

Catheter Ablation of Atrial Fibrillation to Maintain Sinus Rhythm

Jane Dewire and Hugh Calkins, MD

Department of Medicine, Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

Abstract

Catheter ablation of atrial fibrillation (AF) is an important treatment modality for patients with AF. Although the superiority of catheter ablation of AF over antiarrhythmic drug therapy has been demonstrated in middle aged patients with paroxysmal AF, the role of catheter ablation in other patient subgroups, particularly in the elderly, those with heart failure, and those with long standing persistent AF has not been as well defined. Furthermore, although AF ablation can be performed with reasonable efficacy and safety in experienced hands, late recurrences of AF a year or more following AF ablation are not uncommon. Fortunately the techniques and tools used for AF ablation continue to evolve and it is likely that the outcomes of AF ablation will improve further in the future.

Introduction

Over the past 15 years catheter ablation of atrial fibrillation (AF) has evolved from a novel rarely performed procedure to its role today as a commonly performed and widely accepted procedure throughout the world. The purpose of this article is to provide a state-of-art review of the techniques, outcomes, complications, and technologies in the field of catheter ablation of AF. Two major topic areas will be discussed. First, we will review the current techniques, outcomes, and risks of catheter ablation for paroxysmal, persistent, and long-standing persistent AF patients. Second, we will provide a critical review of new and emerging ablation strategies and techniques.

Techniques, Outcomes, and Risks of Ablation of Paroxysmal AF

After much debate and discussion about the op-

timial technique to perform AF ablation, most centers throughout the world use wide area circumferential pulmonary vein isolation (PVI) as the foundation of the procedure.^{1, 2} In 2007, the Heart Rhythm Society (HRS) released a consensus document recognizing the electrical isolation of the pulmonary veins (PV) as the cornerstone of AF ablation.¹ A revised consensus document published in 2012 also included this recommendation.² This AF ablation approach is highly effective in patients with paroxysmal AF (recurrent AF that terminates spontaneously within 7 days). The 2012 HRS consensus document presents a Class I recommendation for catheter ablation of paroxysmal AF that is refractory or intolerant to at least one class 1 or 3 antiarrhythmic medication.² This ablation technique involves delivering a series of point-by-point radiofrequency (RF) lesions which encircle the two left and two right PVs either by creating a single circumferential lesion around the two right PVs and another around the two left

Corresponding Address :Hugh Calkins, MD, FAHA, Sheikh Zayed Tower- Room 7125R, 1800 Orleans Street, Baltimore MD 21287, The Johns Hopkins Hospital.

PVs, or by including lesions between the ipsilateral PVs resulting in a figure eight lesion set. Irrigated RF ablation catheters, used in conjunction with an electroanatomic mapping system are the most commonly employed tools. Cryoablation has emerged as another commonly used approach to isolate the PVs. The endpoint of PVI, whether performed with RF energy or cryoablation, is complete electrical isolation of the PVs confirmed by use of a circular multipolar electrode catheter.^{2,3}

Success rates for catheter ablation of AF depend on a large number of variables.² Of particular importance are the type of AF (paroxysmal, persistent, or long standing persistent), the presence or absence of comorbid conditions such as obesity and sleep apnea, the definition of "success", and the duration of follow-up. The 2012 HRS Consensus Document on AF ablation recommends that success be defined as freedom from symptomatic or asymptomatic AF, atrial tachycardia, or atrial flutter lasting 30 seconds or longer 12 months following AF ablation.² It is recognized that this is a very strict definition of success that is best used for clinical trials. A three-month "blanking period" is recommended. This results from the fact that it is common for patients to develop AF shortly after an ablation procedure, in part because of transient pericardial inflammation. From a clinical perspective, a marked reduction of "atrial fibrillation burden" associated with a reduction of symptomatic AF is commonly considered a clinical success from a patient and physician perspective.

The results of catheter ablation of paroxysmal AF can be derived from a number of different sources. In our experience and based on our review of the literature we would estimate the single procedure efficacy of a PVI ablation in a patient with paroxysmal AF to be between 60% and 80%.⁴⁻⁸ A recent study reported the outcomes of two meta-analyses of the safety and efficacy of catheter ablation of AF and antiarrhythmic drug therapy.⁹ The results of 63 RF ablation studies were included in these analyses. The multiple procedure success rate off AAD was 71% (95% CI 65%–77%), and the multiple procedure success rate on antiarrhythmic or with unknown antiarrhythmic drug usage was 77% (95% CI 73%–81%). It is important to recognize that performing a second or third ablation procedure results in an increase in the cumulative success rate.

There recently have been a large number of studies which have published data concerning the long-term efficacy of AF ablation.¹⁰⁻¹⁶ The first of these studies was published five years ago and described the long term outcomes of a series of 264 patients who were AF free and off antiarrhythmic drug therapy at the 12 month point following an initial ablation procedure.¹⁰ During a mean follow-up of 28 +/- 12 months, AF recurred in 23 patients (8.7%). The actuarial recurrence rate of AF at five years was 25.5%. AF recurrence was more likely in patients with hypertension and hyperlipidemia with a recurrence rate of 75% if both of these risk factors were present. Similar findings have been reported in each of the subsequent trials.¹¹⁻¹⁶ Of particular note is a recent report from a highly experienced EP lab which reported that only 29% of patients who underwent AF ablation at their center were AF free at 5 years following a single ablation procedure.¹⁴ Importantly, in this trial AF ablation procedures were performed in 2001 and 2002 using a segmental approach to achieve PV isolation. A more recent series which employed a circumferential approach to achieve PV isolation reported better long term outcomes with 47% of patients AF free after 4.8 years of follow-up.¹⁵ It is now recognized that when a patient is brought back to the EP lab with recurrent AF, that recurrence of PV conduction in one or more veins is almost universally observed. This finding highlights the difficulty achieving permanent PV isolation with current ablation technologies and approaches being used for assessing PV isolation acutely.

In 2010, the FDA approved Medtronic's Arctic Front Cardiac CryoAblation system in the United States for clinical use for treatment of patients with paroxysmal AF. This balloon based ablation system isolates PVs by freezing the tissue that lies in contact with a balloon which is cooled to as low as -80°C.¹⁷⁻¹⁹ This ablation system has been approved for clinical use for many years in Europe and has recently been released for clinical use in the United States. The results of the clinical trial that supported FDA approval have been published in abstract form but has not been published as a manuscript.²⁰ This study randomized 245 patients to antiarrhythmic drug therapy or catheter ablation. Catheter ablation was successful in 70% of patients (including repeat ablation

procedures) as compared with a 7% success rate for antiarrhythmic drug therapy. A large number of trials have been performed to evaluate the safety and efficacy of the cryoballoon ablation system in Europe. One of the largest and most recent of these studies was published in 2008.¹⁷ This study reported the outcomes of 346 patients with drug refractory predominantly paroxysmal AF. During a median follow-up of 12 months, after one or more procedures sinus rhythm was maintained without the need for antiarrhythmic drug therapy in 74% of patients with paroxysmal AF and in 42% of patients with persistent AF. Although the results of these initial studies suggest promise for the cryoballoon ablation system, the ultimate clinical value of this system will be better defined once electrophysiologists in the United States have gained more experience with it. At the present time it appears to be best suited for patients with paroxysmal AF.

Although some operators have enthusiastically adopted this technology, many other operators prefer to use RF ablation.

Techniques, Outcomes, and Risks of Ablation of Persistent and Longstanding Persistent AF

The efficacy of PV isolation is suboptimal in patients with persistent and longstanding persistent AF (> 12 months of continuous AF) due to the mechanisms underlying the more sustained arrhythmia.² The 2012 consensus document suggests catheter ablation is reasonable for persistent AF and may be considered for longstanding persistent AF, when AF remains symptomatic and refractory to at least one Class 1 or 3 antiarrhythmic medication. The optimal approach to catheter ablation in patients with persistent and longstanding persistent AF remains an area of debate. Whereas many electrophysiologists (EPs) prefer to perform circumferential AF isolation as the initial procedure in all AF patients, there are other EPs who feel strongly about creating linear ablation lesions and also targeted ablation of areas of the atrium demonstrating a high degree of complex fractionated atrial electrograms (CFAE) during AF. A final group of EPs advocate for a step-wise approach to AF ablation whereby the procedure is continued until AF terminates.²¹ Critics of the more extensive ablation procedures argue that these

approaches are in essence “atrial debulking.” Proponents of this approach argue that this results in substrate modification that is critical for the success of the procedure. Whereas the primary goal of the vast majority of electrophysiologists performing AF ablation, in a patient with paroxysmal AF, will be to achieve PV isolation using a circumferential approach, the approaches used for ablation of patients with non-paroxysmal AF is far more varied.^{1,2,21–25}

The quality and quantity of data concerning the outcomes of AF ablation in patients with persistent and long standing persistent AF is considerably less than for patients with paroxysmal AF described above. It is now increasingly well recognized that the duration of continuous AF is an important predictor of the efficacy of AF ablation. The single procedure success rate in a less optimal patient, such as a patient with persistent AF lies between 50% and 70%. The single procedure efficacy of the procedure in a suboptimal patient such as a patient with continuous AF for four years is 40% or less. Several studies that have reported the outcomes of catheter ablation of persistent and long standing persistent AF concluded that the single procedure success rates of the different strategies is similar, provided that circumferential PV ablation is performed with an endpoint of electrical isolation of the PVs.^{22,26–28} It is clear that this is an area where more research is needed to better define the optimal ablation approach and also the anticipated success rate in particular patient populations.

In the last year, two studies have examined the effect of restoring sinus rhythm prior to catheter ablation on procedure time and clinical success in patients with persistent and longstanding persistent AF.^{29,30} In the first study, Rivard and colleagues performed catheter ablation on 40 patients (and 40 controls) in whom sinus rhythm was restored (SR-restoration) by electrical cardioversion (CV) and maintained at least one month prior to ablation. During follow-up (21.1 +/- 9.7 months), no significant differences were found between the clinical success of SR-restoration group (55%) compared to the control group (45%). However, procedure duration, fluoroscopy time, radiofrequency duration, and extent of ablation decreased in the SR-restoration group compared to the control group. Additionally, AF was terminated by ablation more

frequently in the SR-restoration group. In the second study, Kang et al found that successful CV performed prior to ablation procedure was a predictive method in determining the long-term outcome of catheter ablation in 94 patients with persistent and longstanding persistent AF. These results are consistent with reverse remodeling effects previously observed with antiarrhythmic drugs.^{31, 32}

Complications of AF Ablation

Catheter ablation of AF is a demanding and complex interventional electrophysiologic procedure, which is associated with an important risk of major complications. An International Survey of AF ablation procedures in 2005 reported a 6% incidence of major complication.³³ The incidence of cardiac tamponade was 1.2 %, stroke or TIA was 0.94%, PV stenosis was 1.3%, and death was 0.05%. A recent update of this survey reported a 4.5% complication rate.³⁴ The complication rate reported in the large recent meta-analysis of AF ablation was 4.9%.¹ Of particular note is a report from the International Survey of AF ablation of 162 centers which reported details on 32 deaths that occurred during and/or following AF ablation procedures in 32,569 patients (0.1%).³⁵ Causes of death included tamponade in 8 patients (25% of deaths), stroke in 5 (16%), atrial esophageal fistula in 5 (16%), and pneumonia in 2 (6%). There is more recent evidence suggesting that the complication rate of AF ablation is falling.³⁶⁻³⁸ A recent consecutive series of patients undergoing AF ablation reported a major complication rate of 0.8% with no instances of death, stroke/TIA, atrial esophageal fistula, or PV stenosis.³⁶ A review of our complication rate reveals that it has decreased from approximately 11% in 2002 to 1.6% in 2010.³⁸ Based on our review and knowledge of the literature as well as our clinical experience with AF ablation we would estimate that the current incidence of major complications lies between 1% and 5%. The incidence of cardiac tamponade is 0.5% to 2%, stroke/TIA is 0.3% to 1%, vascular injury is 0.5% - 2%, pulmonary vein stenosis <1%, and the risk for development of an atrial esophageal fistula and/or death is less than 0.1%.

Critical Review of New and Emerging Technologies and Tools

Evolving Techniques

Although isolation of the PVs remains the cor-

nerstone of AF ablation procedures, alternative strategies targeting other structures have been developed. In 2004, Nademanee and colleagues first described CFAE-guided ablation.²³ This technique involves detailed point by point atrial mapping using an electroanatomic mapping system. CFAE sites are identified by inspection and were defined in this paper as "1) atrial electrograms that have fractionated electrograms composed of two deflections or more, and/or perturbation of the baseline with continuous deflection of a prolonged activation complex over a 10-s recording period; 2) atrial electrograms with a very short cycle length averaged over a 10-s recording period".²³ Studies reported that areas with CFAEs potentially represent AF substrate sites, and these areas have become target sites for AF ablation.^{2,24,30,39} However, the underlying mechanism of CFAEs remains controversial. Recent studies have shown that fractionated electrograms recorded during SR are normal findings in the left atrium due to wave-front collisions.⁴⁰⁻⁴⁴ A clinical trial is currently underway that may facilitate the identification of CFAE sites critical to perpetuating AF using Ibutilide.⁴⁵ The primary endpoints of the CFAE-guided ablation approach are either complete elimination of the areas with CFAEs, conversion of AF to sinus rhythm (either directly or first to atrial tachycardia), and/or non-inducibility of AF as suggested by the 2012 HRS guidelines.² In their first study, Nademanee and investigators targeted and eliminated CFAE areas in 57 patients with paroxysmal AF and 64 patients with longstanding persistent AF.²³ At a 1 year follow-up, 91% of all patients were free from symptomatic AF. However, these impressive results have not been replicated by any other group. There is evidence that targeting CFAEs as an adjunctive technique to PV isolation may be of added benefit, especially in patients with persistent and longstanding persistent AF.^{2,28,39} Conversely, several studies have concluded that the single procedure success rate is similar for the CFAE-guided ablation and PV isolation.^{22, 26, 27}

The relationship between AF and the autonomic nervous system, first reported by Pappone et al, is another area of intense research.⁴⁶⁻⁵⁴ Investigators have developed data which suggest that the ganglionated plexi (GP) that are located on the heart play an important role in the pathogenesis of AF. In their landmark study, Pappone and colleagues suggested that adjunctive complete vagal

denervation during PVI procedures significantly reduced AF recurrences at twelve months.⁴⁶ Lemery et al found that ganglionated plexi (GP) predominately overlay, or were adjacent to, the PVs in fourteen patients with AF.⁴⁷ Subsequently, several small studies compared the efficacy of conventional PVI ablation alone, anatomic GP ablation alone, a combination of PVI and GP ablation, and ablation of sites where vagal reflexes could be induced by high frequency stimulation (selective GP ablation).⁴⁸⁻⁵³ PVI ablation alone resulted in a lower recurrence rate of AF compared to anatomically guided GP ablation or selective GP ablation.^{49, 50} The results of these studies are very different from other studies that found that anatomic GP ablation followed by PVI yielded significantly better clinical outcomes to PVI ablation alone.^{51,52} More recently, Calo et al assessed the efficacy of GP ablation in the right atrium in patients with vagal AF.⁵⁴ Previous investigators have observed the large number of ganglia in the right atrium extends into and can modulate distant GP in the left atrium.^{47,55-58} Ablation of these GP increased the effective refractory period, decreased the window of vulnerability, and eliminated AF induced by high frequency stimulation.^{58, 59} Based on these studies, Calo et al targeted anatomical GP and areas of vagal reflex evoked by high frequency stimulation for ablation in thirty-four patients with vagal AF. At one year, 88+/-9% of patients who underwent anatomically guided GP ablation in the right atrium were AF-free compared to 35+/-12% of patients who underwent selective GP ablation in the right atrium.⁵⁴ To add to the studies on ablating GPs in the right and left atrium, Pokushalov and colleagues assessed the impact of PVI with renal artery denervation in thirteen patients with drug-refractory AF and drug-resistant hypertension.⁶⁰ This novel method reduced the systolic and diastolic blood pressure by 25mmHg and 10 mmHg, respectively, and resulted in 69% of patients free of AF at twelve months.⁶⁰ These studies taken together provide provocative data supporting ablation techniques targeting the ganglionated plexi. However, the field is still in need of a large, well designed, prospective, randomized study to better define the role of catheter ablation of autonomic ganglia in the treatment of AF. Until more consistent data is available, it is our opinion that the "autonomic hypothesis" does not directly impact the optimal approach to AF ablation.

Recently, research has explored the effect that electrical rotors and focal impulses have on the perpetuation of the AF cycle.^{2,61-65} Experimental models have shown that organized reentrant circuits (rotors) or focal impulses can become disorganized and develop into AF.⁶⁵⁻⁶⁸ Sahadevan et al initially presented the possibility, using atrial electrograms, that drivers in the left atrium cause fibrillatory conduction or clinical AF.⁶¹ Subsequently, Chou and his colleagues determined that rotor ablation in dogs suppressed AF inducibility.⁶² These two studies led Narayan et al to develop a clinical computational approach to mapping that physiologically interprets fibrillatory wave activity by analyzing widely sampled atria sites in the context of rate-dependent atrial repolarization and conduction.^{63,64} Spatiotemporal analyses of AF were performed by analyzing electrograms to construct movies and individualized isochronal maps of numerous AF activation cycles.⁶⁴ These digital electroanatomic atrial maps created with a novel software mapping system and a basket catheter identified localized sources of AF in the form of sustained electrical rotors and repetitive focal impulses in humans.⁶⁴ Narayan et al identified rotors as rotational activity around a center and focal impulses as a point of origin of AF from surrounding diastole.⁶⁴ Using computational maps, the CONFIRM (conventional ablation for atrial fibrillation with or without focal impulse and rotor modulation) trial demonstrated that ablation of patient-specific AF-sustaining sources terminated or consistently slowed persistent and paroxysmal AF in 82.4% of patients after two years.⁶³ Although these results are very provocative, this cannot be considered to be a proven strategy for AF ablation until adequately powered randomized clinical trials are performed which demonstrate the superiority of this approach to conventional ablation strategies.

New and Evolving Tools

In addition to improving ablation strategy, interest exists in developing new tools to improve the safety and efficacy of AF ablation. The majority of AF recurrences result from electrical gaps surrounding PVs following an initial successful PVI.^{3, 69} In the absence of cell death, stunned myocardial tissue can recover its conduction properties, which accounts for the discrepancy between the incidence of acute and chronic PVI.⁷⁰⁻⁷⁴ Con-

tact force between catheter tip and tissue is a key factor to effective lesion formation.⁷² Two contact force sensing catheters are currently available in Europe: the Thermocool SmartTOUCH Irrigated Catheter (Biosense Webster) and TactiCath Force-Sensing Irrigated Ablation Catheter (Endosense). The SmartTOUCH consists of a spring coil near the catheter tip that is surrounded by a magnetic signal emitter and three magnetic signal sensors.⁷⁵ Nakagawa et al presented findings using the SmartTOUCH catheter in canine models at the 2010 Boston atrial fibrillation symposium, and clinical trials are expected to start in the US within the year.⁷⁵ This ablation system has been evaluated as part of an FDA sponsored clinical trial which has completed enrollment. The results of this trial should be available in 2013. Endosense developed TactiCath (TactiCath® Set; Endosense SA, Geneva, Switzerland), an open-irrigated RF ablation catheter with a contact force sensor at the distal tip.^{73,74} This ablation system is also currently being evaluated as part of an FDA sponsored clinical trial (TOCCATA trial). This is a multicenter clinical trial which randomized ablation using the novel catheter combined with Ensite NavX (St. Jude Medical, Inc, Minneapolis, MN) to ablation using a standard approach.⁷³ The results of this clinical trial should be available in 2013.

The success of PVI has generated interest in the development of balloon catheters that can be inserted in each PV and deliver a number of ablations. One of the advantages of these balloon catheters is that 3D electroanatomic mapping systems are not required. Theoretically, balloon catheters should be easy to position and are able to create homogeneous ablation lesions with a single application of energy. The endoscopic ablation system (CardioFocus Inc, Marlborough, Mass) is balloon-based, uses laser energy for ablation and involves three diameter balloon catheters (20 mm, 25 mm, or 30 mm).^{76,77} A diode laser is used to generate a wave of energy at 980 nm to burn myocardial tissue for 60 seconds with a power density of 6.3, 6.9 or 7.6 W/cm.^{76,77} Four trials have been performed to evaluate the safety and efficacy of the endoscopic ablation system.⁷⁶⁻⁷⁹ One of the largest of these studies was by Dukkipati et al.⁷⁸ This study reports the durability of PV isolation in 56 patients with drug refractory paroxysmal AF using the endoscopic ablation system. In this trial, 94.6% of PVs were

completely electrically isolated with the endoscopic ablation system. The mean procedure time was 198 minutes. During follow up at 12 months, the drug-free rate of freedom from AF or atrial tachycardia was 71.2%. Complications were reported in three patients, including one cardiac tamponade, one large groin hematoma, and one phrenic nerve injury. Reddy et al reported the outcomes of 30 paroxysmal AF patients who underwent AF ablation with the endoscopic ablation system.⁷⁷ The mean procedure time decreased from 386 to 283 minutes over the thirty procedures. Electrical isolation was achieved in 92% of the pulmonary veins. Over a 12 month follow-up period 60% of the patients were free from AF without AADs after one procedure. Three complications were reported including one stroke, one cardiac tamponade, and one phrenic nerve injury. The endoscopic system is currently being evaluated for FDA approval in a prospective clinical trial which randomizes patients to ablation with the investigational system to conventional ablation using the ThermoCool Ablation System (Biosense Webster).

Conclusions

Catheter ablation is an important therapeutic modality for patients with AF. Although progress has been made in improving the safety and efficacy of the procedure, much research is still needed. In our opinion, the greatest challenge at this time is to improve the long-term efficacy of a single procedure catheter ablation of paroxysmal, persistent and, particularly, longstanding persistent AF. Despite being superior in efficacy to antiarrhythmic medications, single procedure success rates, which currently vary between 35% and 70%, are suboptimal. Improvements are likely to be achieved by both technological advances in the tools available to perform AF ablation procedures and increased understanding of the precise pathophysiological basis of AF.

The second greatest challenge in the field of AF catheter ablation is to reduce the risks associated with the procedure. Atrial esophageal fistulas, although very rare (<0.1% of patients), continue to occur. Cardiac tamponade is more common (0.5–2.0% of patients) and accounts for many more deaths than atrial esophageal fistula. Cardiac tamponade is unlikely to ever be completely elimi-

nated, but our goal should be to reduce the risk of this complication (and of stroke and catheter access related complications) to less than 1 in 500 procedures.

The progress made in the field of AF catheter ablation is truly remarkable. When radiofrequency catheter ablation of accessory pathways was being developed in the late 1980s, the use of this ablation technology in patients with AF was unimaginable. Now catheter ablation of AF is the most commonly performed ablation procedure in most major hospitals.

Disclosures

No disclosures relevant to this article were made by the authors.

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