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Ablating Persistent Atrial Fibrillation Successfully

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Abstract

The ablation of persistent atrial fibrillation (AF) poses many challenges compared to ablation for paroxysmal AF, including greater procedural complexity, longer procedural time, unclear endpoints, increased patient comorbidity with a greater risk of procedural complications, and lower success rate. Nevertheless, using a combination of patient selection, careful procedural planning of both ablation strategy and endpoints, and by setting realistic patient expectations, successful ablation may be achieved. Further improvements will come from continued technical advances as well as from greater mechanistic understanding of persistent AF, including the physiologically-targeted ablation of localized rotors and focal sources that have recently been shown to maintain human AF.

Keywords

Atrial fibrillation; Catheter ablation; Mechanisms; Complications; Electrical Rotors; Focal Sources; Procedural Outcomes

Introduction

Since the seminal observation of pulmonary vein triggers of clinical atrial fibrillation (AF) [1], ablation has rapidly become a preferred second [2•, 3•] or potentially even first [4] line therapy for the management of symptomatic AF. Currently, approximately 110,000 ablations are performed in the United States and Europe per year [5].

Despite great strides in understanding the mechanisms of AF initiation, and new technologies to deliver durable ablation lesions [6-9], significant limitations remain in our ability to reliably target and cure AF with catheter-based therapies. This is particularly true for the ablation of persistent AF, for which procedural outcomes have shown only modest improvement despite these advances [10]. Accordingly, of the numerous procedural strategies that have been proposed for persistent AF ablation, there is no consensus regarding which is the most efficient. There is also disagreement on fundamental procedural components such as optimal ablation targets outside the pulmonary veins, use of endpoints such as AF termination, the need to demonstrate that AF is no longer inducible after ablation, the use of pharmacologic maneuvers, and methods to reduce late recurrence. Indeed, recent work from experienced centers has shown a 40% 5-year ablation success rate in a mixed population of persistent and paroxysmal AF patients [11•].

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Disclosure

Conflicts of interest

Additional concerns for referring physicians include the fact that catheter ablation for AF carries a moderate risk of complications [12]. These range from relatively insignificant post-procedural bleeding complications, to less common but more serious complications such as pulmonary vein (PV) stenosis or cardiac perforation, to devastating issues such as stroke and death from tracheoesophageal fistula.

The goal of this manuscript is to review current evidence on the ablation of persistent AF, including approaches such as patient selection, careful procedural planning and safety considerations, post-procedure management, and the recent discovery that human persistent (and paroxysmal) AF is sustained by localized sources whose elimination by targeted ablation (Focal Impulse and Rotor Modulation, FIRM) may improve long-term AF elimination after ablation.

Patient Selection

The definition of persistent AF as arrhythmia episodes lasting >7 days [2••] provides a method to identify patients with advanced abnormalities in atrial structure and electrophysiology that make ablation more challenging. As a group, these patients have greater structural remodeling including atrial dilatation, fibrosis and scar that persist after sinus rhythm is restored [13], and concomitant pro-arrhythmic electrical remodeling [14]. Patient selection based on evidence of the impact of measurable atrial remodeling may help identify those who are more or less likely to benefit from catheter ablation.

Left Atrial Size and Scar Assessment

Left atrial size increases with AF duration [15]. The most common assessment of LA size, LA anteroposterior (AP) diameter, is readily measurable by transthoracic echocardiography. Unfortunately, this measure correlates poorly with LA volume, which better reflects LA surface area and remodeling, and has been shown to predict ablation success [16]. Notably, ablation success may be as low as 30% in patients with LA volumes > 34 mL/m² [16]. This information, while not a contraindication to ablation, may be used to counsel patients and families about the realistic chance of success, as discussed below.

Recent work shows that regions of atrial scar may be quantified by delayed gadolinium enhancement MRI (DE-MRI) [17•]. Indeed, work from the Utah group suggests that AF patients with the most extensive scar (Utah IV) may not actually benefit from catheter ablation [17•]. Although atrial DE-MRI is not currently widely available for clinical practice, future strategies may incorporate patient-specific assessments of atrial scar to predict who may and who may not respond to ablation [18].

Atrial Electrophysiology

Atrial electrical remodeling is well described [14]. At its most basic level, numerous studies have shown that as AF begets AF [19]: shortening in atrial repolarization time (action potential duration, APD) and reduction in conduction velocity that promote reentrant mechanisms for AF [13]. Recent studies have shown that clinically relevant atrial electrical remodeling can be quantified in patients by differences in APD restitution [20] and by types of oscillations in repolarization (including APD alternans) [21]. Although currently of mechanistic interest, these studies identify approaches that may ultimately prove useful in identifying patients in whom drug or ablation strategies may be more useful in permanently re-establishing sinus rhythm.

While repolarization data are often not readily available, AF cycle length (the reciprocal of rate) can be assessed from many sources including the surface ECG. AF cycle length is quite well conserved over time in any individual [22, 23], and correlates with ablation outcome.

Patient with shorter CLs have a lower probability of success [24•], and those in whom AF CL < 140 msec should be counseled pre-procedurally regarding the lower likelihood of AF-free ablation outcome [25].

Other Demographic Factors

Although several demographic factors are associated with a higher incidence of AF, evidence from experienced centers suggests that advanced age, higher body mass index [26] and heart failure [27] may not portend a lower success rate from AF ablation.

Procedural Planning

Current Ablation Approaches and Extent

Numerous ablation strategies have been proposed for persistent AF, including elimination of triggers by segmental pulmonary vein isolation [28], wide area circumferential ablation (WACA) [29] and thoracic venous isolation [30], and ‘substrate modification’ based upon ablation of complex fractionated atrial electrogram (CFAE) [31] or other targets. However, there is currently no agreed-upon “best” strategy for these approaches. Current AF ablation guidelines stress the central nature of pulmonary vein isolation and the need to verify PV block [2•], thus eliminating common trigger sites for AF. Additional ablation is at the discretion of the physician, and a fundamental unanswered question is: “What specific arrhythmia mechanisms should be targeted?” Notably, several experienced groups employ quite distinct approaches.

The most common ablation approaches in persistent AF include additional anatomical lesion sets such as linear ablation (particularly a roof line and/or mitral isthmus line), or “electrogram based” ablation that targets CFAE [31] or sites of high spectral dominant frequency (DF). Endpoints are also heterogeneous between groups, including predetermined anatomic lesion sets, elimination of the electrogram characteristics listed above, or procedural AF termination [32]. Each approach has its advocates yet the reported results from these distinct approaches are surprisingly similar.

In a recent randomized, controlled trial of PVI versus PVI plus up to 2 hours of additional CFAE ablation in patients with longstanding persistent AF, success rates were similar between the two groups (36 and 34%, respectively) at 10±3 months [33]. However, in a less remodeled patient population, the addition of CFAE ablation was found to be beneficial [34]. This finding has been supported by a subsequent meta-analysis [35]. Other electrogram targets include the ablation of regions of high spectral DF, that have support from the basic science literature [36] and clinical advocates [37, 38], and are undergoing further investigation.

One novel approach to AF ablation is to target precisely-defined sustaining mechanisms for AF, as opposed to trigger sites or less-precisely defined surrogates [39]. In CONFIRM, a prospective case-cohort trial, rapid targeted ablation at sustaining rotors or focal sources (FIRM) was able to terminate AF predominantly to sinus rhythm within minutes in a large number of patients, rendering AF non-inducible, prior to PV isolation. On long-term follow-up using implanted continuous ECG monitors in 86% of patients, FIRM ablation enabled a 70% greater AF elimination rate than conventional ablation alone [40•]. Validation in additional centers is currently underway.

Important remaining questions are: “How much ablation is enough?” and “How much ablation is too much?” The answers to these questions remain uncertain at the current time. With respect to the minimum effective amount of ablation, however, recent studies using DE-MRI have shown that the extent of LA scarring post ablation correlates with ablation

outcome. When ablation affected >13% of the LA wall muscle, ablation was more likely successful [41]. Thus, there may be a definable minimum of anatomically-based ablation which is required for ablation success. More recent work in persistent AF patients also shows that ablation to AF termination predicts procedural success [24•].

There have been few formalized studies of serious complications resulting from excessive ablation. However a recent notable report documents “stiff left atrial syndrome” with loss of left atrial compliance causing a heart-failure presentation as a significant sequel of extensive LA ablation [42]. The prevalence of this complication requires further definition. Less well defined, it is possible that the prolonged duration of extensive AF ablation may explain its substantially higher risk of adverse events [12] compared to other left atrial ablation procedures (e.g. for accessory pathways or atrial tachycardias). Again, this line of reasoning argues for less ablation whenever possible. As we will describe below, recent work identifying localized sources for human AF provide one potential approach to reduce the extent of ablation.

Endpoints

Currently, the primary procedural endpoint for AF ablation is PV isolation [2••]. Secondary procedural endpoints are less clear, but may include confirmation of conduction block across linear lesions (if performed), and elimination of CFAE (when targeted) [2••]. Of note, unlike most other arrhythmias undergoing ablation, there is ongoing debate whether intra-procedural AF termination, or potentially AF slowing and regularization, are useful adjunctive endpoints for ablation.

Although several small, retrospective studies show that AF regularization may identify patients who are less likely to experience recurrent AF [43, 44], it has not been *prospectively* used to guide ablation approach. Therefore, additional studies are required before a specific index of AF regularization, such as dominant frequency, can be recommended as an ablation endpoint.

Similarly, the literature regarding the use of AF termination as a procedural endpoint is mixed. Several studies confirm that patients in whom AF terminates intra-procedurally have a higher long-term freedom from AF than those in whom AF does not terminate [45•]. However, some experienced groups have used precisely these data to argue the opposite case. Studies have shown that recurrence of any atrial tachyarrhythmia is similar whether AF does or does not terminate by the conventional ablation strategies outlined above; AF termination may simply identify patients in whom recurrences are of atrial tachycardia instead of AF [46]. The final outcome may be subject to individual interpretation, reflecting the preference to perform a repeat procedure for atrial tachycardia or AF, among other factors. Recent data show that FIRM ablation for rotors and focal beats can rapidly terminate AF, and predominantly to sinus rhythm rather than to an atrial tachycardia (unlike previously described AF termination). Ongoing studies will determine whether such AF termination differs in its mechanisms and impact on long-term outcome from previously described AF termination.

Safety Issues

A key component of a successful ablation includes strategies to reduce and avoid complications. Strategies to avoid the main complications of AF ablation: stroke, cardiac perforation, PV stenosis, diaphragmatic paralysis, and esophageal injury, are discussed here.

Stroke is a life-altering complication; present guidelines recommend pre-procedural treatment with warfarin for 3 weeks, and TEE in selected patients to evaluate for LA appendage thrombus [2••]. Many centers, including our own, also routinely perform ablation

with therapeutic INR in addition to intraprocedural heparin anticoagulation (target ACT >350 seconds in our practice). The advantage of this approach is that therapeutic INR is maintained particularly during the post-procedural period, without a significant reported increase in bleeding or severity of cardiac tamponade [47•]. It must be noted, however, that some practitioners remain cautious of performing AF ablation on uninterrupted warfarin. In contrast to the potential advantages of warfarin, treatment with one of the newer oral anticoagulants, dabigatran, has recently been shown to increase risks of bleeding and thromboembolism when used peri-procedurally [48]. Other agents have not been tested prospectively to date, but may have the advantage of rapid reversibility [49] in case of bleeding or other complication.

Cardiac perforation is most commonly encountered during transseptal catheterization, but may also occur during instrumentation of the atrial appendages or roof. Intracardiac ultrasound is commonly used to guide transseptal catheterization and may also help to expedite pericardial aspiration if systemic pressures drop intraprocedurally. Three-dimensional electroanatomic mapping systems, in addition to decreasing the need for fluoroscopy [50], may also assist in manipulating the catheter safely within the cardiac contours [51].

Pulmonary vein stenosis results from scarring of pulmonary veins following ablation within these structures, and may cause severe CHF symptoms and even death in severe cases. A recent study suggests that antral ablation, guided by 3-dimensional electroanatomic mapping, significantly reduces pulmonary vein stenosis versus ostial ablation [52]. Management is typically by pulmonary vein stenting,

Diaphragmatic paralysis occurs with inadvertent ablation of the phrenic nerve, and usually occurs with ablation of the lateral right atrium or anterior portions of the right pulmonary veins [53]. High output pacing prior to ablation in these regions can identify the course of the phrenic nerve to avoid ablation. Fortunately, complete or partial diaphragmatic recovery is observed in the majority of patients.

Severe esophageal injury from ablation of the posterior left atrium that may progress to tracheoesophageal fistula is an uncommon (<1/1000) but life threatening complication of ablation. Prevention is facilitated with the use of a radio-opaque temperature probe or contrast in the esophagus or intracardiac ultrasound [54], allowing visualization of this structure and avoidance of prolonged burns while ablating adjacent atrial tissue. Although many electrophysiologists routinely discharge patients on proton pump or H2 blocking medications following ablation, the incidence of this complication is so low that it is difficult to accrue data to support or deny that this practice decreases the risk of tracheoesophageal fistula.

Post-Procedure Management

Anticoagulation

There is a general consensus that patients should be anticoagulated following ablation [2•, 3•]. Monitoring is continued at 3-6 month intervals until 2 years, and in patients at high risk of stroke we monitor anticoagulation according to consensus recommendations [2•]. However, there have been no conclusive studies showing ablation of AF reduces stroke risk in persistent AF, and further studies are required to clarify this issue.

Antiarrhythmic Medications

The use of antiarrhythmic medications after ablation was evaluated in a prospective, randomized study which showed a significant reduction in arrhythmias immediately

following the procedure [55], but no improvement in long-term procedural success [56•]. A common practice following persistent AF ablation is to continue antiarrhythmic medications for 3 months, after which we typically discontinue antiarrhythmics.

Post-Procedure Monitoring

One significant issue following ablation is that subsequent AF episodes are less symptomatic. This highlights the importance of post-procedure monitoring, as patients may not feel episodes, and thus would be at risk of stroke without realizing.

Prior work highlighted the importance of continuous ECG recording versus symptom-triggered monitoring. In that study, frequent (monthly) Holter monitors outperformed symptom-triggered follow-up in the detection of AF [57]. However, the same study highlighted both the poor sensitivity (71%) and negative predictive value (39%) of intermittent monitoring versus continuous monitoring, even under the best circumstances.

In the DISCERN-AF [58] and CONFIRM [40••] trials, implantable loop-recorders (ILRs, Medtronic, MN) were implanted to monitor AF recurrence. The advantage of ILRs is that of continuous, complete follow-up and convenience to the patient after implantation. The disadvantages include cost, false-positive episodes due to atrial oversensing, and the need to remove the device after battery end-of-life at 2 years. Despite these limitations, the improved monitoring capabilities must be considered particularly when discontinuation of anticoagulation is considered.

Managing Patient Expectations

An important, but overlooked component of ablation is managing patient expectations. Given the current state of persistent AF ablation [59•], it is necessary to inform patients of the reasonable chance they will require 1 or 2 follow-up procedures to have the best chance at decreasing their AF burden. Also, many patients expect to stop anticoagulation post procedure. It is important to educate them about the need for many, if not most [2••] patients with persistent AF require ongoing anticoagulation as dictated by stroke-risk scoring systems.

Future approaches

Clearly there is room for improvement in the present state of the art persistent AF ablation. Conceptually, AF is ablated differently than nearly all other arrhythmias in that the primary targets (pulmonary veins) are sites of arrhythmia triggers but are typically not demonstrated to be the mechanisms that sustain persistent AF. Additional ablation targets, whether anatomical lines or 'electrogram based' ablation of CFAE, are empirical and have yet to be mechanistically linked to the mechanisms that actually sustain human AF [39].

Recent work from our laboratory has shown that human AF is typically maintained by a small number (2-3) of localized sources, in the form of spiral waves ('rotors') or focal beats, whose targeted elimination acutely terminates persistent and paroxysmal AF [60•], and when followed by conventional ablation, substantially improves long-term AF elimination compared to conventional ablation alone [40••].

Focal Impulse and Rotor Modulation (FIRM)

Despite considerable literature from elegant animal models that AF may be caused by rotors [61] or focal sources [62], the existence of such localized mechanisms, and particularly the existence of rotors, had until recently been seriously questioned in human AF [63]. FIRM mapping and ablation involves the use of multielectrode catheters to provide wide field of

view mapping of the majority of both atria. Using this technique, we recently demonstrated that human persistent and paroxysmal AF is typically maintained by localized sources that are conserved in space over time [64•].

Our approach combined wide-field-of view mapping of the fibrillating atria with computational methods to analyze atrial propagation paths based upon our recently published reports on the rate response of human left and right atrial repolarization [20, 21] and conduction [65]. Wide field of view mapping, achieved using 64-electrode basket catheters (Boston Scientific, MA) [64•] improves sensitivity for such mechanisms versus relatively small regions (<20% of total surface area) previously mapped by fixed mapping plaques [63]. Figure 1 (reprinted with permission from Elsevier) illustrates a basket catheter in the left atrium in a 56 year old man during persistent AF, and the resulting AF rotor (color coded from red, early, to blue, late) in the high posterior wall. Ablation at this site (FIRM ablation) alone terminated AF directly to sinus rhythm in less than 5 minutes of ablation, and rendered AF non-inducible in this patient who continues to be AF free on implantable loop recorder [60•]. In the CONFIRM trial [40•], FIRM ablation improved long-term AF elimination by 70% over conventional ablation alone, using implanted continuous ECG monitors for rigorous follow-up in 86% of FIRM-guided patients. FIRM mapping and ablation is undergoing validation in several additional centers, and the short and long term results in these and other larger populations are eagerly awaited.

Conclusions

Persistent AF occurs in the context of marked structural and electrophysiological remodeling of the atria that make long term AF elimination more challenging than for paroxysmal AF. Nevertheless, a combination of patient selection, careful procedural and endpoint planning, rigorous postprocedural management and setting appropriate expectations can enable successful ablation outcomes. Many promising new strategies are emerging, including advances in catheter technology and mapping systems. The identification of patient-specific AF-maintaining rotors and focal beats, whose targeted ablation (FIRM) can acutely terminate AF and improve long-term AF elimination may also hold promise for standardizing procedural outcomes and potentially shortening procedural time. Further advances in all of these areas are eagerly anticipated.

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A. LA Basket Fluoroscopy **B. LA Rotor in AF** **C. Electrograms at LA Rotor** **D. FIRM at LA Rotor Terminates AF (4.75 minutes)** **Figure 1. Left Atrial FIRM Mapping and Ablation of Persistent AF**

(A) Fluoroscopy showing basket and ablation catheters in the Left Atrium During AF (right anterior oblique 30° view); (B) Counterclockwise Rotor in mid-posterior Left Atrium, with collision beyond spiral arms (indicate by double lines); pulmonary vein ostia are indicated by dashed lines. (C) Electrograms recorded from the LA basket catheter showing counterclockwise rotor with variability characteristic of AF; (D) FIRM ablation at LA rotor terminates AF to sinus rhythm with 4.75 minutes of ablation. (Key; ABL=Ablation electrogram; CS=coronary sinus). (Reproduced with permission from: Narayan SM, Patel J, Mulpuru S, Krummen DE: Focal impulse and rotor modulation ablation of sustaining rotors abruptly terminates persistent atrial fibrillation to sinus rhythm with elimination on follow-up: A video case study. *Heart rhythm: the official journal of the Heart Rhythm Society* 2012;published online Mar 28 2012) [60•].