Improvements In Af Ablation Outcome Will Be Based More On Technological Advancement Versus Mechanistic Understanding

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Abstract
Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. Catheter ablation has proven more effective than antiarrhythmic drugs in preventing clinical recurrence of AF, however long-term outcome remains unsatisfactory. Ablation strategies have evolved based on progress in mechanistic understanding, and technologies have advanced continuously. This article reviews current mechanistic concepts and technological advancements in AF treatment, and summarizes their impact on improvement of AF ablation outcome.

Introduction
Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. The last 15 years witnessed advances in mechanistic understanding and technology that fueled the rapid development and refinement of catheter ablation therapy of refractory AF. Despite its status as gold standard and an increasing body of evidence on greater effectiveness over antiarrhythmic drug therapy in preventing clinical recurrence of AF, long-term success rates of catheter ablation remain unsatisfactory. This article highlights current mechanistic concepts and technological advances in AF treatment.

Mechanisms of Atrial Fibrillation
AF is a complex arrhythmia with multiple possible mechanisms including, from an electrophysiological perspective, multiple propagating wavelets, focal electrical discharges, and local reentrant activity, among others. Great progress in mechanistic understanding came with demonstration by Haissaguerre and co-workers that pulmonary veins (PVs) play a critical role in AF generation in humans and that AF could be treated by ablation therapy. PVs and surrounding atrial tissue consequently became the major focus of AF mechanistic research.

It is well accepted that onset and maintenance of AF require both a trigger and a substrate. P, transitional, and Purkinje cells endow human PVs with potential for ectopic beat initiation while muscular discontinuities and abrupt changes in fiber orientation in PVs and the PV-left atrium (LA) junction provide ideal substrates for reentry. Although ectopic beats also can originate in other anatomical structures, including LA posterior wall, superior vena cava, crista terminalis, ligament of Marshall, coronary sinus ostium, and interatrial septum, the PV-LA junction has the highest density of autonomic innervation, and autonomic nerve stimulation which is thought to play an important role in AF initiation can initiate PV firing.

Clinically, abolition of vagal reflexes around PVs during circumferential pulmonary vein isolation (CPVI) benefits AF ablation outcome; this has been further supported by studies directly targeting ganglionated plexi (GP).

Self-perpetuation through induction of atrial structural and electrical remodeling also is an important mechanism for AF. This mechanism undermines outcomes of ablation therapy for AF, as particularly reflected in higher recurrence rate after targeting PV and/or non-PV triggers alone in patients with persistent and long-standing persistent AF.

Ablation Strategies and Their Bottleneck
Based on progress in mechanistic understanding, ablation strategies have evolved from early attempts at replicating the surgical Maze procedure to modification of the trigger(s) and/or substrate for AF.

Ablation Strategy Targeting PV
The crucial role of PVs in AF initiation has rendered ablation targeting PVs and/or PV surrounding atrial tissue as cornerstone procedure in AF treatment. Because of infrequent AF inducibility, difficulty in mapping original triggers, and risk of PV stenosis, the ablation site however has shifted from the PV itself to the atrial tissue located in the antrum. Of the two PV ablation strategies initially proposed, namely segmental and circumferential, the latter is more widely accepted and associated with higher success rate as shown in a randomized study. The larger circumferential area of isolation around PVs not only eliminates PV foci but also contains more of the atrial myocardium surrounding the PVs, i.e., the area with autonomic innervation and substrates for reentry.

The recommended PV ablation endpoint of electrical isolation in PVs is achieved in most cases. However, there is high incidence of...
PV reconnection in patients with clinical recurrence, which is implicated as its predominant mechanism.\textsuperscript{29, 30} Achievement of durable PV isolation, likely requiring continuous and transmural lesion formation, therefore is considered an important goal of AF ablation.

Ablation Strategies Not Targeting PVs

Non-PV Triggers

Non-PV triggers, including LA posterior wall, superior vena cava, crista terminalis, and ligament of Marshall among others, can be identified in some patients during the ablation procedure.\textsuperscript{10} Although it is recommended to eliminate them,\textsuperscript{26} as is the case for PV foci they are infrequently induced and difficult to localize with positioned catheters during routine AF ablation procedures.

Ablation Of Complex Fractionated Atrial Electrogam (CFAEs)

CFAEs, initially reported by Nademanee et al, are defined as electrograms with highly fractionated potentials or with a very short cycle length (<120ms).\textsuperscript{31} Areas with CFAEs are considered substrate for AF maintenance, and their ablation in addition to PVI or as a part of stepwise approach appears beneficial in treatment of non-paroxysmal but not of paroxysmal AF.\textsuperscript{32, 33} However, definitions of CFAEs and endpoints of ablation are inconsistent among trials, extensive areas might be targeted and become arrhythmogenic, and CFAEs mechanism is not totally understood.\textsuperscript{32-34}

Linear Ablation

The most common lines in AF ablation are the mitral isthmus (sometimes replaced by anterior line between roof line and mitral annulus), LA roof and cavotricuspid isthmus lines. Linear ablation, although not recommended for paroxysmal AF because of possible increased atrial tachycardia,\textsuperscript{35} benefits outcome when added to PVI in patients with persistent AF.\textsuperscript{36, 37} The key for linear ablation is line completeness with bi-directional block, which is sometimes challenging.

GP (ganglonated plexi) Ablation

Based on evidence from animal and clinical studies,\textsuperscript{16, 38} recent studies have focused on ablation of GP identified by high-frequency electrical stimulation causing marked slowing of ventricular response during AF\textsuperscript{39} or by an anatomic approach.\textsuperscript{17} Clinical results are inconsistent among studies using GP ablation alone,\textsuperscript{17, 40} while its addition to PVI increases AF-free survival in patients with paroxysmal AF,\textsuperscript{19, 41, 42} and it is superior to PVI plus linear ablation in patients with persistent or long-standing persistent AF.\textsuperscript{43} However, 14.7%\textsuperscript{41} and 26%\textsuperscript{39} of patients with paroxysmal AF experienced AF recurrence in the PVI plus GP ablation group at 12 and 24 months follow-up, respectively, while 66% of patients with persistent AF experienced AF recurrence at 3 years follow-up.\textsuperscript{43}

Concerns about GP ablation include knowing which substrate is destroyed when ablation is performed endocardially; potential autonomic tone imbalance; autonomic reinnervation; and safety of high-power used.

Rotors

Using a recently developed physiologically-guided computational approach, Narayan et al. revealed sustained electrical rotors and repetitive focal beats during human AF; focal impulse and rotor modulation (FIRM)-guided ablation at patient-specific sources acutely terminated or slowed AF, and improved long-term outcome.\textsuperscript{44, 45} Their findings provide novel mechanistic insight into AF.

Technological Advances

Advances in RF (Radiofrequency) Ablation Systems

Radiofrequency is the most-commonly used energy for AF ablation.\textsuperscript{26} As compared to ablation of atrioventricular reentry and non-reentry tachycardia, AF ablation requires multiple, larger and transmural lesions. To this end and relative to conventional 4mm tip ablation catheters, irrigated-tip catheters are more efficient by maintaining a low electrode-tissue interface temperature and impedance during RF application at high power;\textsuperscript{46} and patients undergoing AF ablation with irrigated-tip catheters are less likely to experience AF recurrence.\textsuperscript{47}

Most centers currently use irrigated-tip catheters in AF ablation procedures. Several electrode architectures have been developed with different tip dimensions, temperature sensor location and design of irrigation ports on the tip surface; however, only slight differences have been found in lesion size or safety profile among catheters tested in vitro.\textsuperscript{48}

There is no definitive clinical evidence on which technology is associated with better outcomes or less complications, and all traditional irrigated catheters have been unsatisfactory in achieving long-term success in AF ablation. Besides mechanistic complexity of AF in humans, effect of RF ablation is influenced by transmurality and continuity of lesions created, and most AF recurrence is thought to be related with PV-LA reconnection after initially successful PVI.\textsuperscript{49, 50}

One of the most anticipated features of new-generation irrigated catheters has been contact-force sensing, which helps optimize electrode-tissue contact and provides the operator more quantifiable energy delivery.\textsuperscript{51-53} In clinical trials, contact force information guidance reduced AF recurrence by 20 to 25 percent,\textsuperscript{54, 55} and similarly important, yields more favorable procedural parameters, in particular procedural and fluoroscopy times, without increasing complications (Figure 1).\textsuperscript{54-56}

Because outcome of ablation also is dependent on LA architecture and catheter stability, an auxiliary system for RF ablation mainly including a nonfluoroscopic three-dimensional mapping system and
Cryoballoon technology, developed to simplify and stear the ablation catheter, improved 1-year outcome after AF ablation. The CARTO and the Ensite NavX 3-dimensional systems have been used extensively. With system version updates, efficiency and precision both in atrial geometry reconstruction and catheter guidance have improved continuously, benefiting from technological advances in data collection rate, catheter visualization, gauging and compensation technique, among others. The recently introduced sensor-based electromagnetic tracking system, the MediGuide technology, is easy to integrate into the workflow of AF ablation and allows high-quality nonfluoroscopic 4D catheter tracking while significantly reducing radiation exposure of patients and staff. Also, steerable sheath technology designed to facilitate catheter access, stability, and tissue contact during AF ablation might lead to higher clinical success rate.

**Advances In Other Ablation Systems**

Although RF catheter ablation is used worldwide as standard of care in AF treatment, it leaves room for improvement. The RF catheter ablation procedure is time-consuming and highly dependent on operator’s experience while major complications such as cardiac perforation, PV stenosis, stroke, atraioesophageal fistula and phrenic nerve injury cannot be completely avoided. Also, steerable sheath technology designed to facilitate catheter access, stability, and tissue contact during AF ablation might lead to higher clinical success rate.

Several mapping catheters have been developed for AF ablation. Multipolar catheters, such as Double-loop catheter (Inquiry AFocus IT™, St. Jude Medical, Minneapolis, MN, USA), and Pentaray catheter (PentaRay, Biosense-Webster, Diamond Bar, CA, USA), can improve electroanatomic information collection, which is beneficial for cardiac chamber building, activation analyzing, and voltage/substrate mapping. Another multipolar basket catheter (Constellation, Boston Scientific, MA, USA) has been recently used for FIRM mapping of AF, and along with a novel system (RhythmView, Topera Medical, Lexington, Massachusetts) found to improve long-term outcome of AF ablation.

**Conclusion:**

The mechanism of AF is still not totally understood. Under the present mechanistic understanding, ablation therapy has been documented as an effective treatment, although its long-term outcome especially after the initial procedure remains unsatisfactory. Multiple procedures with current strategies appear to yield more acceptable outcome, and technological advances appear to offer greater impetus to AF ablation outcome improvement than deeper mechanistic understanding. Although indeed we do not fully understand the mechanism of AF, we aim to develop tools to personalize AF treatment (when and what additional ablation is needed), improve outcomes and reduce complications. Technology has helped and will hopefully path the way to that direction.

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