Is Ablation to Termination the Best Strategy for Ablation of Persistent Atrial Fibrillation?

Ablation to Termination Is Not the Best Strategy During Ablation

Rakesh Latchamsetty, MD; Hakan Oral, MD

“I’ll follow him around the Horn, and around the Norway maelstrom, and around perdition’s flames before I give him up.”

-Captain Ahab, Moby Dick

“The mysterious thing you look for your whole life will eventually eat you alive.”

-Laurie Anderson on Moby Dick

Optimal strategy and end points for ablation of persistent atrial fibrillation (AF) have not been well established. Although antral pulmonary vein isolation (PVI) is often effective for ablation of paroxysmal AF, it is an insufficient standalone strategy for many patients with persistent AF. Selection of adjunctive targets and determination of procedural end points are variable and at the discretion of the operator. Several studies suggested that termination of AF should be the procedural end point during ablation in patients with persistent AF, as a higher probability of maintaining sinus rhythm after the ablation was reported, despite a long procedure duration and a high rate of repeat ablation procedures. However, these studies were not consistently reproducible, and conversion usually occurred to an atrial tachycardia rather than sinus rhythm after extensive ablation. In patients with persistent AF, there is insufficient experimental, mechanistic, or clinical evidence to support termination of AF during ablation as a procedural end point.

Response by Lim et al on p 980

Mechanistic Considerations

Rapid and repetitive depolarizations originating within or at the antra of the pulmonary veins (PVs) and the other thoracic veins are the predominant mechanism in the initiation and perpetuation of paroxysmal atrial fibrillation (PAF). Antral isolation of PVs and elimination of focal triggers and drivers from other thoracic veins often result in termination and noninducibility of PAF in response to various pharmacological and pacing protocols. Patients with PAF whose AF terminated during ablation and were rendered noninducible, also were more likely to remain in sinus rhythm during long-term clinical follow-up. In essence, termination and noninducibility in these patients suggested successful elimination of the primary mechanism of AF and absence of additional mechanisms and may have simply facilitated selection of patients whose AF was thoracic vein dependent. The subset of patients with PAF who remain in AF after PVI may have residual mechanisms, which may be fewer, more likely to be focal triggers and more readily amenable to mapping and additional ablation in patients with paroxysmal than persistent AF.

Based on these observations in PAF and limited efficacy of PVI in patients with persistent AF, termination to sinus rhythm was also pursued as a procedural end point in patients with persistent AF using a variety of ablation strategies. The key for evaluating the validity and efficacy of each of these approaches is a sound understanding of the prevailing mechanism(s) of human AF (Figure). However, to date,
these mechanisms have been primarily based on extrapolation of observations from experimental models.

In persistent AF, a multicomponent system is likely to be critical with a continual interplay between a trigger/initiator/driver and a perpetuator(s). Termination of AF has been thought to indicate effective elimination of these components of AF and therefore should subsequently translate into an improvement in clinical outcomes. However, several assumptions are made to reach this conclusion:

1. Although spatiotemporal stability of high-frequency rotors of AF has been demonstrated in experimental models that used optical mapping techniques, it is also recognized that these drivers are stable for only a few hundred milliseconds to a few seconds and meander for several centimeters. It has been suggested that these rotors may have anchor points at usually targeted sites during catheter ablation, such as the antrum of the PVs and fixed anatomical landmarks. It is not clear whether the rotors use the same path or anchor at similar sites during consecutive episodes of AF. Even if rotors could be accurately identified and mapped in real-time, termination of AF during ablation at that time point would only indicate that rotors sustaining AF at that instant were eliminated and no other mechanisms were simultaneously operative. This does not necessarily indicate that the targeted site is no longer able to sustain any future potential rotors nor does it preclude the existence of other potential sites to harbor future rotors.

2. It has long been recognized that pathogenesis of AF is often progressive. Therefore, effective elimination of prevailing mechanisms of AF during ablation may not prevent development of new mechanisms with subsequent clinical recurrences.

3. Even if all mechanisms of AF are successfully ablated, recovery of conduction is a frequent limitation of current ablation technology. Recurrences may not necessarily indicate incomplete ablation.

4. It is important to recognize the nuance between termination and noninducibility of AF. In patients with paroxysmal AF, both termination and noninducibility have been sought as procedural end points and predict a higher probability of maintaining sinus rhythm after ablation. However, in patients with persistent AF, reinduction after termination of AF is often not attempted, as it is likely to reinduce AF. Although termination may indicate effective suppression or elimination of mechanisms of AF operative at a certain point in time, it does not rule out noninducibility.

Figure. A schematic illustration of pathogenesis of atrial fibrillation. Reprinted from Nishida et al with permission of the publisher. Copyright ©2014, Wolters Kluwer Health. AF indicates atrial fibrillation; AP, action potential; and PV, pulmonary vein.
the presence of residual drivers/perpetuators, which may be elicited with attempts at reinduction or potentially be dormant at the time of the procedure. For example, in a recent study, a dominant driver could not be identified for ≈40% of the duration of AF.15
5. Persistent AF encompasses a broad spectrum of patients with mild to severe electroanatomical remodeling. It is well recognized that duration of AF and left atrial size play an important role in response to therapy. A recent study also suggested that the longer the duration of AF, the greater the number of rotors present.15 Therefore, comparative analysis of outcomes can be challenging in patients with persistent or long-standing persistent AF.

Experimental and Clinical Evidence

Surgical Experience

Initial attempts at nonpharmacologic long-term rhythm control for AF consisted of the surgical cut-and-sew maze technique.16 The original version of this technique was ultimately abandoned because of its technical complexity, development of sinus node dysfunction, and left atrial dysfunction.17 Modifications led to the Cox maze III procedure, which mitigated these issues and was technically less demanding.18 Subsequent revisions of the maze technique involved alternative energy sources and less invasive approaches, however, at the cost of a decrease in procedural efficacy.19

Although stand-alone surgical maze procedures have largely been supplanted by less invasive catheter ablation procedures, the original cut-and-sew technique did produce favorable long-term outcomes and at least conceptually provide a paradigm for attainable long-term results through atrial substrate modification. A single-center study of 112 patients who underwent the Cox maze III procedure for lone atrial fibrillation had an 83% freedom from AF off antiarrhythmic medications (no difference between the paroxysmal and persistent groups) at a median follow-up of 5.9 years.20 It is important to note that these results were produced by a purely anatomic strategy designed to compartmentalize the atria and limit adequate substrate to initiate and maintain AF and did not use any real-time mapping strategy to identify drivers or perpetuators of AF. Many of these patients eventually required cardioversion after the procedure or before discharge but still maintained sinus rhythm in the long-term, highlighting the fact that acute conversion to sinus rhythm is not essential for long-term success.

Catheter Ablation

No single strategy has been clearly demonstrated to offer superior outcomes in patients with AF compared with antral PVI. Several studies, however, attempted to determine the role of additional ablation after PVI in patients with persistent AF. These approaches included ablation of complex-fractionated atrial electrograms (CFAE), targeting local cycle length (frequency) gradients, linear ablation between fixed anatomical structures, isolation of the superior vena cava, ablation of the coronary sinus or ligament of Marshall, electrical isolation of the left atrial appendage, targeting ganglionated plexi, or a combination of these approaches as in the step-wise ablation approach.21–28 End points of these ablation strategies can be variable. When an anatomic ablation strategy such as linear ablation and isolation of other thoracic veins is pursued, termination often is not sought after as a procedural end point. However, when electrogram-guided or hybrid approaches (such as in stepwise ablation) are used, either conversion to sinus rhythm or atrial tachycardia or a reduction in AF activation rate is frequently the intended end point of ablation, yet it may not always be achievable. To date, whether termination of AF during ablation indeed improves clinical outcomes remains unclear.

CFAE Ablation

Ablation of CFAEs was originally proposed as a method to eliminate triggers and drivers of AF,29 with termination of AF during ablation in 91% of patients and freedom from AF in 91% of patients at 1-year follow-up (inclusive of 47% patients with paroxysmal AF). However, in subsequent studies, both the termination and clinical efficacy rates have been lower at 33% to 50%.29,30 CFAEs have been defined as atrial electrograms with a short cycle length (<120 ms), fractionation, or continuous electric activity and can be identified either manually or with automated algorithms. CFAEs have been proposed to indicate sites of slow conduction, wavefront collision, pivot points for high-frequency sources, reentrant circuits, ganglionated plexi, or fibrillatory conduction whose benefit as a target can range from specific rotor elimination or containment, to modification of autonomic input, to simple debulking of the atria because of extensive ablation.31–34 CFAEs lack specificity as targets and may prompt extensive unnecessary ablation with the risk of an increase in complications, including atrial contractile dysfunction, proarrhythmia in the form of atrial flutter or tachycardia, inadvertent isolation of the left atrial appendage, and thromboembolic events. Although few earlier studies suggested incremental benefit of CFAE ablation in addition to PVI in patients with persistent AF,35 a recent trial that randomized 589 patients undergoing ablation of persistent AF to PVI alone versus PVI and CFAE ablation versus PVI and linear ablation showed no difference among the groups in terms of freedom from AF at 18 months after ablation (59% versus 49% versus 46%; P=0.15).36

Linear Ablation

Linear ablation can be performed to interrupt existing or potential macroreentrant atrial circuits and can also serve to debulk/compartmentalize the atrial substrate. The most commonly applied linear lesion sets are the left atrial roof and mitral isthmus lines. In patients with persistent AF, linear ablation likely provides additional benefit to PVI in overall sinus rhythm maintenance,37 however, may increase the risk of recurrent macroreentrant atrial tachycardias.38 Although linear ablation alone has previously been shown to convert some patients in AF directly to sinus rhythm,39 it is primarily used to
address macroreentrant tachycardias that AF can organize into (or at times may coexist during AF) and to further debulk atrial substrate. Although linear ablation alone rarely terminates AF, a stepwise ablation strategy, linear ablation was required in ≤80% of patients with persistent AF after isolation of the PVs and ablation of complex electrograms to terminate AF. The 2 possible explanations of this observation are

1. Sites where linear ablation is typically performed usually harbor residual drivers of AF, which become manifest and perpetuate AF after elimination of other drivers elsewhere in the atria.
2. Linear ablation simply results in debulking and compartmentalization of the atria similar to the classic maze procedure and eliminates fibrillatory conduction without targeting specific drivers of AF. In fact, redo procedures are frequently performed after stepwise ablation, and the predominant recurrent arrhythmia is an atrial flutter or tachycardia, which may have been initiated by the same trigger or driver that would have initiated AF if it were not for elimination of fibrillatory conduction by linear ablation.

**Real-Time Mapping of Focal Sources and Rotors**

**Spectral Mapping of Sites With a High DF**

Real-time mapping in an attempt to identify ablation targets through spectral analysis has been proposed following the observation that sites where AF termination occurred during ablation often had higher DF. Decreases in DF as measured in the coronary sinus and elimination of intra-atrial or interatrial DF gradients have been predictive of long-term success and maintenance of sinus rhythm in some studies. However, prospective attempts targeting high DF sites have not consistently produced improved long-term efficacy. The limitations of spectral mapping to identify sites with the highest DF include:

1. Spatiotemporal instability of the high-frequency sources: rotors have been recognized to meander in experimental models and may not last for more than a few hundred milliseconds. Although endocardial ablation can achieve transmural lesions, strictly endocardial mapping to reliably identify high-frequency sources may be inadequate.
2. Most current mapping strategies are limited to the endocardium, whereas studies have shown reentrant circuits also using epicardial and intramural substrates. Although endocardial ablation can achieve transmural lesions, strictly endocardial mapping to reliably identify high-frequency sources may be inadequate.
3. Spectral mapping is sensitive to far-field contamination particularly from the left atrial appendage and the ventricle. Accurate spectral mapping requires high-density mapping, preferably optical mapping, which is not feasible in the clinical setting.
4. A trigger or driver may engage and initiate a perpetuator or rotor, which may have a higher DF than the trigger itself. Ablation of the higher frequency perpetuator may not necessarily result in elimination of the primary driver(s) of AF. In a prior study, rotors were most prevalent around the antrum of the PVs where primary triggers of AF in the form of PV tachycardias have been long recognized to exist.

In a recent study, 117 patients with persistent AF were randomized to PVI alone versus PVI and targeting of areas with high-frequency atrial electrograms. Clinical outcomes were similar at 6 and 12 months. Only 12% of patients converted to sinus rhythm during targeting of high-frequency atrial electrograms.

**Mapping of Focal Sources and Rotors**

Subsequent to the demonstration of rotors as a mechanism critical to perpetuation of AF in experimental models that used optical phase maps with voltage-sensitive dyes, panoramic electrogram mapping of the atria using multipolar basket catheters with off-line phase analysis using Hilbert transformation has been reported to demonstrate rotors in early clinical studies (focal impulse and rotor modulation [FIRM]). These sites were targeted by focal ablation in conjunction with PVI. In the pivotal Conventional Ablation for Atrial Fibrillation With or Without Focal Impulse and Rotor Modulation (CONFIRM) study, an improvement in 1- to 3-year outcomes when compared with a control group of patients who underwent antral PVI was reported. The FIRM-blinded success rates in these studies, however, were considerably lower than in most other studies and reported at 38%, during nearly 3 years of follow-up. Although termination to sinus rhythm was achieved with low duration of energy application, overall conversion to sinus rhythm during ablation was still only near 50% in both persistent and paroxysmal patients. Limitations of the FIRM approach may include:

1. Reproducibility of the results of the original study.
2. Electrograms with sufficient quality for any meaningful analysis can often not be recorded in ≥50% of the electrograms of a basket catheter and interpolation of the missing data is a crucial component of the FIRM analysis. However, interpolation depends on many assumptions, which may not be valid. Moreover, interpolation of data based on reverse solution of a Hilbert transform can be inherently problematic. In a recent study, off-line analysis of data from patients undergoing FIRM-guided ablation demonstrated that there was no difference between rotor and distant sites in DF or Shannon entropy, and there was no rotational activation at FIRM-identified rotor sites in the vast majority of the patients.
3. Phase maps generated by FIRM analysis demonstrate sustained, stable rotors for minutes if not longer. However, both experimental models and analysis of body surface maps suggest that rotors often are not stable for extended periods of time.

**Body Surface Mapping**

In a recent study, ablation was guided by mapping of driver domains using noninvasive body surface mapping in patients with persistent AF. The median number of driver domains
targeted increased from 2 to 6 as the duration of AF became longer. Unlike in FIRM-guided ablation, drivers were often unstable, lasting for a mean of ≈400 ms. There was no driver activity recorded in ≈40% of the duration of AF. It was estimated that 80% of the drivers were reentrant and 20% were focal, and 30% resided in the right atrium. Because the drivers were unstable, the investigators used a density/cluster map of putative target sites in the descending priority of prevalence. AF terminated to sinus rhythm in 30% and to an atrial tachycardia in 55%. There was an inverse relationship between AF termination rate and the duration of AF. Despite additional linear ablation in some patients, AF termination rate was 15% in patients with long-standing persistent AF. Driver regions tended to cluster around the antrum of the PVs and the appendages. Reentrant drivers were also identified close to focal drivers. Compared with patients who had typical stepwise ablation (without body surface mapping), a similar proportion of patients were in sinus rhythm at 12 months of follow-up, however, the duration of ablation was significantly shorter in the driver-mapping group. Although the authors report that patients who had termination of AF were more likely to remain in sinus rhythm than those without termination (85% versus 63%, P = 0.045), patients who had long-standing persistent AF were less likely to terminate.

Therefore, it is possible that termination of AF simply identifies patients who have lesser electroanatomical remodeling and more likely to remain in sinus rhythm regardless of the ablation strategy. Furthermore, termination to sinus rhythm occurred in only 30% and the majority of patients converted to an atrial tachycardia, which may simply be because of elimination of fibrillatory conduction rather than the ablation of specific drivers. These patients may be more susceptible to recurrences either through residual drivers or because of incomplete linear ablation. Limited spatiotemporal resolution, short sampling duration (5 s), the need to sample electrograms in incomplete linear ablation. Limited spatiotemporal resolution, short sampling duration (5 s), the need to sample electrograms in incomplete linear ablation. Therefore, endocardial breakthroughs may not be readily identified. It is also possible that rotors may represent bystander activation in response to adjacent primary focal discharges.

A helpful approach would have been to compare the driver maps before and after ablation in patients who did and did not have termination of AF using both FIRM and body surface mapping approaches. At present, there is limited evidence that rotors play a causal role in perpetuation of human AF and whether what is ablated is a true rotor. There are no established guidelines dictating procedural end points during ablation of persistent AF. A review of recent studies in the past 5 years, in which ablation was performed with a goal of conversion to sinus rhythm in patients with persistent AF shows a large disparity in overall successful conversion to sinus rhythm rate with a range of 14% to 68% (Table). Long-term success rates ranged from 40% to 75% with the majority of follow-up cited at about 2 years, similar to the results of most published studies evaluating outcomes for ablation of persistent AF. Furthermore, these studies were not randomized controlled trials.

### Table. Clinical Studies and Termination of AF During Ablation

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients, AF Type</th>
<th>Primary Ablation Strategy</th>
<th>Percent Conversion to SR During Ablation</th>
<th>Mean Procedure Time</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu et al(^{39})</td>
<td>120, persistent AF</td>
<td>Pure linear ablation with bidirectional block</td>
<td>62.5% (29% directly to sinus, 33% via AT)</td>
<td>145 min</td>
<td>40% at 5.1 y after single procedure</td>
</tr>
<tr>
<td>Miyazaki et al(^{52})</td>
<td>135, persistent AF (76 long-standing)</td>
<td>PVI, LA/RA substrate modification</td>
<td>51% (16% directly to sinus, 36% to AT)</td>
<td>300 min (termination) vs 330 min (CV)</td>
<td>74% free from AF at 15 mo</td>
</tr>
<tr>
<td>Zhou et al(^{54})</td>
<td>200, persistent AF</td>
<td>PVI, roof line, CFAE ablation</td>
<td>47% (16% directly to sinus, 31% via AT)</td>
<td>300 min (termination) vs 330 min (CV)</td>
<td>61.5% free from AF at 46.4 mo</td>
</tr>
<tr>
<td>Komatsu et al(^{53})</td>
<td>132, persistent AF</td>
<td>PVI, CFAE ablation</td>
<td>39% (13% directly to sinus)</td>
<td>184 min</td>
<td>68% free from AF at 20 mo</td>
</tr>
<tr>
<td>Wang et al(^{53})</td>
<td>293, persistent AF</td>
<td>Stepwise ablation</td>
<td>45% (11% directly to sinus)</td>
<td></td>
<td>60% to 67% SR maintenance at 23 mo</td>
</tr>
<tr>
<td>Park et al(^{54})</td>
<td>140, long-standing persistent AF</td>
<td>PVI, left and right CFAE ablation</td>
<td>68% (24% directly to sinus)</td>
<td>328 min (termination) vs 376 min (CV)</td>
<td>43% SR without AAD at 19 mo after 1 procedure</td>
</tr>
<tr>
<td>Elayi et al(^{54})</td>
<td>306, long-standing persistent AF</td>
<td>PVI, CFAE ablation</td>
<td>14% (2% directly to sinus)</td>
<td>249 min</td>
<td>69% SR without AAD at 25 mo</td>
</tr>
</tbody>
</table>

AAD indicates antiarrhythmic drugs; AF, atrial fibrillation AT, atrial tachycardia; CFAE, complex-fractionated atrial electrograms; CV, cardioversion; LA, left atrium; PVI, pulmonary vein isolation; RA, right atrium; and SR, sinus rhythm.
In the largest of these studies by Elayi et al,\textsuperscript{64} ablation was performed in 306 patients with persistent AF. With extensive ablation (mean procedure time, 249±93 minutes), including antral PV and posterior left atrial isolation, elimination of CFAEs, and targeting of all atrial tachycardias including linear ablation, only 14% of the patients ultimately converted to sinus rhythm. Despite this, 69% of patients maintained sinus rhythm at 2 years without antiarrhythmic drugs. In this study, conversion to sinus rhythm actually did not predict long-term sinus rhythm maintenance but rather just the mode of atrial arrhythmia recurrence. In the next largest study by Wang et al, 293 patients underwent stepwise ablation for persistent AF during which 45% of patients eventually were ablated to sinus rhythm. Sinus rhythm maintenance at nearly 2 years was similar between patients ultimately ablated to sinus rhythm versus patients who underwent cardioversion (67.2% versus 59.8%, \(P=0.198\)). Only few patients (11.3%) who converted directly to sinus rhythm were found to have improved long-term outcomes.

A recently published study reported the long-term outcomes of a strategy of ablation of persistent AF with a stepwise approach using PVI, linear ablation, and electrogram-guided ablation with a procedural end point of AF termination.\textsuperscript{59} This study did report a high rate of conversion during ablation to sinus rhythm at 80% with a mean procedure time of 264 minutes. However, single procedure success rate at 70 months was only 15%. After a mean of 2.1 procedures per patient, successful maintenance of sinus rhythm was achieved in 65% of the patients without antiarrhythmic drugs after a median follow-up of 58 months, although long-term monitoring in these patients was limited. Despite the high conversion rate during ablation, these outcomes are not remarkably higher than in other studies with much lower rates of conversion to sinus rhythm, suggesting the benefit during the stepwise approach lies not primarily with acute AF termination but rather the broader electroanatomic changes to the atrial substrate. This is supported by the findings in another recent prospective study that randomized patients undergoing ablation of persistent AF to the stepwise ablative approach versus a fixed anatomic approach consisting of PVI, mitral isthmus and roof lines, and a cavo-tricuspid isthmus line. This study showed no significant difference in freedom from atrial arrhythmias at one year after the ablation despite shorter procedural and radiofrequency time with the fixed anatomic approach.\textsuperscript{56}

With the current technology and available outcomes data, there is lack of sufficient experimental and clinical evidence to support termination as the procedural end point during ablation in patients with persistent AF. Extensive ablation in pursuit of the often elusive goal of AF termination may lead to unnecessarily lengthy procedures with the risk of an increase in complications without an improvement in long-term outcomes.

Conclusions

Three fundamental questions remain unanswered: (1) What are the specific mechanisms of human atrial fibrillation? (2) Can these mechanisms be accurately identified and targeted? and (3) Do targeted ablation strategies improve patient outcomes? Until these important questions are answered, there is little or no justification for pursuing termination of AF as a procedural end point during catheter ablation of persistent AF.

At an age when we can land a spaceship on a comet; when we can receive and process signals from outer space, millions of light-years away; and when we can identify the Higgs boson, can we really not map and understand the mechanisms of human AF?

We should be able to. However, this will require a broad scale, open-source, and open-minded collaboration among physicians, engineers, scientists, and clinicians across the world with a focus on observing and understanding the nature first rather than trying to prove a hypothesis. After all, as Thomas Huxley once said “It is about what is right, not who is right (or more contemporarily, not whose hypothesis or technology will prevail).”

It is time…

Disclosures

Dr Oral is a founder and equity holder of Rhythm Solutions. Dr Latchamsetty reports no conflicts.

References


Response to Rakesh Latchamsetty, MD, and Hakan Oral, MD

Han S. Lim, MBBS, PhD; Nicolas Derval, MD; Yuki Komatsu, MD; Stephan Zellerhoff; Arnaud Denis, MD; Ashok J. Shah, MD; Frédéric Sacher, MD; Mélèze Hocini, MD; Pierre Jais, MD; and Michel Haïssaguerre, MD

Latchamsetty and Oral acknowledge that current ablation strategies are not well established, and that pulmonary vein isolation is an insufficient stand-alone strategy for many patients with persistent atrial fibrillation (PsAF). The authors correctly identify some of the challenges facing PsAF ablation, such as the lack of a distinct procedural endpoint, inconsistent findings between different studies, current technological limitations, and the broad spectrum of patients with PsAF. However, it is precisely in addressing these issues that AF termination plays a key role. Numerous animal, pharmacological, cardioversion, and ablation studies have demonstrated that successful termination of the arrhythmia by the various means is associated with improved outcomes.

Termination of AF indicates successful elimination of the drivers or perpetuators in a particular patient such that AF can no longer be sustained. The authors discussed several mechanistic considerations for AF termination including the notion that pathogenesis of AF is often progressive. This is most likely because of the underlying risk factors for AF causing progressive substrate changes, as shown in recent studies. Therefore, AF ablation should be complemented with strict management of underlying cardiovascular risk factors and efforts to minimize the extent of atrial remodeling and duration of PsAF before ablation. From the ablation perspective, termination of AF offers the greatest possibility that AF drivers at the time of the procedure are eliminated. It is true that PsAF encompasses a broad spectrum of patients with mild-to-severe atrial remodeling. A strategy aiming for AF termination would stratify these patients to mild forms of PsAF where less ablation is required, to more severe forms of PsAF necessitating further substrate ablation. As mentioned by the authors, catheter ablation endpoints can be variable—AF termination provides a nonambiguous endpoint that can be measured across different studies. Indeed, complex-fractionated atrial electrograms lack specificity. Newer mapping techniques, such as panoramic noninvasive and invasive mapping, provide increased specificity in identifying AF drivers and an unprecedented view of the global AF process. However, these studies also revealed the dissemination of arrhythmogenic substrate within a 6 to 12-month time frame, confirming experimental studies, and the involvement of widespread biatrial regions in long-standing PsAF. In the latter cases, the incidence of AF termination is much lower and difficult to achieve, and it would be important to evaluate if certain driver regions may diminish during reverse remodeling and thus be spared from extensive ablation to the point of AF termination. Although current means for achieving AF termination are constrained by technological limitations, they do not signify that the ends of achieving AF termination are unfitting.

In addressing the current challenges facing PsAF ablation, AF termination provides (1) a distinct procedural endpoint, (2) an objective measure that can be compared across studies, (3) improved long-term clinical outcomes, (4) a patient-tailored approach such that patient-specific drivers are targeted, and (5) stratification of the extent of ablation to determine which patients may require further ablation beyond pulmonary vein isolation, and which patients in whom extensive ablation may be avoided across the broad spectrum of patients with PsAF.
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*Circ Arrhythm Electrophysiol.* 2015;8:972-980
doi: 10.1161/CIRCEP.115.001722

Circulation: Arrhythmia and Electrophysiology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3149. Online ISSN: 1941-3084

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