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Ablation of Atrial Fibrillation

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Abstract

Ablation is increasingly used to treat AF, since recent trials of pharmacological therapy for AF have been disappointing. Ablation has been shown to improve maintenance of sinus rhythm compared to pharmacological therapy in many multi center trials, although success rates remain suboptimal. This review will discuss several trends in the field of catheter ablation, including studies to advance our understanding of AF mechanisms in different patient populations, innovations in detecting and classifying AF, use of this information to improve strategies for ablation, technical innovations that have improved the ease and safety of ablation, and novel approaches to surgical therapy and imaging. These trends are likely to further improve results from AF ablation in coming years as it becomes an increasingly important therapeutic option for many patients.

1. Introduction

Ablation therapy is widely used to treat atrial fibrillation (AF), a disease that affects approximately 30 million individuals worldwide¹ and is a major cause of stroke, heart failure and death. The use of ablation has been encouraged by the disappointing results of important trials that question both pillars of pharmacological therapy – to strictly control ventricular rate² or to maintain sinus rhythm^{3, 4}. Buoyed by the success of ablation for 'simple' supraventricular and ventricular arrhythmias, ablation is increasingly used for AF⁵ and is superior to pharmacological therapy for patients with early (paroxysmal)^{6, 7} to advanced (persistent) AF⁸. Nevertheless, fibrillation is a complex disease and the overall success of ablation remains lower⁹ for AF than for other arrhythmias^{6, 7, 10-13} – despite remarkable successes in individual patients. This has fueled a vibrant culture of intense

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patient-focused translational research that has characterized the field since its earliest days¹⁴⁻¹⁶. This review addresses trends in the field of catheter ablation, focused on defining AF mechanisms and translating them to improved strategies to ultimately improve outcomes in individual patients.

2. Explaining the Diverse Trends in AF Ablation Success Rates

The success of AF ablation is widely quoted as 60-80% at 1 year for multiple procedures (average of 1-2) and 40-60% at 1 year for a single procedure^{12, 17}. However, these figures mask a remarkable heterogeneity between patients (figure 1). The most common approach to AF ablation is pulmonary vein isolation (PVI) to prevent triggers from the pulmonary veins from initiating AF (figure 2). However, data consistently show that this uniform procedural goal, applied with the same diligence by experienced operators, may produce robust long-term result in one patient yet minimal impact in another with the same AF 'type'. In experienced centers, single-procedure success at an average of 2 years ranges from $\approx 44\%$ to $\approx 63\%$ (average 54%) in paroxysmal AF, and more widely from $\approx 25\%$ to $\approx 61\%$ (average 42%) in persistent AF¹⁷. Although procedural variations such as additional lesions (figure 2C) contribute to heterogeneity, it is not clear that they drive it^{18, 19}.

An important trend in improving ablation outcomes is to attempt to define which subset(s) of patients will benefit – i.e. to classify patients functionally in those whose mechanisms may be eliminated by a specific therapy. AF is currently classified into paroxysmal AF, that self-limits in < 7 days, persistent AF, that is continuous for > 7 days and requires interventions to terminate it, and longstanding persistent AF, that is continuous for > 1 year²⁰. Although straightforward, this classification yields therapeutic confusion: 46% of patients with paroxysmal AF do not respond, yet 42% of patients with persistent AF do respond to a single PVI procedure¹⁷. These limitations largely reflect the dependence of this classification on temporal trends of AF that are dependent upon the methods used to detect AF, rather than on mechanisms. AF is often asymptomatic^{21, 22}, and intense monitoring shows that many patients with persistent ('continuous') AF actually have intermittent sinus rhythm – and may even regress to paroxysmal AF²³. A recent study using sensitive implanted continuous ECG recorders showed poor correlation between the clinical diagnosis of 'paroxysmal' and 'persistent' AF and the actual amount ('burden') of AF in 1195 patients in 2 multicenter trials²⁴. Continuous ECG monitors are increasingly easy to implant, and the trend towards their increased use is likely to alter disease classification and may further reduce reported ablation success.

These results raise important points on how ablation success is measured. The ultimate endpoint¹² of the absence of sustained AF (i.e. < 30 seconds) clearly reflects monitoring intensity. For instance, a 7 day event monitor every quarter, a rigorous regimen by clinical trials standards, records only 7.7% of the year while an implanted ECG records for 100% of the year²². Since treatment for thromboembolic sequelae is based on comorbidities such as CHA2DS2VASc score²⁵, and not AF burden, a reasonable clinical endpoint¹² is thus to eliminate symptomatic AF²⁶. Of course, this endpoint cannot be interpreted as AF elimination, and has negative clinical implications given recent evidence that subclinical AF detected by implanted ECGs even in patients without clinical AF^{27, 28} predicts stroke or

thromboembolism²⁷⁻²⁹. Thus, varying endpoints are used, with AF elimination favored in clinical trials and mechanistic studies, and elimination of symptomatic AF often used in clinical practice.

Finally, at what point in time should ablation success be measured? This question acknowledges that, in many cases, AF is a progressive disease³⁰. Ablation for supraventricular tachycardias from congenital abnormalities such as Wolff-Parkinson-White syndrome³¹ or AV node reentry³² typically leads to a durable cure. A single PVI procedure certainly has the potential to produce durable success in AF patients, but such individuals are usually identified post-hoc^{12, 33}. Whether early or late AF recurrence can be reduced by novel patient-tailored mechanistic approaches³⁴, identifies patients in whom AF is progressive³⁵ or can be treated by intervening on comorbidities³⁶ with ablation³⁷ are active areas of study. Societal guidelines currently recommend 1 year as the definition of long-term success¹².

3. Trends in who to ablate?

Societal guidelines reserve ablation for patients with symptomatic AF¹², and several studies show that ablation in such patients improves quality of life compared to pharmacologic therapy³⁸⁻⁴⁰. Nevertheless, this reveals an inconvenient paradox, since success is measured (appropriately) by eliminating asymptomatic and symptomatic AF. If the results of major ongoing studies including CABANA ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00911508): NCT00911508), CASTLE-AF ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00643188): NCT00643188) or EAST ([Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01288352): NCT01288352) show improved survival from ablation compared to pharmacological therapy, then AF ablation may be extended to patients with asymptomatic AF. Ablation is typically reserved for patients who have failed or are intolerant to anti-arrhythmic agents based on several clinical trials¹², although studies in aggregate now show benefit in patients who have not yet used anti-arrhythmic agents^{11, 26, 41}.

Many groups are attempting to identify populations in whom PV isolation is most successful. PVI is less successful in patients with non-paroxysmal AF (with the above caveats) or with co-morbidities of sleep apnea⁴², heart failure, renal dysfunction, obesity^{36, 37}, metabolic syndrome⁴³ and hypertrophic cardiomyopathy¹⁸.

Several studies also suggest that response to PVI is less favorable in patients with structurally dilated atria (LA diameter > 4.3cm¹⁸) or extensive gadolinium enhancement on magnetic resonance imaging⁴⁴ that may indicate scar⁴⁵. Electrically, patients with very rapid atrial rates in AF⁴⁶ may also be less likely to respond to PVI.

However, these predictors are not biomarkers of mechanisms. As a result, even patients with unfavorable co-morbidities, dilated atria or the above risk factors can have reasonable outcomes¹⁸ and even multiparameter classifications have poor predictive value⁴⁷. At the current time, these criteria are thus best used not to deny patients treatment but to make them aware of the decreased likelihood of success and possibility of multiple procedures with current ablation strategies.

4. Trends in Mechanistic Understanding to Improve Ablation of AF

It is generally acknowledged that a better mechanistic understanding of human AF will enable better ablation tailoring to patient-specific mechanisms, i.e. a therapeutically focused functional disease classification. There has been intense investigation into this area in recent years, with several promising advances.

Tachyarrhythmias initiate from a “trigger” such as a premature beat, and are then maintained by sustaining mechanisms (“substrates”). In AF, the terms trigger and substrate are imprecisely defined, but in traditional arrhythmias a trigger is the single or few ectopic beats that initiate tachyarrhythmia, while a prolonged tachycardia is typically considered a sustaining rhythm (‘substrate’). In AF, triggers are well studied. In 1998, Haïssaguerre et al. reported that paroxysmal AF may be triggered by ectopy¹² from the pulmonary veins (PVs), leading to PV isolation as the predominant ablation approach. AF recurrences from PVI have caused growing recognition that AF can be caused by other regions that may represent non-PV triggers⁴⁸⁻⁵⁰ or AF-maintaining substrates^{12, 51}. However, which regions to actually ablate in an individual patient is the subject of intense debate (figure 2).

The limitations of PVI (figure 1) may reflect many factors. Technically, it is widely acknowledged that durable PV isolation is difficult to achieve over the long term¹². There are also mechanistic arguments. AF can often be triggered from outside the PVs^{48,49, 50}, to the extent that some authorities advocate exhaustive ablation of non-PV sites⁴⁹ as a core of trigger-based ablation. Translational studies show that triggers are stimulated by innervation from the cardiac autonomic ganglia^{52, 53} (figure 2C,E), which is another area of study because such regions can also maintain AF, i.e. act as substrates.

Mapping and ablating AF substrate is one of the most activated debated topics within the field of ablation today, and is motivated by the large number of patients in whom AF recurs after eliminating PV^{6, 7, 10-13} or non-PV triggers⁵⁴, by evidence⁵⁵⁻⁵⁸ that conventional ablation may inadvertently target substrates^{52, 59}, and by the fact that we ablate substrates (not triggers) for other arrhythmias.

The central dichotomy is whether AF substrates represent organized sources that produce ‘downstream’ disorganization, or whether disorganization itself sustains AF without sources. In the former scenario, limited ablation is possible; in the second scenario, the only effective approach can be extensive ablation that limits the so-called ‘critical mass’ required for wavelets to meander.

Until recent advances in mapping, ablation of AF “substrate” was synonymous with extensive lesions, with variable results^{19, 60-62} and damage to atrial function⁶³. One perceptible trend is to perform less extensive AF ablation, because widespread ablation may increase complications and reduce atrial function⁶³, from the disappointing efficacy of extensive ablation of complex fractionated electrograms^{19, 61, 62} and from mechanistic trends to identify targets amenable to localized ablation lesions.

Localized sources for AF were postulated by Garrey, Mines and Lewis in the early 20th century, and discovered by Jalife et al⁶⁴⁻⁶⁶ who revealed electrical rotors that perpetuate AF

in elegant animal models. Conversely, disordered or multiple wavelet reentry postulates that AF comprises meandering waves that collide and extinguish⁶⁷ to sustain AF without sources, and is often used to explain the success of Maze surgery and ablation lines to ‘limit’ wavelet migration (figure 2B). Nevertheless, extensive ablation and even the Maze procedure may fail in a substantial proportion of patients¹² while, conversely, very limited ablation can modulate paroxysmal or persistent AF⁶⁸⁻⁷¹ in some cases. These observations support the role of localized sources over multiwavelet reentry – at least in these patients.

In 2011, the CONFIRM trial⁷² (Conventional ablation with or without focal impulse and rotor modulation, FIRM) showed that AF was sustained by localized rotors and focal circuits in most patients, identified using novel physiologically based computerized mapping⁷³⁻⁷⁵⁷⁶⁻⁷⁸. This concept has been supported mechanistically by early data in which ablation at sources alone can eliminate AF on follow-up⁷⁹. Several groups have now shown that FIRM improves the results of PVI alone^{34, 80, 81}, and have used diverse methods to confirm rotors in human AF⁸²⁻⁸⁴.

At the current time, randomized clinical trials are ongoing to support 1 year^{68, 80, 84} and longer term³⁴ data on the success of AF rotor ablation, while data comparing different approaches to rotor ablation are anticipated.

5. Evolving Technical Aspects of Ablation: Less is more

A recent trend is to attempt to limit the amount of tissue destruction during ablation, exemplified by the promise of individualized strategies based on mapping AF^{68, 84} that may reduce ablation yet improve long term outcomes³⁴.

Nevertheless, there are still patients in whom catheter ablation may not result in long-term freedom from AF. While our understanding of the mechanisms involved in patients with grossly dilated atria and longstanding persistent AF improves, surgical AF ablation is an option. The results of surgical AF ablation have been proven over time^{85, 86}, although procedural complexity may limit its use to a small subset of patients.

Catheter ablation has evolved in many approaches to create linear lesions or “lines” at anatomic locations such as the isthmus between the left inferior pulmonary vein and mitral annulus (“mitral line”) and the left atrial roof between the superior pulmonary veins, to mimic the surgical lesions of a Maze procedure (figure 2B), or non-PV lesions such as the left atrial appendage⁴⁹. There has been much debate over lines – in terms of their function, where they should be placed, and if they should be created at all. Mechanistically, lines were designed to ‘constrain’ wavelets in human AF, but whether this is feasible is debated⁷⁵ and it has been shown that lines may interrupt localized sources⁵⁹. A full discussion is outside the scope of this review, but since lines may be difficult to complete and incomplete lines may cause iatrogenic atrial tachycardias¹², there is a perceptible trend towards reduced creation of lines (particularly the mitral).

In patients with paroxysmal AF, where PV isolation alone is initially performed by most operators, a rapid trend has been to perform the procedure as quickly as possible with the use of “single shot” devices. The dominant such device is the cryoballoon⁸⁷, now on its

second iteration, with circular RF ablation catheters and a laser balloon also available⁸⁸. While these technologies are easy to use, and have been shown in small trials to be at least as efficacious as point-by-point ablation, they may increase the prevalence of complications such as phrenic nerve injury⁸⁹ and asymptomatic cerebral emboli⁹⁰, and their effects involve more tissue destruction⁹¹. Mechanistically, whether these devices produce more durable PV isolation is being tested in the Fire and Ice trial (NCT01490814).

More recently, the convergent procedure⁹², which combines endoscopic surgical access to the epicardial space via the diaphragm for ablation of the posterior left atrium with catheter-based endocardial ablation, has shown promise (figure 3E). The thoracoscopic approach avoids direct trauma to the chest compared to traditional surgical approaches, while direct visualization can reduce complications while allowing large atrial areas to be targeted while confirming success via traditional electrophysiologic endpoints. Recent single-procedure success of 52% (and multiprocedure on-drug results of 80%)⁹² are promising, and longer term assessments of success, safety and atrial function are anticipated.

Increasing safety is a major trend for AF catheter ablation, and has been a notable success for many technical innovations. Although X-ray doses used during fluoroscopy for AF ablation (figure 3A) are often modest, novel imaging modalities have further reduced fluoroscopy exposure and even provide the ability to perform AF ablation without X-ray⁹³. Robotic and magnetically guided catheters allow a reduction in irradiation to the operator while maintaining equivalent results to traditional systems⁹⁴. A recent innovation is the use of a novel magnetic based tracking system combined with stored fluoroscopic images⁹⁵ that has further reduced the already low fluoroscopy times seen with contemporary mapping systems (figure 3B).

A lack of real time feedback of contact force during ablation⁹⁶ has limited ablation efficacy and safety. A recent innovation has been the introduction of force sensing catheters⁹⁷ (figure 3D), which may help to reduce the problem of recurrent PV conduction⁹⁸ in tandem with new methods to directly visualize lesion formation⁹⁶.

Many other advances have made AF ablation more technically satisfying by merging patient anatomy between modalities or using specialized steerable sheaths⁹⁹ but have not been universally shown to improve outcome¹⁰⁰ (figure 3C).

6. Management of Anticoagulation

Minimizing the risk of stroke is a central pillar of AF management, regardless of whether patients are being ablated. Recent landmark trials with the non-vitamin K oral anticoagulants (NOACs) have shifted emphasis away from warfarin¹⁰¹, although actual prescribing habits vary geographically¹⁰². Specific challenges of AF ablation in patients using NOACs were the relative lack of data during cardioversion since anticoagulant activity is rarely monitored for the 3 preceding weeks, although recent studies confirm safety¹⁰³, and ablation, since it is difficult to reverse the action of NOACs if complications arise. The trend to performing ablation procedures on uninterrupted warfarin, which was shown to reduce the risk of complications¹⁰⁴, has become more complicated given that there are now 3 NOACs on the market with differing mechanisms of action, half lives and renal clearance. A number of

randomized controlled trials of ablation of AF patients using NOACs are currently recruiting and will hopefully address this knowledge gap.

7. Complications of AF Ablation

The specific risks of AF ablation reflect potentially extensive ablation as well as the proximity of atria to adnexae such as the esophagus, phrenic nerves and other vasculature^{105, 106}. Awareness of these risks has improved procedural technique, e.g. eliminating PV stenosis by ablating widely outside PVs (figure 2B) instead of close to the thin-walled PVs, while better sheath management and anticoagulation can reduce thromboembolic risk. Accordingly, AF ablation procedural safety has increased with very low mortality in multicenter surveys^{107, 108} and data from both the US¹⁰⁹ and Europe¹¹⁰. Data have consistently shown^{107, 108} that procedural outcomes improve with center experience. U.S. registry data from over 93,000 patients in the U.S. national inpatient sample database⁵ showed an *in-hospital* mortality rate of 0.42%, and an overall complication rate of 6.29% (figure 4) that were lower in high volume centers. The possibility that complication rates are trending higher in some studies⁵, although not others¹⁰⁷⁻¹¹⁰, may reflect treatment of more complex, older patients with persistent AF¹¹¹ in whom widespread ablation and long procedure times may cause complications. This again argues for a more targeted, mechanistic approach to AF ablation.

7. Conclusions

Ablation for AF is increasingly used because it has been shown to improve maintenance of sinus rhythm compared to drug therapy in numerous multicenter trials. Although success rates remain suboptimal, the remarkable success of ablation in many patients provides a foundation to advance the field. A mechanistic classification of AF will enable better guidance on how to direct ablation to specific populations, and should also lead to improved patient-tailored ablation. Technical advances have improved the ease of performing AF ablation, and its safety profile. However, caution is still required given the diversity of outcomes. These trends are likely to further improve results from AF ablation in coming years as it becomes an increasingly important therapeutic option in many patient populations.

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Figure 1. Meta-analysis of single procedure success rates from AF ablation
(A) in paroxysmal and non-paroxysmal AF by study (see reference¹⁷ for details) **(B)**
Higher success for paroxysmal than non-paroxysmal AF, but with considerable overlap.
Multiple procedure success rates are higher.

Figure 2. Trends in Mechanism-Based AF Ablation Sets

(A) Triggers initiate AF, then increasingly well-defined mechanisms sustain AF (with permission from Calkins, et al. (12)). (B) Conventional ablation lines are designed to isolate triggers (PV isolation), empirically target other potential mechanisms, or (C) target localized regions, all predominantly in the left atrium (with permission from Calkins, et al. (12)). (D, E) Actual ablation lesions for PVI combined with ablation of ganglionic plexus sites (with permission from Katritsis, et al. (53)). There are trends for patient-specific mechanism-targeted ablation in both atria. (F) Focal Impulse and Rotor map showing bi-atrial mechanisms sustaining AF in a specific patient, including a right atrial rotor and a left atrial

focal driver, and (G) actual lesions delivered at RA rotor (LA lesions of similar area, out of plane in this view) (with permission from Narayan et al. (59).

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Figure 3. Technical Advances in AF Ablation

(A) **Typical fluoroscopy** showing a circular mapping catheter, a decapolar catheter in the coronary sinus and an ablation catheter. Using fluoroscopy alone is technically challenging when moving in a 3D structure. An improvement is the addition of (B) **Rotational angiography**, in which a 3D representation of patient anatomy is generated at the time of ablation using X-ray images acquired during a contrast injection. (C) **Electro-anatomic mapping showing catheters**. In this image, the Velocity system (St Jude Medical, Sylmar, California) uses catheter impedance within the chamber to depict atrial contours and catheter

location (in this case, 64 pole basket catheters for FIRM-guided ablation). An imaging trend is to display more than just atrial anatomy. (D) Electro-anatomic mapping showing ablation lesions. In this image, the CARTO system (Biosense-Webster, Diamond Bar, California) shows left atrial geometry, catheters and user-defined parameters for lesion formation plotted onto the shell. In this instance, lesions are automatically placed on the shell only when a pre-specified force, catheter stability and impedance drop have been achieved. (E) **The Convergent Procedure.** Due to prolonged ablation time and poorer outcomes of catheter ablation in patients with longstanding persistent AF, this hybrid procedure was developed in which the surgeon enters the pericardium via the diaphragm to ablate almost all of the posterior left and right atria. The electrophysiologist then ensures PVI with additional ablation. Results have been promising in small series.

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	Overall	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	P Value
Any procedural complications	6.29	5.33	5.53	6.01	7.17	6.32	5.10	6.17	6.66	5.93	6.49	7.48	0.108
In hospitalization death	0.42	0.44	0.55	0.63	0.30	0.61	0.15	0.45	0.53	0.27	0.52	0.47	0.492
Vascular complications	1.53	0.89	0.66	1.16	1.12	0.95	1.31	0.60	0.97	1.02	0.97	1.33	0.500
Postop hemorrhage	3.38	1.78	2.54	2.53	2.39	3.38	2.77	3.13	3.52	3.75	3.46	4.90	<0.001
Postop hemorrhage requiring transfusion	0.58	0.30	0.22	0.32	0.30	0.61	0.34	0.45	0.87	0.65	0.44	1.03	0.020
Vascular complications including	1.01	0.30	0.11	0.21	0.22	0.26	0.34	0.05	0.10	0.03	0.04	0.04	0.060
Cardiac complications	2.54	1.63	1.66	1.37	2.69	2.42	1.90	1.69	2.90	2.90	3.06	3.53	<0.001
Iatrogenic cardiac complications	1.18	1.33	0.88	0.63	1.19	1.13	0.83	0.90	1.54	1.33	0.93	1.76	0.050
Pericardial complications	1.52	0.74	0.44	0.63	1.49	0.87	1.31	1.00	1.83	1.84	2.14	2.24	<0.001
Myocardial infarction	0.37	0.30	0.55	0.32	0.60	0.69	0.29	0.30	0.34	0.37	0.32	0.26	0.650
Requiring open heart surgery	0.28	0.44	0.22	0.11	0.07	0.09	0.24	0.30	0.24	0.24	0.36	0.47	0.460
Respiratory complications	1.3	1.48	1.66	1.27	1.79	1.21	1.12	1.59	1.79	1.16	1.09	0.77	0.109
Pneumothorax	0.39	0.59	0.66	0.63	0.82	0.52	0.44	0.50	0.29	0.31	0.24	0.04	0.020
Postop respiratory failure	0.77	0.74	0.88	0.53	0.75	0.61	0.49	0.90	1.16	0.68	0.85	0.73	0.575
Other iatrogenic respiratory complications	0.18	0.15	0.33	0.11	0.30	0.09	0.24	0.20	0.43	0.20	0.00	0.00	0.030
Neurological complications (postop stroke/TIA)	1.02	0.89	1.11	1.79	1.57	1.13	0.68	1.39	0.53	0.78	0.93	1.20	0.013
Postop infectious complications	0.38	0.15	0.11	0.21	0.45	0.43	0.29	0.50	0.72	0.24	0.40	0.43	0.235

AF indicates atrial fibrillation; Postop, postoperative; and TIA, transient ischemic attack.

Figure 4. Trends for the In-hospital complications from AF ablation using the Nationwide Inpatient Sample in 93, 801 procedures in the U.S. from 2000 to 2010. Complication rates were lower in higher volume centers (see text) (With permission from Deshmukh et al. (5).