produced by the procedures are all very similar (Figure 1).

With growing experience, AF ablation has proven itself to have consistent success rates as reported by several groups. In the past, success rates ranged widely from 6-93%,[24] but these studies were published very early on in the ablation experience. Furthermore, the definition of "success" varied with some groups using off-drug cure as the definition of success while others included patients in sinus rhythm on AAMs. Recent publications of extraostial PV isolation show a consistent cure rate off drug therapy of 80.5% overall (Table 1). [30,35] A further 10-20% become responsive to previously ineffective AAM.[36] The cure rates are not 100%, but they are two to three times better than AAMs. Furthermore, the results seem durable, given that very late recurrences beyond one year are rare. [37] These results are now being confirmed in multicenter, prospective clinical trails, as opposed to solely single-center experiences. Success rates of ablation may even get better as adjuvant lesions are applied in conjunction with PV antral isolation, such as linear lesions, [38] ablation of fractionated electrograms, [39] or targeting regions based on spectral analysis.[40] And while initial studies included only paroxysmal ptients with

Table 1 Success Rates of Most Recent Studies Employing Ablation of All Pulmonary Veins Outside of Tubular Segment

Study [reference]	Year	Pts	Age (years)	Parox	Tool(s)	Endpoint	AF-Free (off drugs)	Follow-up (days)
Ouyang et al. [44]	2005	100	60±9	88%	CARTO	PV Isolat'n	71%*	240
Hocini et al. [42]	2005	90	55±9	100%	NAVX	PV Isolat'n	87%	450
Mansour et al. [43]	2004	40	55±10	80%	CARTO	PV Isolat'n	75%	330
Kanj et al. [41]	2007	180	59±9	86%	ICE	PV Isolat'n	80%	270
Oral et al. [40]	2006	77	55±9	0%	CARTO	EGM Red'n	74%	365
Pappone et al. [39]	2006	99	55±10	100%	CARTO	EGM Red'n	86%†	365
Total		586					79.3%	

PAbbreviations: AF=atrial fibrillation, CARTO=electroanatomical mapping system (Biosense Webster), EGM Red'n= reduction of local
EGM amplitude (usually >70%), ICE=intracardiac echocardiography, PV Isolat'n = pulmonary vein isolation, NA=not available, NAVX = electroanatomical mapping system (St Jude Medical)
* Success was 95% off drugs after a second procedure
† Success was 93% off drugs after a second procedure

minimal structural heart disease, good results can now be obtained in persistent AF ,[41] patients with heart failure,[42] hypertrophic cardiomyopathy, [43] moderate valvular heart disease, [44] and advanced age. [45]

The incidence of complications with AF ablation is also very low, and continues to fall as experience grows. Complications include vascular complications cardiac perforation/tamponade, valvular injury, embolic stroke or systemic embolism, esophageal injury, PV stenosis, and proarrhythmia due to reentrant tachycardias. When only recent reports using a more consistent technique are reviewed, the complication rates low (Table 2). The complication rates are continuing to fall with more recent modifications to the technique. Higher ACT levels of 300-400 sec can reduce thromboembolic risk .[46] Esophageal injury can be avoided with strict limitations on RF energy output .[47] Procedural-related atrial flutters can also be reduced to < 5% if care is taken to document total electrical isolation of the PVs at the level of the antra [48] and with the addition of linear ablation lesions, such as a line across the mitral valve isthmus. [49] Newer technologies to reduce complications and improve the ease of performing ablation are also imminent, including robotic/magnetic-controlled catheter systems and balloon-guided systems. [50-52]

With such a high success rate and a low attendant complication rate, current evidence suggests that AF ablation may not only be better than medical therapy, but may reduce both the morbidity and mortality associated with AAMs. For example, strokes are uncommon among most post-AF ablation patients, so coumadin may be stopped in all but the highest risk patients.[53] In a controlled, long-term study (median follow-up 900 days), 589 patients who underwent AF ablation had significantly improved survival compared to 582 matched patients who received AAM,[54] although this study was a retrospective, singlecenter, population-matched study and not prospective. In a randomized pilot study comparing first-line ablation to first-line drug therapy, AF recurrence rates were significantly lower in the ablation arm (13% vs 63%, $p<0.05$) (Figure 2). Others have also reported similar results in head-to-head comparison [30,55] and other trials are underway. Ablation is even more cost effective than medical therapy with the cost of ablation being offset by the higher cure rate within 2-4 years.[56]

First-Line Ablation May be Reasonable for Some

Based on all of the preceding arguments, AF ablation may be reasonable as first-line treatment for some AF patients. Large-scale, comparative clinical trials are still ongoing and this data will be required before recommending ablation as first-line for a very broad AF population. Patients with highly symptomatic paroxysmal or persistent AF and minimal structural heart disease experience considerable morbidity and mortality from AF. For these patients, AAM is not always effective and may be poorly tolerated. Therefore, if first-

Table 2 Complication Rates Compiled From 586 Patients In The Studies From

Complication	Number	%	Range in Studies
Transient Ischemic Attack	4	0.7%	0-5%
Permanent Stroke	1	0.2%	0-1%
Severe PV Stenosis (>70%, symptomatic)	1	0.2%	0-1%
Moderate PV Stenosis (40-70%, asymptomatic)	0	0.0%	0%
Tamponade/Perforation	6	1.0%	0-5%
Severe Vascular Access Complication	2	0.3%	0-5%
Phrenic Nerve Palsy	1	0.2%	0-1%
Atrioesophageal Fistula	0	0.0%	0%

Abbreviation: PV=pulmonary vein

line ablation is offered, it should at least be considered for those patients with symptomatic AF, mild-moderate structural heart disease, and paroxysmal or persistent AF. Ablation may particularly benefit younger patients with "lone AF," for whom very long-term antiarrhythmic and potential anticoagulation may pose potential risk and cost.

There are obviously some patients in whom AF ablation may not every be a good option. Patients with extensive comorbidity or totally asympto atic patients may not derive benefit. Patients with extensive atrial scarring or severe left atrial enlargement (>55 mm) also do not respond to ablation.[57] Operator experience is also an important consideration when contemplating ablation. It is prudent that only centers with considerable experience in performing AF ablation should consider offering ablation as first-line therapy. Only these centers can offer the favorable risk-benefit ratios required to justify first-line ablation. As technology improves, however, robotic or magnetic controlled catheter navigation may help reduce the influence of operator experience.

Conclusions

AF is associated with both morbidity and mortality, so it is in the patient's best interest to pursue effective and safe treatment to maintain sinus rhythm. AAMs are ineffective, and increase mortality. In experienced hands, AF ablationis an effective and safe treatment that offers an excellent chance for a lasting cure. Thus, AF ablation should be considered as a first-line option for selected patients with this disease.

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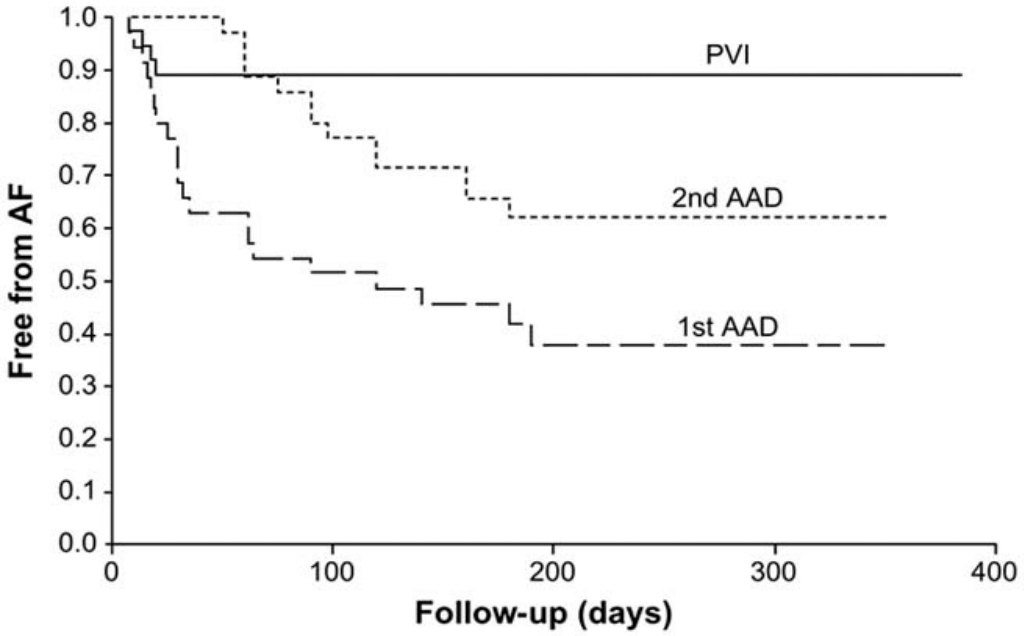
Figure 2: Kaplan-Meier curves depicting freedom from atrial fibrillation (AF) in patients undergoing AF ablation by pulmonary vein antrum isolation (PVI) compared to being treated with an antiarrhythmic drug (AAD) from the pilot study of the Radiofrequency Ablation for Atrial Fibrillation Trial (RAAFT). Seventy patients with symptomatic, mostly paroxysmal AF, were randomized to PVI (n=33) or AAD (n=37). Overall recurrence of symptomatic AF was 13% in the PVI group compared to 63% in the AAD group treated with their first drug ($p<0.05$, mean follow-up time 8.5±3.2 months). Even after patients were switched from a first AAD to a second AAD, recurrence still remained significantly higher compared to the PVI arm ($p<0.05$). (Reproduced from Verma et al, Circulation 2005, 112:1214-22 with permission from publisher Lippincott Williams & Wilkins).



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