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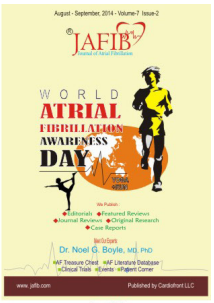

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New Technologies In Atrial Fibrillation Ablation

John Rickard MD, MPH[1], Saman Nazarian MD, PHD[1,2]

[1]Division of Cardiology, Section for Cardiac Electrophysiology. [2]Department of Epidemiology, Johns Hopkins University, Baltimore, MD.

Abstract

Atrial fibrillation (AF) is a major public health issue worldwide, the incidence of which is likely to continue to rise. With the birth of pulmonary vein isolation(PVI), cardiac ablation has emerged as key strategy for the treatment of AF. PVI using traditional point by point radiofrequency ablation is time consuming and technically challenging. Refining patient selection for PVI also remains an important goal. New ablative strategies using catheter-based balloon technologies, such as cryothermy and laser-based systems, may simplify PVI. In addition, new MRI-based techniques offer the hope of refining patient selection prior to ablation. Lastly, FIRM mapping represents an entirely new approach to AF ablation via the targeting of mechanisms that perpetuate AF rather than simply targeting triggers alone.

Introduction

Atrial fibrillation(AF) remains the most common sustained arrhythmia in the United States affecting greater than 3 million individuals, a number likely to rise dramatically by 2015.[1] AF is associated with symptoms such as a palpitations, lightheadedness, fatigue, and may precipitate heart failure. In addition, it has been associated with an increased risk for stroke, increased hospitalizations, and increased mortality.[2] For many years, anti-arrhythmic medications were the only options for the treatment of patients with symptomatic AF. Such medications are associated with relatively poor long-term efficacy profiles as well as many known toxicities.[3] In 1998, Haissaguerre and colleagues made the observation that triggers from within the pulmonary veins were often the precipitating event in AF initiation thus providing a potential target for ablation.[4] Initial strategies of AF ablation were surgical and while fairly successful were also associated with significant morbidity.[5,6] Building off the experience of the COX MAZE procedure, catheter ablation procedures were developed to isolate the pulmonary veins from the left atrium via circular radiofrequency ablations surrounding the pulmonary veins. Over the last decade, catheter ablation has become an effective tool in the management of symptomatic, drug refractory AF demonstrating superior results at one year compared to anti-arrhythmic medications alone.[7] Currently, radiofrequency energy is the main energy source for pulmonary vein isolation(PVI) procedures. PVI currently involves either dragging or point by point lesion creation. As such, procedure times can be lengthy and often necessitate the use of significant amounts of fluoroscopy particularly in the case of lower volume operators.[8] In addition, such procedures are technically difficult and are associated with rare but significant complications such as pulmonary vein stenosis and atrio-esophageal fistulas.[9] Therefore, new ablative technologies have emerged in the hopes of improving patient selection, shortening and simplifying the procedure,and preserving if not improving efficacy and safety. In addition, a new mapping strategy known as FIRM mapping has attempted to target the mechanisms perpetuating AF rather than the triggers themselves. The field of AF ablation is rapidly evolving as new technologies become available.

Magnetic Resonance Imaging For Patient Selection And Procedural Guidance

Late gadolinium enhanced (LGE) magnetic resonance imaging (MRI) of left atrial (LA) scar was first performed by Peters and colleagues in 23 patients with AF in 2007.[10] The investigators found no pre-ablation LGE, suggestive of baseline scar, in any participants.[10] After ablation, 38% of patients had less than 90% circumferential LGE of the pulmonary veins.[10] Following this work, Marrouche and colleagues reported on a series of 46 patients that underwent MRI prior to and after AF ablation.[11] In this cohort, baseline LGE was observed in 8.7% of patients.[11] In a later study which focused on patients with lone AF, the Utah investigators categorized patients by the extent of baseline LGE on LA images, dividing patients into four groups: I (<5%), II (5-20%), III (20-35%), and IV (>35%).[12] Procedural outcomes were predicted by baseline LA scar burden in this cohort of patients.[12] After a mean follow up of 324 days all patients in group I were free of AF, in contrast with only 4% of patients in group IV which remained free of AF.[12] In subsequent reports, the Utah investigators have proposed that the strategy used during AF ablation, such as stand alone PVI versus coupling of pulmonary vein isolation with linear ablations or debulking, be informed by scar burden as assessed by LGE MRI.[13,14] The use of

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Corresponding Author:
John Rickard, MD, MPH
The John Hopkins Hospital
Division of Cardiology
Baltimore, MD.

LGE MRI, however, requires significant expertise for appropriate image acquisition and analysis. To improve the generalizability of MRI scar mapping to clinical settings, our group focused on MRI T1 mapping, an emerging tool for objective quantification of myocardial fibrosis. We performed LA myocardial T1 mapping in 51 patients before AF ablation and in 16 healthy volunteers. We found that the median LA T1 relaxation time was shorter in patients with AF compared to healthy volunteers and was shorter in patients with AF with prior ablation compared to patients without prior ablation. In a generalized estimating equations model, adjusting for data clusters per participant, age, prior ablation, AF type, hypertension, and diabetes, each 100-ms increase in T1 relaxation time was associated with 0.1 mV increase in intracardiac bipolar LA voltage (P=0.025). This novel methodology, which provides an objective and easy to measure estimate of diffuse fibrosis, may improve the quantification of fibrotic changes in thin-walled myocardial tissues.[15] We have also developed and validated a normalized measure, the image intensity ratio (IIR), for the assessment of LA scar on LGE MRI. In an LGE MRI study of 75 patients prior to AF ablation, each unit increase in local IIR was associated with 91.3% decrease in bipolar LA voltage (P < .001) after accounting for within patient clustering, and adjusting for age, LA volume, mass, body mass index, sex, CHA_2DS_2-VASc score, atrial fibrillation type, history of previous ablations, and contrast delay time. Local IIR thresholds of >0.97 and >1.61 corresponded to bipolar voltage <0.5 and <0.1 mV, respectively.[16] Detection of LF fibrosis based upon the LGE MRI or T1 mapping techniquesappears to provide measures that are closely associated with intracardiac voltage as a surrogate of atrial fibrosis. These measures may have important implications regarding appropriate patient selection for catheter ablation.

A number of other studies have focused on the potential utility of LA LGE imaging after ablation. In a study of 144 patients post AF ablation, Marrouche and colleagues reported that the LA total LGE burden and the degree of circumferential isolation of pulmonary vein ostia were directly proportional with freedom from AF after the procedure.[17] It has also been proposed that post-procedure LGEmay be used to assess the adequacy of ablation, and to guide repeat ablation after the initial procedure.[17,18] However, the resolution of CMR in our hands remains sub-optimal for identification of conduction gaps in lesion sets. In 10 patients, undergoing repeat ablation for AF recurrence, we noted a significant association between scar identified by LGE and low-voltage regions of the LA. However, there was no association between scar gaps and PV reconnection sites.[19]

Real-time MRI guidance for AF ablation is the ultimate goal for all centers engaged in AF imaging research. The ability to use real-time MRI for procedural guidance would a) provide better real-time visualization of the LA geometry, PV position, and anatomic features, b) reduce radiation exposure, c) improve the rapid recognition of complications such as pericardial effusion or collateral damage to adjacent structures such as the esophagus, d) provide real-time information about targets for ablation such as regions with heterogeneous fibrosis or adjacent fat pads, and e) provide real-time feedback regarding the completeness of linear ablation sets.[20-21] While we and others have made significant advances toward integration of real-time CMR guidance for ablation procedures, many technical challenges remain before real-time CMR guidance can be fully integrated into standard EP laboratories.

Cryoballoon Ablation

Cryoablation results in tissue injury through the generation of extremely low temperatures(between -30 to -90 degrees Celsius). The mechanism by which cryothermy generates tissue ablation is multifactorial.[22] At temperatures reaching -20 degrees Celsius, extracellular ice formation occurs resulting in an osmotic shift of water from inside the cell to out. At lower temperatures still, intracellular organelle damage occurs. In addition, cryothermic damage to vascular structures aswell as hyperemia from rewarming contribute to tissue injury.[22]

While cryothermic ablation has been available for years for the treatment of arrhythmias, only recently has it been used for PVI. Compared with traditional RF energy, cryoablation for PVI has several potential advantages. First, cryoablation is associated with less patient discomfort than RF, a characteristic that is particularly advantageous in centers where PVI is performed under conscious sedation rather than general anesthesia. Second, the use of cryoablative catheters results in freeze-mediated catheter adhesion, a trait that can enhance catheter stability particularly in traditionally challenging areas to ablate such as the ridge between the left atrial appendage and left sided pulmonary veins. Lastly, cryoablation has been shown to be associated with less platelet and coagulation cascade activation leading to a lower risk of thrombus formation.[23,24]

In the early 2000's, several investigators examined the feasibility of using focal cryoablation catheters for PVI.[25,26] These studies showed that cryoablation for PVI was effective and safe but associated with a frequent need for a repeat procedure.[26] In 2005, Sarabanda and colleagues were amongst the first to report on the use of cryoballoon technology in a study of 8 mongrel dogs. Using a 23-mm balloon, 83% of targeted pulmonary veins could be successfully isolated.[27] With the development of the Arctic FrontTMcryoablation system, cryoballoon ablation for PVI in human subjects was introduced in Europe in 2006 and was FDA approved for use in the United States in 2011. This technology utilizes a cryoballoon catheter placed in the left atrium following transseptal access via a 12 French inner/15 French outer deflectable catheter over a 0.035 inch guide wire via femoral vein access. The Arctic FrontTMballoon is available in two diameters (23 mm and 28mm). The guidewire is placed in branches of the target pulmonary vein and the inflated balloon is advanced over the wire to the ostium of the vein. Contrast can be injected through the catheter to assess for complete venous occlusion. Nitrous oxide (N2O) is delivered into the balloon and freezing times range from 240-300 seconds per freeze. To assess for pulmonary vein isolation without the need of a second transseptal access, the AchieveTM catheter was developed. This catheter is an 8 pole lasso that can be deployed through the guidewire lumen and hence advanced into the vein with the Arctic FrontTM catheter in place. The freezing procedure is repeated sub-selecting different pulmonary vein branches for all four veins until complete isolation of all veins is achieved.

Neumann and colleagues reported on outcomes and complications in a large scale observational series of patients undergoing cryoballoon ablation.[28] In 346 patients(293 with paroxysmal AF and53 with persistent AF), 97% of targeted pulmonary veins were successfully isolated using the cryoballoon technique.[28] Maintenance of sinus rhythm was achieved in 74% of patients with paroxysmal AF and 42% with persistent AF.[16] Right phrenic nerve paralysis was noted

in 26 patients.[28] van Belle and colleagues reported on a cohort of 57 patients with paroxysmal AF undergoing cryoballoon PVI. 84% of pulmonary veins were successfully isolated and right phrenic nerve paralysis occurred in four patients.[29]

Kojodjojoand colleagues reported a series of 124 patients undergoing cryoballoon ablation.[30] At 12 months 77% of patients with paroxysmal AF and 48% of those with persistent AF were free of AF.[30] 2 cases of transient phrenic nerve paralysis were reported.[19] Lastly, Malmoborg and colleagues reported a series of 40 patients undergoing cryoballoon PVI.[22] Complete PV isolation was noted in 39 of 43 procedures(91%).[29] Phrenic nerve paralysis was observed in 2 patients.[31]

The first randomized controlled trial of cryoballoon ablation for PVI was the STOP AF trial published by Packer an colleagues in 2013.[32] This study was a prospective, multicenter, randomized controlled trial comparing cryoballoon therapy to anti-arrhythmic drug therapy in patients with paroxysmal AF refractory to at least one anti-arrhythmic drug.[32] The trial enrolled a total of 245 patients, 163 in the cryoballoon arm and 82 in the drug therapy arm.[30] Isolation of at least three pulmonary veins was accomplished in 98.2% of patients and all four veins in 97.6% in those receiving PVI.[32] The primary endpoint was freedom from treatment failure defined as absence of the following:any detectable AF, use of a non-study anti-arrhythmic drug, or any non-protocol AF intervention(radiofrequency PVI e.g.).[32] At 12 months, the primary endpoint was achieved in 69.9% of patients randomized to the cryoballoon arm and 7.3% randomized to the anti-arrhythmic drug arm.[32]

In terms of complications, 29 of 259 cryoballoon procedures were associated with phrenic nerve paralysis in the STOP AF trial of which 25 had resolved at 12 months of follow up.[32] Given the risk of phrenic nerve injury, pacing in the right atrium to stimulate the phrenic nerve and hence assess functionality in realtime during freezing (particularly the right superior PV), is advisable. In addition 5 cases of pulmonary vein stenosis were noted. This complication had previously not been appreciated with cryoballoon PVI in the single center cohort studies. The authors postulated that deep ablation within the pulmonary vein with a smaller balloon size may have been the reason for this. Lastly, it had been postulated that one of the benefits of cryoballoon PVI compared with traditional RF would be prevention of atrio-esophageal(AE) fistula formation, a dreaded but rare complication seen in RF PVI procedures. In the STOP AF trial no AE fistulas were noted. Esophageal ulcers with cryoablation therapy have been reported.[33,34] More recently, however, several cases of AE fistulas have been reported following cryoballoon PVI.[35] Currently, in real world practice, at least in the hand of experienced operators the overall complication rates seem to be comparable between RF and cryoballoon ablation, however type of complications vary significantly.[36,37]

Recently, a second generation cryoballoon was introduced with the goal of isolating each pulmonary vein with fewer number of freeze applications. The first generation ArcticeFrontTM balloon catheter utilized four injection ports through which N_2O refrigerant was sprayed in a region of the balloon just distal to the equator.[38,39] This resulted in a gradient of cooling such that higher temperatures were seen at thedistal poles of the balloon compared to the equator.[38,39] In this situation, if the balloon was placed In an off-axial position, antral freezing and hence isolation may not be achieved. In the second generation cryoballoon, the coolant was directed homogeneously in the distal half of the balloon in the hopes of remedying this problem. When compared with the first generation balloon, the second generation design showed improved first freeze isolation and shorter procedural times.[40,41] While an improved procedural and mid-term efficacy has been welcomed the safety profile of the new cryoballoon needs further investigation. By using careful monitoring of the phrenic nerve during freezes of the right superior pulmonary vein the most feared complication of phrenic nerve paralysis may be overcome and an esophageal probe to monitor esophageal temperature during the freezes should be used as well as in RF ablation procedures.[42-46]

Laser Balloon Catheter

Recently, the CardiofocusTM endoscopic ablation system was introduced in Europe as an alternative to radiofrequency and cryoballoon catheters for PVI. This novel system is comprised of a non- steerable catheter with a compliant (9-35 mm diameter) balloon at the tip.[47] The catheter is introduced into the left atrium via a transseptal puncture via access obtained via the femoral vein. The transseptal sheath has a 15 French outer diameter. The system was originally designed necessitating two operators, one to navigate the balloon to the pulmonary vein ostium and the other to guide laser application. The system was recently redesigned for use by a single operator. The balloon is inflatedwith a solution of radiopaque "heavy water" (deuterium oxide). Occlusion of the vein permits direct visualization of the PV antrum via a novel 2 French fiberoptic endoscope. A 980 nm diode laser is housed in the central lumen of the catheter. Laser application is performed in a point by point fashion around the pulmonary vein. The CardiofocusTM catheter has no electrodes therefore checking for vein isolation requires placement of a second catheter into the left atrium.

The ability of laser energy to achieve PVI was first demonstrated by Reddy in colleagues in 2004 in a study of 19 goats.[48] In 2006 Thermistoclackis demonstrated the ability to directly visualize the antrum of the PV endoscopically.[49] Human studies of the CardiofocusTM laser have been largely limited to small single center studies. The first human study using endoscopic laser technology was performed by Reddy and colleagues in 2009.[50] In the initial experience of 30 patients, 91% of PV's were successfully isolated, and the drug free freedom from AF rate was 60% at 12 months.[50] One episode each of tamponade, stroke, and phrenic nerve paralysis were noted.[50] The first generation system used by Reddy and colleagues employed a non-compliant balloon and a large laser arc. In the second generation device, the balloon was made compliant and the laser arc decreased to 30 degrees.[47] Schmidt and colleagues assessed the safety and efficacy profile of the second generation endoscopic laser system.[51] In 30 patients, complete PVIwas achieved in 114 of 116 veins (98%) with a total procedural time of 250±62 minutes and a mean fluoroscopy time of 30±18 minutes.[51] Of note, 4 patients(15%) showed esophageal ulceration post procedure.[51] In addition, 1 case of tamponade and 1 case of phrenic nerve paralysis was noted.[51] The most recent worldwide experience of the endoscopic laser balloon was presented by Schmidt and colleagues at the Heart Rhythm Society 2012 Scientific Sessions.[52] The authors reported on 406 patients from 16 centers.[52] The acute PVI rate was 98% with 79% isolated on the first visually guided attempt.[52] At 12 months, 60% of patients remained in sinus rhythm.[52] Recently, Metzner and colleagues compared different energy levels during endoscopic ablation and found that higher energies were associated with a higher

rate of achieving PVI without an increased risk of complications.[53] Caution with using increased energy is advisable, however, given the small numbers observed in this study. The ability to achieve PVI with the endoscopic laser balloon versus the cryoballoon was assessed in a prospective study of 144 patients.[54] At 12 months, recurrence of AF occurred in 37% of patients in the cryoballoon group and 27% in the laser group (p=0.18).[54]

FIRM Mapping

While PVI has provided an important tool in combating AF, success rates despite multiple procedures, especially in patients with persistent AF, obstructive sleep apnea, systolic dysfunction, and metabolic syndrome, remains modest.[55-57] Reasons for this may be related to non-pulmonary vein triggers and the fact that PVI does not target the mechanisms that sustain AF. Recently, FIRM mapping has been introduced as a method of targeting mechanisms that perpetuate AF.[58] This technique involves theplacement of large 64 pole basket catheters in both the left and right atrium. Using a novel mapping system, AF propagation maps are created.[59] Two types of sources of AF are identified: electrical rotors and focal impulses.[59] It has been hypothesized that ablation of these sources could improve procedural success in AF ablation. In the CONFIRM trial, patients treated with PVI plus FIRM mapping with ablation of sources of AF were compared to patients treated with PVI alone.[59] The authors found that localized rotors or focal impulses were present in 97% of patients undergoing AF ablation.[59] At a median of 273 days, 82.4% of patients receiving FIRM guided ablation in addition to PVI were free of AF compared with 44.9% receiving PVI alone.[59] Of interest, patients with factors traditionally associated with lower success rates with PVI (obstructive sleep apnea, increased left atrial diameter, and lower systolic function) had more sources of AF in more widespread distributions.[60] While FIRM mapping has sparked significant interest, whether it will represent a paradigm shift in the way AF is treated remains yet to be determined.

Contact Force Catheters

To achieve pulmonary vein isolation, the creation of transmural, circumferential lesions are necessary. If even one lesion fails to achieve transmurality, healing can occur leading to reconnection of the vein. Pulmonary vein reconnection has long been recognized as a cause of atrial fibrillation recurrence.[61] Tissue contact force has long been recognized as an important predictor of ultimate lesion size.[62,63] Left atrial anatomy and respirations may lead to problems with catheter contact with left atrial tissue limiting transmural lesion formation. While the use of deflectable catheters, general anesthesia, and even JET ventilation have improved stability, adequate tissue contact has remained a challenge particularly in areas such as the ridge between the left pulmonary veins and left atrial appendage. The development of contact force catheters have been introduced in the hopes of improving tissue contact via real time feedback with the operator. Contact force catheters utilized a contact force sensor located in the catheter tip. Via deformation of optical fibers, contact force is determined.[62] In a study of 10 dogs, Yokoyama and colleagues demonstrated that tissue temperature and lesion size increased with increasing contact. In addition, the incidence of steam pops increased with increasing force.[62]

The safety of a new novel contact force catheter was demonstrated in the Toccata study which evaluated acute outcomes in 77 patients (43 undergoing a right-sided supraventricular tachycardia and 34 with AF.[64] One complication (tamponade in 1 patient in the AF cohort) was noted. The area of highest contact force was commonly the anterior/rightward roof near the ascending aorta.[65] Of interest, high contact force was noted not only during ablation but also with simple catheter manipulation.[65] Amongst 32 patients with PAF in Toccata, at 12 months, 100% of patients with an average contact force <10 grams experienced recurrences.[65] 80% of patients with an average contact force >20 grams were free of AF at 12 months.[65]

Conclusion:

AF is a major public health problem in the United States, the burden of which is likely to continue to increase. With the seminal discovery that triggers for AF often arise from muscle sleeves within the pulmonary veins, the advent of PVI has proven to be a major advance in the treatment of AF. Late gadolinium enhanced magnetic resonance imaging of the left atrium has the ability to quantify atrial scar and may enhance patient selection for AF ablation. Traditional PVI procedures have used radiofrequency energy which is time consuming and requires considerable skill. New advances using balloon based catheters employing either cryothermy or laser-guided therapy represent exciting new technologies with the potential to simplify the procedure. However, given the importance of targeting non pulmonary vein triggers and substrates in the setting of permanent AF, in our opinion, balloon based therapies are currently suitable for treatment of paroxysmal AF. FIRM mapping represents an entirely new strategy for AF ablation where sources of AF perpetuation are targeted rather than triggers themselves. While early data utilizing FIRM mapping are encouraging,large-scale studies are needed prior to widespread use. Contact-force sensing catheters represent an important new advance providing real time operator feedback in terms of tissue contact. Such information may be used to ensure transmurality of lesions as well as prevent complications.

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