Introduction

Atrial fibrillation (AF) affects approximately 3.03 million Americans in 2005 and is projected to increase to 7.56 million in 2050. These recent estimates based on over 21 million patients from a large national database outpace the estimates from a previous sentinel paper, which additionally noted that AF contributes to approximately 5 million physician office visits and $7 billion USD in expenditures each year. The incidence and prevalence of AF increases with age with a median age of 75, but with the aging population, the projected number of adults with AF will increase markedly in the next few decades. Risk factors for AF include age, presence of valvular heart disease, increasing left atrial size, coronary artery disease, use of diuretics, systolic blood pressure, plasma glucose, height, high levels of alcohol intake, obesity, and obstructive sleep apnea.

New onset AF is most commonly triggered by myocardial tissue that extends onto the pulmonary veins (PVs) of the left atrium either from repetitive firing from a single source or more commonly from episodic reentrant activation from multiple wandering wavelets. Spectral analysis and mapping has demonstrated that in paroxysmal AF, the PV ostial region was most frequently the source of triggers and AF can be terminated by ablation to those sites in 87% of patients. The risks, complications and patient features associated with it are increasingly recognized. A recent worldwide survey has shown an increasing number of medical centers that are practicing catheter ablation of atrial fibrillation, predominantly with pulmonary vein isolation techniques. However, catheter ablation is an invasive therapy in AF and is associated with a few major complications. Patient selection, ablation technique, and catheter energy source all influence the efficacy and safety of the procedure. Finally, while several randomized control trials have compared the efficacy of catheter ablation versus antiarrhythmic drug therapy, a number of trials are on the horizon to explore its role as a first line therapy for atrial fibrillation. New energy catheter energy sources are also being explored.
which allows smaller and more atrial reentry circuits and other electrophysiological changes \textsuperscript{10-11}. Atrial remodeling resulted in several non-PV region triggers with no dominant trigger in longstanding persistent AF.\textsuperscript{8} These changes have implications for the timing of catheter ablation in the treatment of AF and its success.

**Catheter Ablation of Atrial Fibrillation**

In 2011, the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the European Society of Cardiology Committee for Practice Guidelines published updated practice guidelines on the management of patients with AF.\textsuperscript{12,13} These updated guidelines continued to define the role of catheter ablation as reserved for antiarrhythmic drug (AAD) therapy failure for the maintenance of sinus rhythm in patients with intolerable symptoms from AF.

As a Class I indication, the guidelines suggested that “catheter ablation performed in experienced centers is useful in maintaining sinus rhythm in selected patients with significantly symptomatic, paroxysmal AF who have failed treatment with an antiarrhythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease.”\textsuperscript{14-27} It further recommends as a Class IIa indication that “catheter ablation is reasonable to treat symptomatic persistent AF,” and as a Class IIb indication that “catheter ablation may be reasonable to treat symptomatic paroxysmal AF in patients with significant left atrial dilatation or with significant LV dysfunction.”\textsuperscript{9,20,27,33}

Similarly, the European Society of Cardiology and European Heart Rhythm Association published guidelines for management of AF in 2010 that recommends as Class IIa guidelines that “catheter ablation for paroxysmal AF should be considered in symptomatic patients who have previously failed a trial of antiarrhythmic medication, and “ablation of persistent symptomatic AF that is refractory to antiarrhythmic therapy should be considered a treatment option.”\textsuperscript{34}

Other factors to consider include age, LA diameter, and duration of AF. Catheter ablation of AF carries greater risks of cardiac perforation and thromboembolic complications in very elderly patients,\textsuperscript{35} lower rates of success in patients with longstanding persistent AF\textsuperscript{25} and/or marked dilatation of the LA.\textsuperscript{3-5} Moreover, patients may seek to have AF ablation in the hopes of discontinuing long-term anticoagulation; however, no large prospective randomized clinical trial has been done to establish the safety of discontinuing anticoagulation especially in light of a not insignificant rate of late recurrence of AF post-ablation.\textsuperscript{36-38}

**Techniques for AF Ablation**

Since approximately 90% of AF trigger foci were localized to the PVs in paroxysmal AF,\textsuperscript{9} early efforts at ablation targeted these foci within the PV which resulted in unacceptable rates of PV stenosis secondary to ablation energy. Since these early efforts, PV isolation with radiofrequency catheter (RF) ablation has become the cornerstone for AF ablation with complete electrical isolation as the goal. In a recent survey on methods, efficacy, and safety of catheter ablation for human AF,\textsuperscript{25} 48.2% of centers who participated in the survey used Carto-guided LA circumferential ablation and another 27.4% of centers practiced Lasso-guided ostial electric disconnection. Both methods attempt to achieve complete electrical isolation of the PVs. The Lasso-guided ostial electric disconnection method places a “lasso” catheter at the orifice of a PV and multiple electrodes on the catheter determine the precise location of sites of electrical connection which are then ablated. The circumferential ablation method creates confluent ablation lesions that encircle the ostia of the PVs and often include connecting lines to other anatomic landmarks, most commonly the mitral annulus to prevent macroreentrant circuits that can lead to atrial flutter. The comparable efficacy between the two approaches has not been established. Additional ablation lines at the left atrial roof, the posterior wall, and mitral isthmus have been studied and showed increased efficacy.\textsuperscript{39-41}

Other techniques, in descending prevalence, include 3D noncontact ablation, catheter ablation of fragmented atrial electrograms, catheter ablation of the triggering focus, basket ablation, and right atrial compartmentalization.

**Efficacy**

Cappato et al. in Circulation Arrhythmia and
Electrophysiology also reported the efficacy of AF ablation. This worldwide survey was sent to 521 centers from 24 countries in 4 continents. 67% of centers responded but only 85 centers returned complete interviews. In these centers, 20825 catheter ablations were performed on 16309 patients with AF between 2003 and 2006. 95% of centers reported drug refractoriness as a prerequisite for ablation. All centers performed ablations on paroxysmal AF. 85.9% of centers performed ablations on persistent AF and 47.1% ablated long-lasting AF. Of the 16309 patients followed for an average of 18 months, 70% became asymptomatic without AADs, another 10% became asymptomatic in the presence of previously ineffective AADs. Success rates were significantly higher in those with paroxysmal AF compared to persistent AF which was in turn significantly more successful than ablations of those with long-lasting AF.

Randomized Control Trials Comparing Catheter Ablation and Antiarrhythmics

There have been at least seven randomized clinical trials performed of catheter ablation of AF. Other than one of the studies, enrolled patients had either paroxysmal or persistent AF or a combination of the two, and were refractory to at least one AAD. Patients were randomized and treated with catheter ablation versus second line AADs and followed for 12 months. Each of the seven studies demonstrated a higher freedom from arrhythmia at the end of follow-up for the catheter ablation group. Notably, no study showed an improvement in mortality due to insufficient power. 

Risks from Catheter Ablation

The risks of catheter ablation depend on technique used, patient selection, and operator and center experience. In the worldwide survey conducted between 2003-2006 there were 25 procedure-related deaths at a rate of 0.15% 25. Cardiac tamponade, from catheter perforation, was the most frequent major complication occurring at a rate of 1.31%. However, two other recent studies showed tamponade in 2.4% to 2.9% of procedures. 44,45 The higher incidence of cardiac tamponade in catheter ablation of AF arises from the need for two or more transseptal punctures and the need for systemic anticoagulation. The other complications, in descending incidence, included total femoral pseudoaneurysm (0.93%), transient ischemic attack (0.71%), total arterovenous fistulae (0.54%), PV stenosis requiring intervention (0.29%), stroke (0.23%), permanent diaphragmatic paralysis (0.17%), pneumothorax (0.09%), valve damage requiring surgery (0.07%), atrium-esophageal fistulae (0.04%), hemotorax (0.02%), and sepsis, abscesses, or endocarditis (0.01%). All totaled, the rate of major complications including death equaled 4.54%. Iatrogenic flutter resulting from the procedure, not listed as a major complication, occurred at a rate of 8.6%. In comparison to a prior survey conducted between 1995-2002, the number of patients being treated with catheter ablation nearly doubled, and more centers included patients with persistent and longstanding AF. The overall incidence of major complications was 4.5% in the updated survey compared with 4.0% in the former survey. However, iatrogenic flutter was significantly more frequent in the updated survey, 8.6% compared with 3.9%. It is important to also note that given the voluntary nature of the study, the inherent center-to-center variability in safety, and the potentially self-selective reporting of complication rates, the rate of major complications is possibly higher than the reported numbers. Most recently, stiff atrial syndrome and valvular damage have been described and should be considered as potential complications as well.

Transient ischemic attacks and stroke are due to embolism of thrombus or air and are both relatively common and potentially devastating. Other than cerebral compromise, thromboembolic events can cause coronary and peripheral vascular compromise as well. Thromboembolic events tend to occur within 24 hours of the procedure and most events occur within 2 weeks. The risk of embolism in patients undergoing cardioversion of AF without antithrombotic therapy has been reported in a meta-analysis to be 2% while with thrombolytic therapy the risk drops to 0.33%. The risk of embolism is due to clots prior to cardioversion and from “myocardial stunning” resulting in de novo clot formation on return to sinus rhythm, which has been described after catheter ablation of AF as well. While the risk is reduced with antithrombotic therapy, even in patients who have undergone 3-4 weeks of antithrom-
botic therapy prior to cardioversion, there is still a minority with persistent clots.\textsuperscript{51,52} Since there is mechanical manipulation of the left atrium during catheter ablation of AF which could dislodge these persistent clots, many operators in the field perform a transesophageal echocardiogram (TEE) to evaluate for a thrombus even in patients who are anticoagulated with warfarin prior to cardioversion. The Venice Chart consensus document and Heart Rhythm Society expert consensus both recommend the employment of TEE in this circumstance.\textsuperscript{53,54} Intra-procedurally, use of increase intensity anticoagulation between an ACT of greater than 300 seconds was associated with reduced incidence of embolic events.\textsuperscript{55,56} and using high-dose heparin transseptal sheath flush was associated with decreased thrombus formation on the sheath.\textsuperscript{57}

Asymptomatic cerebral lesions have been described by magnetic resonance imaging following AF ablation procedures and were most often smaller than 1 cm with the majority resolving without scarring.\textsuperscript{58} While the significance of these lesions are not yet established, they are found more frequently in catheter ablations performed with multielectrode catheter ablation compared with radiofrequency and cryoballoon ablation.\textsuperscript{59,60}

The European Society of Cardiology and the Venice Chart consensus document both suggest 3 months of post-procedural anticoagulation,\textsuperscript{34,53} after which each patient’s requirement for long-term anticoagulation should depend on risk factors of stroke by measures such as the CHADS\textsubscript{2} score.\textsuperscript{61} There is no evidence that maintenance of sinus rhythm after cardioversion is associated with a reduced risk for thromboembolism. Air embolism causing a transient ischemic attack or stroke is most commonly caused by introduction of air into the trans-septal catheter sheath either during introduction of the infusion line or when catheters are removed.\textsuperscript{62,63} An air embolus could also cause acute inferior ischemia and heart block during a procedure when the embolus enters into the right coronary artery.\textsuperscript{64}

Pulmonary vein stenosis is a result of thermal injury and, while incompletely understood, a progressive replacement of necrotic myocardium by collagen has been suggested.\textsuperscript{65} The incidence of pulmonary vein stenosis has fallen dramatically due to the increased recognition of this complication, better imaging modalities, and avoidance of ablation within the pulmonary vein. Pulmonary vein stenosis manifests as chest pain, dyspnea, cough, hemoptysis, and recurrent lung infections but even severe pulmonary vein stenosis can be asymptomatic.\textsuperscript{66}

A rare but dreaded complication in catheter ablation is esophageal injury and development of an atrial-esophageal fistula.\textsuperscript{67,68} It often presents as fever, chills, and recurrent neurological events and leads to mediastinal infection, stroke, and most often death. While it is thought that decreased power delivery, delivery time, and tissue contact pressure, along with pre-procedure or real-time visualization with modalities such as intra-cardiac echocardiography would decrease the rate of esophageal injury, the rarity of this complication has made it hard to study the efficacy of these interventions. Energy delivery in the left atrial posterior wall has also been proposed as the cause of acute pyloric spasm and gastric hypomotility described as abdominal bloating and discomfort thought to be due to periesophageal vagal plexi damage.\textsuperscript{69} For two of the four patients described in the series, the symptoms were self-limiting. Another case series described two patients undergoing circumferential pulmonary vein ablation for atrial fibrillation who developed symptoms of endocarditis 3-5 days after the procedure and subsequently developed gaseous and/or septic embolic. An atrial-esophageal was found in both patients.\textsuperscript{66} The employment of intra-procedural intracardiac echocardiography, lower energy settings, and duration of power delivery, have been suggested to decrease esophageal involvement.

Phrenic nerve injury is a rare complication of AF, most often involving the right phrenic nerve with ablation near the right superior pulmonary vein and superior vena cava.\textsuperscript{70,71} Symptoms include dyspnea, hiccups, atelectasis, pleural effusion, cough and thoracic pain and can be diagnosed by unilateral diaphragmatic paralysis by radiography. The phrenic nerve can recover function as quickly as 1 day and as long as 12 months; however, there have been reports of permanent phrenic nerve injury.\textsuperscript{54}

Recurrent arrhythmia occurs in about 45% of patients during the first 1-3 months of follow-up despite AADs.\textsuperscript{72} While early AF prognoses treatment failure, immediate re-ablation is unnecessary as up to 60% of cases are self-limiting.\textsuperscript{72,73} Age

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AF are numerous and at times life-threatening. The radiation exposure for such a complex procedure is also higher than that of simpler catheter ablation procedures, and carries with it increased acute and sub-acute skin injury and increased lifetime risks of malignancy. However, improvements in complication rates, other than an increase of iatrogenic flutter, has followed the increasing experience with catheter ablation of AF. In another report of a retrospective study of 517 patients undergoing 641 catheter ablations for AF at a single institution between 2001 and 2007, complication rates were found to be higher (9%) in the first 100 cases than during the subsequent 541 (4.3%), again suggesting the role of experience and volume in the reduction of complication rates. The same study also showed that age > 70 and female gender were predictors of major adverse events.35

Catheter Energy Selection and Safety

Radiofrequency energy is the dominant energy source in catheter ablation of AF in 98.8% of cases, either with irrigated, cooled, 8-mm standard, or conventional 4-mm tip. There have been small trials studying the comparative efficacy irrigated tip and large tip versus conventional catheters showing their increased efficacy, but there have been no large trials exploring their comparative safety. As for other energy sources in catheter ablation, cryoablation is the most common. In the STOP-AF trial, 245 patients with paroxysmal AF were randomized to catheter ablation or to AADs. In terms of safety, the overall incidence of adverse events in the cryoablation arm was 6.1%; stroke was 2.5%, transient ischemic attacks 1.8%, myocardial infarctions 1.2%, tamponade 0.6%, and death 0.6%. On the other hand, the German Ablation Registry reported low incidence of in-hospital complication (1.4%) for 776 patients who underwent cryoballoon ablation. The lower reported incidence could be due to the voluntary nature of the registry. The complication rates observed in the Updated Worldwide Survey where radiofrequency was the dominant energy source totaled 4.5%.25

General anesthesia has been proposed to reduce fluoroscopy and procedure time and increase cure rate in catheter ablation of AF when compared to conscious sedation. However, general anesthesia carries its own complications including malfunction of gas delivery equipment, adverse respiratory events, burns, awareness during anesthesia, and nerve injury. Contact force monitoring during catheter ablation of AF has also been recently explored for its efficacy and safety but its comparative benefit has not been established. The risks and complications of catheter ablation of AF are numerous and at times life-threatening. The radiation exposure for such a complex procedure is also higher than that of simpler catheter ablation procedures, and carries with it increased acute and sub-acute skin injury and increased lifetime risks of malignancy. However, improvements in complication rates, other than an increase of iatrogenic flutter, has followed the increasing experience with catheter ablation of AF. In another report of a retrospective study of 517 patients undergoing 641 catheter ablations for AF at a single institution between 2001 and 2007, complication rates were found to be higher (9%) in the first 100 cases than during the subsequent 541 (4.3%), again suggesting the role of experience and volume in the reduction of complication rates. The same study also showed that age > 70 and female gender were predictors of major adverse events.35

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Other less-explored alternative energy sources
include high-frequency ultrasound, microwave, and laser energy. These energy sources are more prevalent in surgical ablation of atrial fibrillation and are applied on the epicardial surface. A review of surgical literature suggests several theoretical safety benefits and risks of each of these energy sources in comparison with radiofrequency energy.\textsuperscript{89–91} In epicardial high-frequency ultrasound, ultrasound waves can be focused at certain depths without dissecting epicardial fat and in theory without concern for coronary artery injury. In microwave energy, the generated electromagnetic energy is independent of current flow from ablation catheter to tissue, and therefore is not influenced by contact pressure, orientation, and tissue desiccation. However, the unfocused heat energy can cause collateral injury. Finally, laser energy has the advantage of making deep, uniform, and narrow lesions at low temperatures. But, unlike radiofrequency energy where impedance rises at increased temperatures, serving as a protective mechanism, laser energy does not have this benefit. In a recent first-in-human study, 30 patients with paroxysmal atrial fibrillation underwent pulmonary vein isolation with laser energy. Adverse events include one case of cardiac tamponade, one stroke, and one asymptomatic phrenic nerve palsy.\textsuperscript{92} In another recent study, high-intensity focused ultrasound was employed to achieve pulmonary vein isolation with esophageal temperature guided safety algorithm. However, in 28 patients, major complications occurred in six cases including an unexplained death and another lethal atrioesophageal fistula.\textsuperscript{93}

Recently, several robotic navigation systems have been developed for catheter ablation of atrial fibrillation. From single-center experiences with small numbers of patients, feasibility has been demonstrated. Robotic navigation systems may have the potential to reduce fluoroscopy time without compromising efficacy of the ablation. The comparative complications are yet to be elucidated\textsuperscript{94–96}.

**Future Directions**

While the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial showed in AF patients high risk for stroke and death, it also showed that there were no significant differences in all-cause death between rhythm using the most effective AAD and rate control.\textsuperscript{97} A subsequent on-treatment analysis showed that sinus rhythm is associated with survival but that AADs are not associated with improved survival, suggesting that the beneficial effects of being in sinus may be offset by the adverse effects of AADs.\textsuperscript{98} In one study evaluating symptom control in patients with paroxysmal atrial fibrillation, rhythm control was associated with better quality of life scores.\textsuperscript{99}

Several large trials are underway to investigate catheter ablation of AF as first line therapy for maintaining sinus rhythm. The Catheter Ablation versus Antiarrhythmic Drug Therapy for Atrial Fibrillation (CABANA) trial is currently enrolling patients and will compare drug therapy (rate and rhythm control) with catheter ablation in AF and also compare the cost of care and their impact on quality of life.\textsuperscript{100}

The First Line Radiofrequency Ablation versus Antiarrhythmic Drugs for Atrial Fibrillation Treatment (The RAAFT Study) has completed enrollment and is ongoing and will compare pulmonary vein isolation catheter ablation of AF with conventional AAD therapy in order to investigate the role of catheter ablation as first line therapy for AF.\textsuperscript{101}

Medical Antiarrhythmic Treatment or Radiofrequency Ablation in Paroxysmal Atrial Fibrillation (MANTRA-PAF) again is another study that is ongoing comparing catheter ablation versus AAD therapy with a longer 24-month follow-up in patients with paroxysmal AF without prior antiarrhythmic drug therapy.\textsuperscript{102}

**Conclusions**

In summary, catheter ablation of AF remains reserved for selected patients with intolerable symptomatic AF refractory to AAD or for younger individuals for paroxysmal lone AF who have failed AAD therapy. Updated guidelines set forth by ACC/AHA/ESC in 2011 more specifically defined its role for symptomatic paroxysmal AF, symptomatic persistent AF, and paroxysmal AF with significant left atrial dilatation or with significant LV dysfunction.\textsuperscript{12} Successful catheter ablation of AF should not be an indication for discontinua-
tio of previously indicated long-term anticoagulation of AF with high risk of stroke and transient ischemic attacks. As for any complex procedure, the safety and efficacy of catheter ablation is often operator and institution dependent, and improves with their increasing experience. Major complications occur at least at a rate of 4.5%, with tamponade as the most common complication. Operators and institutions should be aware of the risks of catheter ablation of AF and be prepared to optimally manage complications as they occur. New energy source, catheter designs, and pre-procedure and real-time imaging modalities are being explored as are several large studies exploring the role of catheter ablation as first line therapy for rhythm control in lieu of AADs.

References


