Catheter Ablation of Atrial Fibrillation

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Atrial fibrillation is the most common arrhythmia encountered in clinical practice and can result in significant morbidity and mortality. Catheter ablation has become a feasible therapeutic option for the management of this complex and challenging arrhythmia. In this article, we have discussed the mechanism of atrial fibrillation, different imaging modalities used for atrial fibrillation ablation, different ablation strategies targeting non-pulmonary veins, complications associated with atrial fibrillation ablation and its management, alternative energy sources for ablation and new antiarrhythmic drugs.

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Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia seen in clinical practice and results in significant morbidity, mortality and healthcare costs. Catheter ablation has emerged as an important treatment strategy for the eradication of AF. Centers that are extensively experienced in performing AF ablation report long-term success rates ranging from 75–90%. This paper will review the mechanism of initiation and perpetuation of AF, the role of imaging in catheter ablation, various catheter ablation strategies, complications of AF ablation, alternative energy sources used for ablation and new antiarrhythmic drugs (AADs).

Mechanism of Atrial Fibrillation

AF is characterized by the presence of multiple activation waves within the atria. The mechanisms by which these activation waves occur have been hotly debated for many years. The focal source hypothesis states at a single rapidly firing focus acts as a driver, causing the rest of the atria to go into AF. Studies in the 1950s demonstrated that local injection of aconitine into the atria could result in a rapidly firing focus that drives the atria into AF.1) A sustained reentry2) can similar act as a driver and generates AF. On the other hand, multiple wavelet hypothesis states that heterogeneity in atrial repolarization is responsible for the generation of multiple wavelets that sustain AF. If true, the multiple wavelets hypothesis suggests that AF is self-sustaining and does not need a driver. Central to these hypotheses are thoracic veins, which have been shown to be highly arrhythmogenic. In 1998, Haissaguerre et al.3) reported that repetitive rapid discharges from the pulmonary veins (PVs) were responsible for triggering AF in a series of 45 patients with symptomatic paroxysmal AF. Radio-frequency ablation of these PVs foci successfully
eliminated AF in up to 62% with a median follow-up period of 7 months.

Humans have a significant amount of left atrial myocardial tissue cardiac muscle which extends into PVs. The myocardial architecture in normal human PVs is also highly variable. In addition, aging may result in fibrosis at the PV antral (PVA) junctions, which further produces greater anisotropy in these veins. Several investigators have demonstrated that in animal models, PVs are capable of generating independent electrical activity. Perez-Lugones et al. examined PV tissue from five autopsies out of which four had a history of AF and demonstrated that under electron microscopy, four out of five had morphological features consistent with that of Purkinje cells in the PVs. It is conceivable then that triggered activity and/or automaticity may have a role in initiating and sustaining AF.

In addition, we have come to realize over the years that other thoracic veins such as the superior vena cava (SVC), the ligament and/or vein of Marshall, the coronary sinus musculature are also highly arrhythmogenic and may play a role in the initiation and maintenance of AF.

Imaging in AF ablation

Most AF ablation requires LA instrumentation via transseptal puncture and up to 3 punctures is made depending on the strategy adopted. In most cases, fluoroscopy provides sufficient information for safe transseptal punctures. However, fluoroscopy may be limited in the presence of intratrial septal variations, atrial or aortic root dilatation, prior LA instrumentation and the need to introduce up to 3 sheaths into the LA. Transesophageal echocardiography (TEE) allows identification of the fossa ovalis and its surrounding structures, provides real time assessment of the procedure, and visualizes tenting of the fossa ovalis, the subsequent entry and advancement of the sheath into the LA. However, the TEE probes obstructs fluoroscopic field and is utilized in only in-anesthetized patient, thereby preventing periodic neurological assessment of the patient. Intracardiac echocardiography (ICE) provides similar information as TEE but it can be used in a conscious patient and does not obstruct fluoroscopy. In addition, phased array transducers allow visualization of LA structures and a slightly posteriorly directed transseptal puncture can be safely performed to facilitate placement of mapping and ablation catheters at various PV antrum regions.

The goal of present day ablation strategies is to electrically isolate the PVs from the rest of the LA. Importantly, ablation performed at the PV antrum-LA junction decreases the incidence of PV stenosis. However, PV anatomy in humans is highly variable. Furthermore, variation in orifice size, orientation and diameter occurs during the cardiac cycle and is further accentuated by respiration. Given this marked variability, information on the number and anatomy of the PV is essential in performing successful and safe ablation. This can be performed pre-procedurally using computerized tomography (CT) or magnetic resonance imaging (MRI). Furthermore, these CT or MRI images can be fully integrated with Carto (Biosense Webster, Diamond Bar, CA, USA) or side by side with NavX (EnSite, St. Jude Medical, St Paul, MN, USA) 3D mapping system. The clinical usefulness of these 3D mapping systems during ablation will be dependent on the accuracy of image integration.

Venography, TEE and ICE can be performed to provide real time imaging of the PVs. Wood et al. compared imaging of PV ostial anatomy with CT, TEE, ICE and venography in 24 patients undergoing AF ablation. CT and ICE were superior to TEE in identifying the number of PV ostia. Ostial diameter was overestimated by venography and underestimated by TEE. Both CT and ICE yielded similar ostial diameters. This discrepancy could be due to the elliptical shape of the ostia whereby measurement in one plane will either under or over estimate its true diameter. Recently, multislice CT scanning is superior to ICE in demonstrating the oval shape of the ostia.

ICE is able provide real time assessment of the PVs and the PVA junction. Titration of energy delivery during RF ablation by the development of microbubbles can be performed with this imaging utility, thereby providing real time information on lesion formation only in non-open irrigated catheter ablation systems. Both ICE and TEE are also useful for monitoring complications within the LA. Its ability to provide real time imaging identifies LA appendage, clot formation and the detection of pericardial tamponade. Recently, ICE allows early detection of small thrombi formation on the transseptal sheath that allows appropriate sheath management to avoid inadvertent dislodgement and a potential catastrophic thromboembolism.

Catheter Ablation of Atrial Fibrillation

Catheter ablation for the treatment of AF has evolved over the years. The concept of PV isolation (PVI), was initially limited to the PVs, and has been modified by The Cleveland Clinic to involve the LA myocardium surrounding the PV to achieve
complete electrical isolation of the PV antra as a procedural endpoint, namely the LA-PV antrum isolation (PVAI).\(^{15}\) In addition to circular mapping catheter guided PVAI, we electrically isolate further AF trigger sites, modify the substrate for AF maintenance, and are possibly modulating cardiac autonomic tone at various LA, right atrial (RA) sites and within the coronary sinus to achieve a higher AF free success rate.

Under light sedation to facilitate periodic neurological assessment, ICE (10 Fr phased array, Siemens AG Inc., Malvern, PA, USA) guided double transseptal punctures are performed using Mullins and SRO sheaths at the midposterior septum, through which a 10 pole, 20 mm diameter circular mapping catheter and an open irrigated ablation catheter are introduced respectively. In patients with severe LA enlargement, a J-curve ablation catheter is preferred to the usual F-curve ablation catheter. Heparin boluses are given prior to the first and second transseptal puncture and subsequent heparin infusion is started to achieve an activated clotting time $\geq 350\text{ s}$.

**Pulmonary vein antrum isolation**

An ablation strategy that only isolates the PV with spontaneous or provoked AF triggers has been associated with higher recurrence rates.\(^{16}\) These findings led to the current strategy of empirical PVAI for all 4 PVs without provocative measures, in an attempt to reduce AF recurrence (Figure 1). Isolation of the PVs is usually performed in the following order: left superior, left inferior, right superior and right inferior. The circular mapping catheter is placed at the PV antrum-LA junction defined by ICE. RF ablation is performed at sites where PV potentials are recorded in the mapping catheter. With an open irrigated catheter system, a temperature of 45°C and a maximum power of 50 W is used. As the PV antrum is a large structure, multiple movements of the circular mapping catheter are required to identify potentials at various regions of the respective PV antra. An esophageal temperature probe is inserted prior to ablation and to titrate energy delivery during ablation of the posterior wall of the LA. Energy delivery is halted temporary when the esophageal temperature exceeds 38.5°C. Using this approach, we are fortunate not to have any cases of atrio-esophageal fistula thus far. To reduce fluoroscopy, ICE imaging, ablation artifact on the circular mapping catheter and 3D mapping systems (CARTO, NavX) are used as surrogate markers of catheter position. The end point for PVAI is to eliminate potentials at the respective PV antra. Entry block is verified when no PV potentials can be recorded at the antrum or within the PV by the circular mapping catheter. Occasionally, electrical dissociation of the PV from the LA confirms exit block. At the end of the procedure, all four PV antra are extensively remapped to identify remnant or recovered potentials for ablation to achieve complete electrical isolation.

**Non pulmonary vein ablation**

The incidence of non-PV triggers giving rise to AF has been reported to be approximately 20–32%\(^{17}\) (Figure 3). The SVC is a common site for non-PV triggers in patients with paroxysmal AF. In humans, cardiac excitation has been registered up to 5 cm above the anatomical junction of the SVC and RA, defined at the base of the RA appendage.\(^{18}\) It contains atrial myocytes capable of exhibiting

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**Figure 1** Anatomic definition of pulmonary vein ostium and antrum using 3D CT imaging (A) and ICE (B). Note that the right and left pulmonary vein antra include the posterior wall of the left atrium. LSPV: left superior pulmonary vein; RSPV: right superior pulmonary vein.
enhance automaticity and afterdepolarization. In a series of 240 patients who had a total of 359 ectopic foci initiating AF, 20% originated from non-PV sites. Of which the SVC accounted for 37% of these non-PV sites either exclusively or otherwise. RF ablation of the ectopic SVC sites eliminated paroxysmal AF and up to 86.7% of patients with exclusive SVC foci were free of AF without AADs. In our series of 407 patients who underwent catheter ablation for AF, SVC triggers were identified in 12% of the initial 190 patients in the setting of intravenous isoprotenerol up to 20 μg/min. In view of this finding, empirical SVC isolation was performed in the rest of the 217 patients. 16% of these patients had recurrence of AF during long-term follow-up. Of these, 25 patients underwent a repeat procedure and 5 patients were identified to have SVC triggers. Of note 4 out of these 5 patients did not have a prior SVC isolation. At our centre, empirical SVC isolation is performed after PVAI. The catheters and sheaths are pulled into the RA. The SVC is mapped with the circular mapping catheter at the lower border of the pulmonary as identified on ICE. Isolation of the SVC is then performed at this level. High voltage pacing at the lateral portion of the SVC is performed to check for phrenic nerve stimulation as well. If phrenic nerve stimulation is present, these sites are precluded from ablation. Otherwise complete isolation of the SVC is performed.

The crista terminalis (CT), a structure in the right atrium, has been identified as a source of non-PV triggers. These triggers appear to be catecholamine sensitive and have been implicated in the initiation of AF following cardioversion in patients with chronic AF, which was observed in 37.5% of our series of 48 patients, with majority of foci arising from the mid to superior aspect of the CT. In a small series of 5 patients who underwent PVI and SVC isolation, non-contact mapping was used to identify several areas around the crista terminalis, which have spontaneous activity that initiate AF. Subsequent ablation of these sites abolished the CT free of ectopy-initiating AF.

The CS musculature is also an origin of focal atrial tachycardias. Repetitive rapid discharges from the CS musculature may be a potential driver for AF and these triggers have been documented in 2 patients who underwent prior PVI and substrate modification with linear lesions for chronic AF. Electrical disconnection from the adjoining atrial myocardium permanently eliminated drivers maintaining AF. Furthermore, electrical isolation of the CS from the LA has been shown to decrease AF inducibility in patients with paroxysmal AF.

The ligament of Marshall (LOM) is a vestigial structure of the left primitive veins. It runs from the CS superiorly on the posterior wall of the LA to the region near the orifice of the left superior PV. In some cases, this LOM connects to a small auricular vein that drains into the CS. This vein is called the vein of Marshall (VOM). The muscle extensions of the LOM is complex, with multiple myocardial tract insertions into the LA free wall and coronary sinus (CS). These myocardial tracts exhibit electrical activity and may display enhanced automaticity during isoprotenerol infusion. Furthermore, these ectopic potentials have been recorded and ablated in the vicinity of the left superior PV in patients with non-PV triggers. The VOM has also been cannulated to guide mapping and ablation of LOM ectopic activity initiating AF.

The persistent left SVC (LSVC) may generate repetitive rapid discharges that initiate AF. Hsu et al. described the role of persistent LSVC as the arrhythmogenic source of AF in 5 patients after PVI. The LSVC was electrically connected to the lateral LA and via the CS to the RA. The CS-LSVC and LA-LSVC connections were mapped with the
circular mapping catheter and ablation was performed to achieve electrical isolation of the LSVC as confirmed in 4 out of 5 patients. These 4 patients remained in sinus rhythm as a mean follow-up period of 15 ± 10 months without the need of any antiarrhythmic drugs. We described a series of 6 patients with LSVC, 4 of which developed recurrence of AF post PVAI.30) The PVs of these 4 patients were found to be isolated during a subsequent repeat procedure. Spontaneous atrial ectopy was observed in 3 out of 4 patients, of which AF was initiated in one patient. Circular mapping catheter guided RF ablation electrically isolated the LSVC-LA-CS connections. All patients remained in sinus rhythm without any antiarrhythmic drugs at mean follow-up period of 13 ± 7 months.

The LA appendage as a source of ectopy for the maintenance of AF has been described in a single case report. 31) Circumferential ablation of the ostium of the LA appendage eliminated AF resulting in complete electrical isolation as evidenced by dissociated trigger potentials originating from the LA appendage was achieved. At 5 months follow-up this patient remained in sinus rhythm without any thromboembolic events while on anticoagulation.

The inferior vena cava (IVC) has rarely been documented to have AF triggers. A survey of the literature identified 3 cases. In two cases, ectopic activity was mapped to the posterolateral aspect of the IVC ostium and these were successfully ablated.32) In a separate report, non-PV triggers after PVI was mapped to a site deep in the IVC. Focal ablation guided by a circular mapping catheter eliminated the trigger and subsequent IVC isolation was performed at the IVC-RA junction.33) The sinus node region as a non-PV trigger for AF following surgical Maze procedure in patients with chronic AF has been reported. The PVs were found to be isolated while triggers in the sinus node region were identified. Following ablation linear lesions isolation the triggers, AF was eliminated. Unfortunately, the patient had AF recurrence 3 weeks post procedure.34)

Substrate Modification

A survey of the literature has identified strategies in addition to PVI to improve long term success rates without concomitant antiarrhythmic drugs administration. These strategies include extensive or limited linear lesions, ablation of complex fractionated atrial electrograms, regions that display dominant frequency during atrial fibrillation and ablation of autonomic ganglionated plexuses. The following section aims to review the rationale of these strategies, its application and clinical outcome.

Linear ablation

Biatrial surgical Maze procedure pioneered by Cox et al. was effective at segmenting the atria to prevent the occurrence of reentrant activity. Subsequently, modification in this surgical procedure was able to achieve up to 95% success rate at long term follow-up with equivocal results between patients with or without structural heart disease and in paroxysmal or persistent AF.35) This surgical technique forms the basis for percutaneous catheter based techniques in substrate modification.36) Linear lesions were placed in both RA and LA. Although effective, this percutaneous catheter based Maze strategy was limited by long procedural time, high thromboembolic risk and potential proarrhythmia due to incomplete lesion continuity between anatomical obstacles. Adjunctive linear ablation following PVI has been assessed in patients with either paroxysmal or persistent AF. Haissaguerre and colleagues37) performed linear ablation with an open irrigated catheter system to join the superior PVs, which then connect to the anterior mitral annulus in addition to a cavotricuspid isthmus ablation. Complete linear block was achieved in 14 patients (58%) of which 9 (64%) remained AF free without antiarrhythmic drugs at 28 ± 4 months of follow up. Of those who did not achieve complete linear block, only 30% remained AF free. Subsequently, the same investigators assessed the efficacy of mitral isthmus...
Ablation in patients with paroxysmal AF following PVI. Mitral isthmus conduction block was achieved in 88% of the patients, but this approach often required ablation within the CS. This adjunctive ablation strategy safely increased success rate to 79%.38) The strategy of adjunctive LA roof linear lesions and mitral isthmus ablation in addition to wide area circumferential PV ablation has been also demonstrated to effective.39) Ernst et al. created one of four linear ablation configurations with a 4 mm tip catheter using the CARTO electroanatomic mapping system. The long-term success rate in patients with completed linear lesions reached 76%.40)

The Cleveland Clinic performs SVC isolation as an adjunct approach to ICE-guided PVAI. This has been shown to be safe and effective strategy in treating patients with all paroxysmal, persistent or permanent AF.41) This approach has accounted for a long-term success rate of 85.4% in paroxysmal AF and 74.9% in persistent/permanent AF.42) A repeat procedure increases the success rate to 94.6% and 92.9% respectively (Figure 4).

Complex fractionated atrial electrogram ablation

Complex fractionated atrial electrogram (CFAE) during AF as a substrate modifying strategy has been studied. These CFAEs have first been identified during surgical epicardial mapping as sites exhibiting slow conduction, functional conduction block and with pivot points.43) These complex electrical activities exhibit short cycle lengths and heterogeneous temporal and spatial patterns.44) Mapping and ablation of CFAEs has been performed in patients with PAF and chronic AF.45) CFAEs were defined as fractionated atrial electrograms (EGMs) with two or more deflections and atrial EGMs with cycle length <120 msec (averaged over 10 seconds). The CARTO system was used for electroanatomic correlation, dividing the RA and LA into nine distinct areas. Based on CFAE distributions three types were described: Type I CFAEs were found in only one area and focal ablation terminated AF; Type II in two areas; Type III required three or more areas of ablation (PV was one area regardless of how many PVs expressed CFAEs). CFAE ablation terminated AF in 95% patients (28% required concomitant ibutilide). Type III distribution was more commonly identified in patients with chronic AF. The interatrial septum was the most common site for CFAEs, which were not present in the appendages. At the 1-year follow-up, 91% patients were free of arrhythmias and symptoms, with 20% requiring a second procedure.

Ablation targeting dominant frequency sites during atrial fibrillation

Previous investigators have observed that administration of antiarrhythmic drugs can decrease the frequency of fibrillatory waves in the surface ECG. A low dominant frequency (DF) associated with a high degree of organization predicts a higher success rate for electric cardioversion of AF. Such observations were seen in intracardiac recordings of isolated sheep hearts under acetylcholine infusion. In addi-
tion, Jalife et al. provided evidence for spatiotemporal organization due to the presence of AF. They also reported a variable DF between the intracardiac mapping sites and sites with the highest DF are regarded as source of AF. In a series of 32 patients, frequency mapping identifies localized sites of high frequency activity during AF in humans with different distributions in paroxysmal and permanent AF. Patients with paroxysmal AF frequently harbored DF within the PVs. Ablation of these DF sites slowed and terminated 87% of patients with paroxysmal AF but none in those with permanent AF. Spectral analysis and frequency mapping can identify high-frequency activity potentially correlating with rotors responsible for the maintenance of AF. The efficacy of this novel strategy for AF ablation remains to be shown prospectively using real-time spectral analysis.

Ablation of autonomic ganglionated plexuses

Localization and ablation of autonomic ganglionated plexuses (GP) in the LA have been evaluated in animal and clinical studies. The GPs, present in epicardial fat pads, were identified by high-frequency stimulation (HFS—at PCL 50 msec, 12 V, PW 1–10 msec) at the PV and PVA (endocardial and epicardial sites). A positive response to HFS was indicated by induction of AF and/or increased vagal tone leading to bradycardia or AV block. HFS identified GPs at four distinct locations: anterior to the right PVs, inferior to the RIPV (right inferior pulmonary vein), superior and medial to the LSPV, and inferior to the LIPV. For GPs ablation, a median of 2–6 RF applications was required to eliminate the vagal response to HFS. Interestingly, GPs ablation abolished PV firing in 95% of patients, but did not affect sustained AF inducibility either prior to or following PVAI.

In the 33 patients undergoing this combined approach, all patients with PAF and 81% with persistent were AF free at a median follow-up of 5 months. The same investigators had observed that GPs are commonly located within three major CFAE areas of the LA. They have also shown that GP stimulation can automatically induce conversion of PV focal firing to AF and that this response is eliminated by injecting neuronal blockers into the fat pad. Experimental and clinical findings suggest that LA autonomic denervation targeting GPs may downregulate PV firing and suppress AF inducibility. In our clinical experience with HFS, the GP sites identified by vagal response were tagged and blinded to the operator performing ablation. Following our standard PVAI procedure without targeting the GPs, vagal response was abolished in all patients. This suggested nonintentional GP modulation during PVAI. Interestingly, in another group of patients presenting with recurrent AF following PVAI, HFS failed to produce vagal response in all patients. We have also assessed the long-term effect of GPs ablation in a canine model and found that the denervation effects achieved by ablation had disappeared on repeat evaluation at 4 weeks postablation.

Optimizing the cure of atrial fibrillation

The reported successes with various ablation strategies underline the complex pathogenesis of AF. Different centers have utilized various combination ablation strategies to further improve the success rate. Linear LA lesions across areas of CFAE as an adjunct to LA circumferential ablation have been studied in a series of 100 patients with paroxysmal AF. Following LA circumferential ablation to encircle the left and right-sided pulmonary veins during AF, with additional ablation lines in the posterior left atrium and mitral isthmus with an 8-mm-tip catheter were performed. After completing this lesion set AF was still present or induced in 60% of patients. These patients were randomized to either no ablation (Group 2, 30 patients) or further additional ablation lines (Group 3, 30 patients) along the left atrial septum, roof, and/or anterior wall targeting fractionated electrograms. At 6-month follow-up, 67% of patients in group 2 were free of AF without drug therapy compared with 86% of patients in group 3 (p = 0.05).
The same investigators randomized 80 patients with chronic AF to either LA circumferential ablation (n = 40) or nonencircling linear ablation (n = 40).\(^{54}\) In LA circumferential ablation, the PVs were encircled, with additional lines made in the mitral isthmus and posterior wall or roof. In non-encircling linear ablation, 4 ± 1 ablation lines were created targeting areas of complex electrograms with the objective of voltage abatement. Linear lesions were created in the roof, anterior wall, septum, mitral isthmus and posterior annulus. At 9 ± 4 months follow up, 68% of patients who underwent LA circumferential ablation remained free of AF without the need of antiarrhythmic drugs compared to 60% of patients who underwent nonencircling linear ablation.

A stepwise ablation curative approach with high incidence of AF termination has been evaluated in 60 patients with long lasting persistent AF.\(^{55}\) A randomized ablation sequence including PVI, SVC, and CS isolation and atrial ablation at sites exhibiting continuous electrical activity or CFAE terminated AF in 53% of patients. The addition of linear lesions at the LA roof, mitral isthmus, and cavotricuspid isthmus accounted for AF termination in a total of 83% of patients. Termination of AF to either atrial tachycardias or sinus rhythm was typically preceded by lengthening of AF cycle length. Only 13% of patients converted directly to sinus rhythm, while the majority developed atrial tachycardias. Activation and mapping entrainment was subsequently performed to identify its mechanism. Focal atrial tachycardias were localized to the PVs, LAA, and CS and these sites were subsequently ablated. All focal atrial tachycardias were interrupted with up to 2 RF applications. Macroreentrant atrial tachycardias utilized the mitral isthmus, LA roof or the cavotricuspid isthmus and linear lesions were created at these sites. The LAA, CS, and PV-LA junctions contained the initiators of AF in most patients. Lesser critical LA structures included the roof, septum, posterior wall, and mitral isthmus. However, 24 (40%) patients developed atrial tachycardia by 3 months out of which 22 were sustained AT. Of these, 23 underwent repeat procedure of 55 ATs. 4 patients required 3 procedures in total. In these 23 patients, focal AT was localized to similar sites as identified by the first procedure. Similarly, macroreentrant ATs utilized the gaps or recovered conduction of previous linear ablation at the mitral isthmus, LA roof or cavotricuspid isthmus. With this approach, 95% of patients remained in sinus rhythm at 11 ± 6 months of follow-up with majority of them without taking any antiarrhythmic drugs.

At the Cleveland Clinic, AF nest ablation guided by real-time spectral mapping in SR as an adjunctive approach to ICE-guided PVAI and SVC isolation has been evaluated in a randomized. Real-time spectral mapping using fast Fourier transform (FFT) in SR has identified atrial sites with unusually high frequencies, namely, fibrillar myocardium or AF nest\(^{56}\) at the LA appendage, left intraatrial septum, inferior posterior LA along the mitral annulus, SVC/RA junction, crista terminalis and the CS os (Figure 6). The AF nests may exhibit anisotropic conduction and short refractoriness. This highly resonant tissue may harbor sites expressing CFAE during AF. Ablation of atrial tissue identified as AF nests as a sole approach without intentional PVI, has maintained SR in 94.1% patients at 9.9 ± 5 months follow-up. However, 41.1% remained on previously ineffective AAD. Importantly, full lesion thickness is not required to normalize the spectrum and may be less likely to create a substrate for macroreentrant ATs while sparing viable atrial myocardium. RF delivery for 20–30 seconds typically abolishes the high-frequency potentials and normalizes the spectrum of the local bipolar EGM. This approach may be preferable to targeting continuous electrical activity or CFAE sites that may be unrecognized due to their temporal variability. We have been evaluating the adjunctive role of empirical ablation of typical AF nest regions in addition to ICE guided approach to PVAI and SVC isolation in a prospective randomized study. Initial results of 157 patients with persistent or paroxysmal AF were promising. We randomized these patients to either PVAI + SVC isolation + empirical ablation of typical AF nest regions (group 1) or conventional PVAI and SVC isolation (Group 2). The ablation strategy for patients in Group 1 was safe and resulted in significant reduction of AF recurrences as compared to group 2. We eagerly await completion of this study.

### Complications of Catheter Ablation of Atrial Fibrillation

Extensive ablation within the atria coupled with instrumentation with various catheters in the setting of aggressive anticoagulation during AF ablation sets the stage for potential complications. A variety of these complications have been reported and some of them have been fatal. While the majority occurred during or within 48 hours of the procedure, some are known to have an insidious course. This section reviews these complications with an objective to suggestive preventive and definitive measures.
Cerebrovascular events

The incidence of thromboembolism in AF ablation ranges from 0.5 to 2.8%.\(^{57}\) A worldwide survey reported periprocedural deaths due to massive cerebral thromboembolism in two patients out of 8745 patients.\(^{58}\) Prevention remains the best strategy in reducing thromboembolic events during AF ablation. At our centre, warfarin therapy is not discontinued prior to ablation. If patients with persistent AF arrive to the EP laboratory with a non-therapeutic INR, a TEE is performed prior to the ablation procedure to exclude any intra-atrial clots. Prior to the first transseptal puncture, a bolus of heparin of about 100 mg/kg is given and an infusion is started to maintain an ACT of 400 to 450 s. Both transseptal sheaths are continuously perfused with heparinized saline and meticulously flushed when catheters are exchanged. In addition, we minimize char formation during lesion creation by titrating power delivery to prevent abrupt impedance rise. ICE is routinely used for early detection of intra-cardiac thrombi. Despite these measures, we report a cerebral thromboembolic rate of 0.6% in 3060 patients who underwent PVAI at our centre (unpublished data). Only two deaths were reported, one within one month and the second death occurred 4 years after the procedure. The rest of the patients experienced full neurological recovery.

PV stenosis

The incidence of PV stenosis, defined as >70% narrowing, was reported to occur in 3.4%\(^{59}\) of patients. The pathogenesis of PV stenoses is due to an initial ablative insult that precipitates a healing reaction culminating in an endovascular contraction and proliferation of elastic lamina/intima. The incidence of PV stenosis has decreased due the current technique of PVAI that targets antra far from PV ostia. Clinical diagnosis of PV stenosis is often difficult and a high index of suspicion is required.

Figure 6

Panel A: The typical locations exhibiting fibrillar myocardium (AF nest) during real-time spectral mapping in sinus rhythm, following PVs and SVC isolations, are shown in a segmented 3D contrast cardiac CT of a patient presenting for AF ablation. Note in Panel B, the frequency spectra of two consecutive bipolar electrograms recorded from the CS (arrow in Panel C). The high-frequency components characteristic of AF nests are indicated by the arrow in Panel B. Radiofrequency delivery up to 35 W for 20 seconds eliminated the fibrillar pattern (shown in Panel D).
These patients present a variety of respiratory symptoms, including cough (89%), hemoptysis (63%), dyspnea (58%), pleuritic chest pain (58%) and wheezing (42%). However up to a third of patients with severe PV stenosis remained asymptomatic while symptomatic patients were erroneously diagnosed as having pneumonia, new onset asthma, pulmonary embolism and/or lung cancer. At present, the gold standard for diagnosis of PV stenosis is spiral computed tomographic angiography and/or magnetic resonance. In a series of 23 patients with severe PV stenosis, balloon angioplasty alone or with stenting immediately relieved symptoms. However, in-stent or in-segment stenosis occurred in 61% of patients during a 17-month follow-up. Neumann et al. reported the long-term outcome of primary angioplasty versus primary angioplasty with PV stenting for symptomatic severe PV stenosis in 12 patients with a total of 15 PV stenoses. PV stenting resulted in no restenosis over the 12-month follow-up while those who underwent PV angioplasty had a high recurrence rate of 73%.

We recently described 18 patients who progressed to total PV occlusion, defined as ≥95% stenosis or complete loss of patency of the PV on CT scan. Of 1,780 patients who underwent AF RF ablation during the period of 1999 to 2004 at our institution, 16 (0.9%) were found to have pulmonary vein occlusion (PVO) of at least 1 PV, whereas 2 additional patients were referred from other institutions for further evaluation and management of their occluded PVs. The clinical presentation of these patients was variable: 4 (22.2%) patients were totally asymptomatic throughout their course (defined as grade 0), 2 (11.1%) had mild symptoms of dry cough or dyspnea on moderate/severe exertion (NYHA class I; grade 1), 4 (22.2%) had moderate symptoms of dyspnea on mild exertion (NYHA class II/III), together with persistent cough (grade 2). Three (16.7%) patients had severe symptoms as severe dyspnea (NYHA class III/IV) with hemoptysis, fever, or pleuritic chest pain (grade 4) at their initial presentation, whereas 5 other patients (27.8%). CT scan identified a total of 24 occluded veins in 18 patients, with a mean of 1.4 veins per patient. Of these 24 occluded veins, the left superior PV had the greatest incidence of occlusion (54.2%), followed by the left inferior PV (29.2%), right inferior PV (8.3%), and the right superior PV (8.3%). By considering the total venous drainage of each independent lung, the percentage of stenosis of the affected veins on the same side were added together to yield an average cumulative stenosis of the vascular cross-sectional area draining the affected lung (cumulative stenosis index [CSI]). CSI = sum of percent stenosis of the unilateral veins divided by the total number of ipsilateral veins. We concluded that patients with a CSI ≥ 75% and a relative lung perfusion of ≤25% based on lung perfusion scan have the greatest risk of severe symptoms and lung diseases. In these patients, early and, when required, repeated PV intervention should be considered for restoration of pulmonary flow and prevention of associated lung disease.

Esophageal injury and fistula

The posterior wall of the LA is adjacent to the esophagus and RF ablation procedures may substantially elevate the temperature within the esophageal lumen (Figure 7). Atrial-esophageal fistulas may result from this thermal injury leading to tissue necrosis. Esophageal damage, perforation, and atrioesophageal fistulas were first described after posterior left atrial radiofrequency ablation performed during open-heart surgery. Subsequently, three patients with this complication after percutaneous radiofrequency catheter ablation from experienced centers were published in 2004. We reported a series of 9 patients who had this devastating complication via an anonymous volunteer reporting method. Clinical presentations occurred within about 2 weeks of the ablation procedures (mean, 12 days [range, 10 to 16 days]). Patients presented with general malaise, leukocytosis, and persistent fever of undetermined origin. All patients developed septic shock and cardiovascular collapse. Eight patients had neurologic findings consistent with multiple embolic strokes. Of these, 2 had intravascular air on computed tomography. Six patients had echocardiographic features of endocarditis. Two patients presented with symptoms consistent with transient angina associated with ST-segment elevation on electrocardiography. Three patients reported substantial gastrointestinal bleeding, but five patients had occult bleeding documented by fecal testing. Unfortunately, all 9 patients died and autopsy confirmed the presence of atrioesophageal fistula.

Although atrioesophageal fistula formation is apparently rare, it seems to almost always be fatal. Therefore, evaluation and management of patients presenting with this potential complication must focus on rapid diagnosis and triage. Fever, malaise, leukocytosis, dysphagia, and neurologic symptoms in patients with a recent catheter ablation procedure should raise suspicion of atrioesophageal fistula. The diagnosis must be rapidly confirmed by noninvasive imaging techniques, including transthoracic echocardiogram, magnetic resonance imaging, or com-
puted tomographic scan, especially when combined with water-soluble contrast.\(^{68}\) Any form of esophageal instrumentation should be avoided in these patients. Once diagnosed, prompt surgical intervention is required. Recently, a case of successful temporary esophageal stenting to seal off the esophageal perforation following LA catheter ablation was reported.\(^{69}\)

We studied the influence of LA ablation by measuring intraluminal temperature via an esophageal thermometer in 81 patients who underwent PVAI.\(^{70}\) The esophageal intraluminal temperature was significantly higher when ablation was performed at the posterior LA, adjacent to the esophagus. This was also associated with microbubbles generation detected by ICE. We concluded that titration of RF delivery with ICE in non open irrigated catheter systems and/or continuously monitoring esophageal temperature may be an option to enhance safety for posterior LA wall ablation. Since utilizing this strategy, we report no atrioesophageal fistulas. Alternative strategies in visualizing the esophagus during AF ablations include ingestion of Gastrografin dye, tagging the esophagus on 3D electroanatomic mapping system and merging 3D recreated image of the esophagus with an electroanatomic shell of the LA.

Pericardial effusion and cardiac tamponade

Pericardial effusion is not uncommonly observed in patients undergoing AF ablation. However, the reported incidence of cardiac tamponade is 1.22% (Worldwide survey of AF ablation). The common mechanisms include cardiac perforation by various catheters or steam pops. We identified 26 (7.4%) out of 352 patients who had steam pops over a three-month period during RF ablation for AF.\(^{71}\) There were 44 steam pops at these locales: left interatrial septum (36.4%), PVA area (20.5%), right atrium (18.2%), left atrial roof (11.4%), left atrial posterior wall (6.8%), mitral annulus (4.5%) and left atrial anterior wall (2.3%). Majority (>90%) of pops occurred with the catheter orientated perpendicularly to the tissue. Seventy-five percent of these pops occurred with a power \(\geq 35\, \text{W}\), temperature \(\geq 39\, ^\circ\text{C}\) and impedance \(\geq 90\, \text{ohms}\). There was not an observable decrease in impedance prior to steam pops and no acute procedural complications. Preventive strategies include titrating RF energy to prevent sudden impedance rise during ablation. In open irrigated catheter systems, we do not observe such rise in impedance prior to the occurrence of steam pops. Titrating RF energy to prevent sudden rise in catheter tip temperature may be a more practical option.

Organized atrial tachyarrhythmias

Left atrial tachycardia (AT) following segmental or wide area circumferential PVI and LA circumferential ablation with additional linear ablation has been variably reported as ranging from 2.5% to 27%. The mechanism of these ATs has been described as macroreentry AT due to reentry related to gaps in the linear ablation line. These gaps have been identified as a slow conduction isthmus in the reentry circuit primarily located at the LA posterior wall or mitral isthmus. These macroreentry ATs are often symptomatic necessitating a repeat ablation. On the other hand, focal ATs typically originate from PV ostial segments that have partially recovered conduction.

Figure 7 Three-dimensional computed tomographic reconstruction of the left atrium in relation to the esophagus.
to the LA. Of note, centers that adopt a strategy of wide area circumferential PV ablation and linear LA ablations\textsuperscript{72,73} appear to experience an increased prevalence of AT. This may imply that the inability to create contiguous linear lesions and/or recovery of partial conduction along such lesions can be proarrrhythmic. We adopt the strategy of PVAI without empirical linear lesions in the LA in an effort to minimize the incidence of iatrogenic AT in our centre.

Phrenic nerve injury

Phrenic nerve injury (PNI) is a rare complication that may occur as a result of different catheter ablation procedures. The course of the right phrenic nerve is lateral and slightly posterior to the SVC and RA, and descends anteriorly to the right superior PV near the right superior PV-LA orifice alongside of the pericardium, anterior to the lung hilum before reflecting into the right diaphragm.\textsuperscript{74} Sanchez-Quintana et al.\textsuperscript{75} showed that the minimum distance between the right phrenic nerve and the right superior PV or SVC was shorter than that between the right phrenic and right superior PV-LA or SVC-RA junction.

We studied 17 patients who sustained PNI following catheter ablation with a variety of energy sources including RF ablation (13 patients), cryoablation (1 patient), ultrasound balloon ablation (2 patients) and laser balloon ablation (1 patient).\textsuperscript{76} Two patients with RF ablation-induced transient right phrenic nerve paresis were detected on fluoroscopy during energy delivery. Diaphragmatic movement spontaneously recovered upon cessation of RF delivery. The temporal correlation with onset and offset of energy delivery and the observed transient nerve dysfunction may suggest a current mediated electromagnetic effect. RF currents can alter the action potential duration and amplitude of the nerve, thus producing a conduction block before injury takes place.\textsuperscript{77} Symptoms of PNI are variable depending on patient’s preexisting lung condition. Fifty percent of our patients were asymptomatic while the majority of the remaining patients had mild symptoms and did not need special therapy. Only two patients developed lung complications that required respiratory treatment. In our experience, all patients who suffered from persistent PNI due to catheter ablation clinically recovered within a median time of 6 months.

Early detection of transient PNI by fluoroscopy could result in fewer cases of persistent PNI. While high-output pacing prior to ablation in certain cases is a valuable tool to prevent phrenic nerve damage, the most effective way is to deliver energies away from the phrenic nerve. Ablation at the level of the PV antrum or the SVC-RA junction when performing isolation of these veins for AF could represent a potential strategy to minimize the risk of PNI. A novel method of protecting the phrenic nerve during epicardial catheter ablation by using a balloon catheter in the pericardial space to mechanically separate the left phrenic nerve from the ablation catheter has been recently reported.\textsuperscript{78}

Other complications of extracardiac damage included four patients in whom acute pyloric spasm and gastric hypomotility were observed following posterior LA lesions.\textsuperscript{79}

Energy Sources for AF Ablation

Radiofrequency ablation is widely used in catheter ablation of atrial fibrillation. The placement of ablation lesions may be tedious and time consuming especially in patients with persistent AF. Contact with the atrial tissue is paramount to effective energy delivery for creation of transmural lesion. As such, non-transmural lesions in linear ablations are proarrrhythmic to macroreentrant atrial tachycardias. The risk of thrombus formation occurs especially when the electrode-tissue interface exceeds 80°C. With RF ablation there is a risk of cardiac perforation associated with the use of high power in the LA. Such limitations create an impetus to develop technologies that use alternative forms of energy delivery. Any technology that can create uniform and transmural lesions, decreases the need of contact to deliver sufficient energy, reduces procedure time and improves safety (Table 1).

Ultrasound energy

Ultrasound propagates sound waves at 2 to 20 MHz to cause oscillation of molecules and atoms for heat generation. Ultrasound energy decreases proportionally with distance, unlike that of RF energy that decreases by the square of the distance. Perhaps, the main advantage is its ability to be collimated as it passes through a fluid media. This forms the basis of a High-Intensity Focused Ultrasound Balloon Catheter (HIFU-BC) for PVAI in patients with AF. A feasibility study including 27 patients with AF has just been reported.\textsuperscript{80} The 14 Fr HIFU-BC has been developed to simplify PVAI with lower risk of thrombus formation, PV stenosis and left atrial perforation.\textsuperscript{81} It uses a parabolic watercarbon dioxide balloon interface to focus a 20,25 or 30 mm diameter ring of ultrasound 2 to 6 mm forward of the balloon to produce a circumferential
transmural LA lesions with each application. The HIFU-BC successfully isolated all PV antra in 74% of patients. At 12 months follow-up, 57% of patients were free of symptomatic atrial arrhythmias. There were no PV stenosis or thromboembolic complications. One patient sustained pulmonary hemorrhage due to perforation of the lingular branch of the left superior PV during manipulation of the guidewire. There was a case of phrenic nerve palsy in a patient with a usually large right superior PV. The main advantages were low risk of thromboembolism since no direct heating of blood occurs to form thrombus. Internal irrigation of the balloon also minimizes formation of thrombus on its surface. Complete circumferential contact is not required for lesion placement. The limitations include the need to position the HIFU-BC over a guidewire necessitating instrumentation of individual PVs, non-deflectable and difficulty in completely sonication of the left PVs as the balloon often extended over the LA appendage ridge, leaving a small segment non-isolated. Improvement in the design incorporating a deflectable curve may produce better results.

Cryoablation

Cryoablation causes direct cell injury and induces vascular mediated tissue injury. The advantages include minimal endocardial disruption with preservation of underlying tissue architecture, less platelet activation, lower thrombogenicity and stable adhesion of the catheter to the tissue during freezing. Recent clinical studies have shown that transvenous cryoablation is a safe and feasible method for PV isolation with acute procedural success comparable to conventional RF ablation. Although the long-term success rate appeared to be lower, no patients developed PV stenosis. Further refinement of catheter designs to improve/increase tissue contact surface area or delivery of lower temperature may improve its efficacy.

Microwave energy

Microwave generates heat by inducing oscillation of dipoles in a medium such as water. Hence, tissue with high water content will allow better energy transfer and heat generation. This may be useful in scarred myocardium, as viable myocardium will be

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Table 1 Features of different energy sources for catheter ablation of atrial fibrillation.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Radiofrequency</th>
<th>Cryothermy</th>
<th>Laser</th>
<th>Microwave</th>
<th>Ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Experience</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Potential for endocardial disruption</td>
<td>High</td>
<td>Lower</td>
<td>Low</td>
<td>Low/medium</td>
<td>Low</td>
</tr>
<tr>
<td>Thrombogenicity</td>
<td>High</td>
<td>Low</td>
<td>High</td>
<td>Medium</td>
<td>Medium</td>
</tr>
<tr>
<td>Mapping capability</td>
<td>Limited</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ability to Create transmural lesions</td>
<td>Requires optimal contact</td>
<td>Requires optimal contact</td>
<td>Requires optimal contact</td>
<td>Optimal contact and orientation preferred</td>
<td>Required optimal Orientation</td>
</tr>
<tr>
<td>Lesion size</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Linear lesion</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Perforation rate</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Procedure time</td>
<td>Short</td>
<td>Long</td>
<td>Short</td>
<td>Medium</td>
<td>Short</td>
</tr>
<tr>
<td>Injury to adjacent structures:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phrenic nerve</td>
<td>++</td>
<td>–/+</td>
<td>+/−</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Esophagus</td>
<td>+++</td>
<td>–</td>
<td>+/−</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Coronary artery</td>
<td>+++</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>PV stenosis</td>
<td></td>
<td></td>
<td></td>
<td>Comb. with electromagnetic interference</td>
<td>Comb. with ultrasound system for direct lesion visualization</td>
</tr>
<tr>
<td>Other advantages</td>
<td>+++</td>
<td>Lack of electromagnetic interference</td>
<td>Combined with fiberoptic catheter for direct lesion visualization</td>
<td>Combined with ultrasound system for direct lesion visualization</td>
<td></td>
</tr>
</tbody>
</table>

+ = Positive; − = negative
preferentially heated, creating deeper lesions with less surface heating and subsequent endocardial disruption or coagulation formation. Unlike RF ablation in which lesion expansion was minimal after 60 s, the depth of microwave lesion size could still expand in depth. This may potentially damage adjacent structures such as the esophagus, phrenic nerve and coronary arteries. Although tissue contact with the catheter is of less importance, a parallel antenna orientation to the tissue is required for effective heating. Microwave ablation in the surgical treatment of AF has been proven to be safe and effective with similar clinical efficacy comparable with conventional RF ablation. However, currently there is limited data on transvenous microwave catheter ablation and it remains an investigational product.

**Laser energy**

Laser (light amplification by stimulated emission of radiation) emits photons in a monochromatic coherent beam. Absorption of laser energy creates heat by induction of oscillation in water molecules. It could potentially create deeper lesions with reduced coagulum formation. In experimental model, lesions created are sharply demarcated without epicardial crater or endocardial thrombus formation. Laser energy delivery requires a fiberoptic system that can double up as an angioscopy. Diode laser is a low energy laser with a wavelength of 980nm. Using a linear diffuser, linear ablation can be delivered. Recently, a laser balloon catheter has been designed to allow PV isolation by delivering circular beams of energy at the PV antra. However, clinical experience in humans is scarce and the use of laser energy in a fiberoptic balloon catheter ablation for PV isolation remains an investigational tool.

**New Antiarrhythmic Agents for Treatment of AF**

**Dronedarone**

Dronedarone is a new synthetic non-iodinated derivative of amiodarone undergoing phase III clinical trials. Similar to amiodarone, dronedarone possesses in vitro electrophysiologic characteristics of all four classes of antiarrhythmic action. Specifically, it blocks sodium channels at rapid pacing rates, prolongs cardiac action potentials and refractoriness, and possesses Ca$^{2+}$ antagonistic properties. Additionally, dronedarone shows a non-competitive antiadrenergic action. Dronedarone at the dose of 400 mg twice daily was effective in preventing both symptomatic and asymptomatic recurrences of atrial fibrillation or atrial flutter and had a safety profile similar to that of placebo. The added advantage was an absence of thyroid and lung side effects. Moreover, there was no proarrhythmic effects or torsades des pointes seen and its effect on QT prolongation is at most modest. However, in the ANDROMEDA trial, patients with recent class III or IV congestive heart failure and left ventricular ejection fraction < 35% had an excess mortality with dronedarone therapy vs placebo, leading to early discontinuation of the trial. Hence, further experimental studies and long-term clinical trials are required to provide additional evidence of efficacy and safety of dronedarone.

**Azimilide**

Azimilide is another investigational Class III antiarrhythmic agent. It blocks the slow delayed rectifier potassium current (IKs) in addition to the rapid delayed rectifier outward potassium current (IKr). Initial studies showed promising results in prolongation in the time to the first recurrence of AF or atrial flutter compared with placebo with acceptable risk of torsade de pointes (0.9%) and early reversible severe neutropenia (0.2%). However, recent trial showed otherwise. 658 patients with symptomatic persistent atrial fibrillation were randomized to either placebo, azimilide or sotalol and all received planned cardioversion. Median time to AF recurrence was 14 days for azimilide, 12 days for placebo, and 28 days for sotalol. Of note, 5 patients on azimilide developed torsades de pointes and marked QTc prolongation occurred in 3.5% of patients on sotalol and 7.6% on azimilide resulting in interruption of the study. These investigators concluded that azimilide is slightly inferior to sotalol with at modest antiarrhythmic effect, thus limiting its administration for the treatment of AF.

**Future Directions**

Curative AF ablation requires significant expertise in operator skills, various ablation tools and imaging to deliver safe and effective therapy. It will be ideal to pursue tools to shorten procedure time while delivering effective lesions safely, thereby avoiding potentially life threatening or limiting complications. Remote magnetic navigation (Stereotaxis, Inc., St. Louis, MO, USA) and the robotic steerable guide catheter (SGC, Hansen Medical, Inc., Palo Alto, CA, USA) are two technologies that could greatly facilitate movement of intracardiac catheter. Research on different energy delivery systems is ongoing and we are hopeful of an ablation tool that
creates larger area of lesions in a controlled fashion. Ablation strategies incorporating a combination of PV isolation and various forms of substrate modification for treatment of persistent AF are under investigation.

Acknowledgements

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Table 1: Reproduced with permission from Journal of Cardiovascular Electrophysiology

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