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Catheter Ablation of Atrial Fibrillation

The Search for Substrate-Driven End Points

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Indications for catheter ablation of atrial fibrillation (AF) have expanded to include increasingly complex cases, such as long-standing persistent AF and structural heart disease. Although pulmonary vein isolation remains essential for most ablation procedures, the role of substrate modification has taken on increasing importance. Despite the various ablation strategies available, single-procedure efficacy remains suboptimal among patients with structural heart disease or long-standing persistent AF, where recurrence rates may exceed 50% after a single procedure. These high rates of AF recurrence support the notion that currently available procedural end points are ineffective in identifying which patients are most likely to benefit from substrate modification and defining when that substrate has been sufficiently modified such that additional ablation is unnecessary. In order to improve outcomes, the next generation of procedural end points should seek to define specific properties of the underlying atrial electrical substrate and characterize the impact of catheter ablation on those electrophysiologic properties. The use of substrate-driven end points would be a major step in the process of moving from empiric ablation lesions to a customized ablation strategy based on atrial physiology. In this article, we review current approaches to catheter ablation of AF and discuss specific procedural end points as they pertain to each ablation strategy. We also provide a paradigm for the future development of novel substrate-driven procedural end points. (J Am Coll Cardiol 2010;55:2293–8) © 2010 by the American College of Cardiology Foundation

Catheter ablation is an established therapeutic option for certain patients with atrial fibrillation (AF). The highest procedural success rates after catheter ablation are typically seen in patients with paroxysmal AF and minimal structural heart disease (1). Recent data also support the use of catheter ablation in clinical settings previously deemed unsuitable, such as long-standing persistent AF (2) and left ventricular dysfunction (3).

Although the specific mechanisms that give rise to AF have not been completely elucidated, a paradigm of triggers and substrate has emerged. According to this model, when high-frequency discharges from focal triggers encounter a sufficiently heterogeneous atrial substrate, they give rise to fibrillatory conduction, which manifests clinically as AF. Although the relative importance of triggers and substrate may vary from patient to patient, considerable experimental (4,5) and clinical (6) evidence suggests that as AF progresses from paroxysmal to persistent, the atrial substrate becomes increasingly abnormal and may play a relatively more important role in maintaining the arrhythmia.

Building on this paradigm, current catheter ablation strategies fall into 2 broad categories: ablation or isolation of focal triggers to prevent AF initiation and atrial substrate modification to impede AF perpetuation. With these approaches, single-procedure success rates (variably defined) are approximately 60% to 80% for patients with paroxysmal AF, with 30% to 40% of patients requiring a second procedure to achieve long-term freedom from AF (7). These success rates suggest that the most widely used procedural end points to document complete electrical isolation of the pulmonary veins (PVs) during ablation of paroxysmal AF are reasonably effective in defining a procedural end point for most patients. Even among patients who do experience clinical AF recurrence, the dominant mechanism of recurrence in most cases seems to be reconnection

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Abbreviations and Acronyms

AF = atrial fibrillation

CFAE = complex fractionated atrial electrogram

DF = dominant frequency

HFS = high-frequency stimulation

PV = pulmonary vein

of the PVs (8,9), suggesting that the ability to create more permanent ablation lesions may also provide an important opportunity to improve outcomes (10). This review focuses on the role of novel procedural end points as a means to improving outcomes, but the importance of enhanced energy delivery systems to create more permanent lesions cannot be overlooked.

Although many patients with late recurrence after paroxysmal AF ablation have reconnected PVs, a smaller percentage of patients undergoing repeat procedures for AF recurrence are found to have non-PV foci that may not have been identified or targeted during the initial procedure. Estimates vary, and 4% to 42% of patients having repeat ablation procedures for paroxysmal AF need ablation of non-PV foci during the follow-up procedure (9,11,12). In these patients, the role of non-PV triggers and atrial substrate may play a more important role in maintaining AF. The use of novel procedural end points may provide an opportunity to identify these patients and perform additional, non-PV–targeted ablation during the index procedure.

Moving from paroxysmal to persistent AF, the goal of identifying robust substrate-driven procedural end points takes on even greater importance. Although complete isolation of the PVs is recommended as the cornerstone of most ablation procedures, there is widespread recognition that among patients with long-standing persistent AF, PV isolation alone may be insufficient (1,13). The efficacy of AF ablation is related to the extent of ablated tissue (14,15), and because ablation is being performed in increasingly complex patients, there has been a trend toward more extensive lesions performed in a stepwise manner (16,17). However, concerns have also been raised that more extensive ablation may increase the risk of complications (18) and impair left atrial mechanical properties (19,20).

The importance of robust procedural end points stems from the need to balance efficacy and safety. Current data suggest that both the efficacy of ablation and the risk of complications may be related to the extent of tissue ablated. Currently available procedural end points have largely focused on documenting the completeness of a particular ablation lesion set or on slowing the AF cycle length and terminating the arrhythmia. However, these end points provide limited information about the long-term profibrillatory potential of the atrium and cannot necessarily be used to guide decisions regarding the risks and benefits of additional ablation. Therefore, the development of new end points that can be applied in real time to determine when enough ablation has been performed to sufficiently modify the atrial substrate may be critical to improving safety and efficacy.

In this paper, we will briefly discuss the pathophysiologic basis for various AF catheter ablation techniques and review the currently available procedural end points for each ablation strategy. We conclude with a discussion about future directions in the search for new substrate-driven procedural end points.

Ablation Targeting PV Foci

Building on the seminal observations of Haissaguerre et al. (21), a number of groups have reported high success rates for paroxysmal AF treated with catheter ablation to isolate PV foci (Fig. 1) (22–28). These studies have demonstrated the presence of tissues capable of generating spontaneous electrical activity within the muscular sleeves that extend around the PVs and that focal discharges from these sites are capable of initiating AF. As outlined in the recent consensus statement on AF ablation (1), isolation of the PVs remains the backbone of most AF catheter ablation procedures, and therefore the use of procedural end points to define the completeness of isolation is an important step in achieving a high success rate.

However, end points to confirm the adequacy of PV isolation vary. Both entrance block with the use of a circular mapping catheter with tightly spaced electrodes (29) and exit block by pacing within the PVs (30) have been advocated as end points. But even with the use of both entrance and exit block, early PV reconnection can be seen. As such, employing a waiting period of 30 to 40 min after ablation followed by repeat assessment of block has been advocated as an adjunctive end point (30), although later electrical reconnection of PVs is frequently seen and can be,

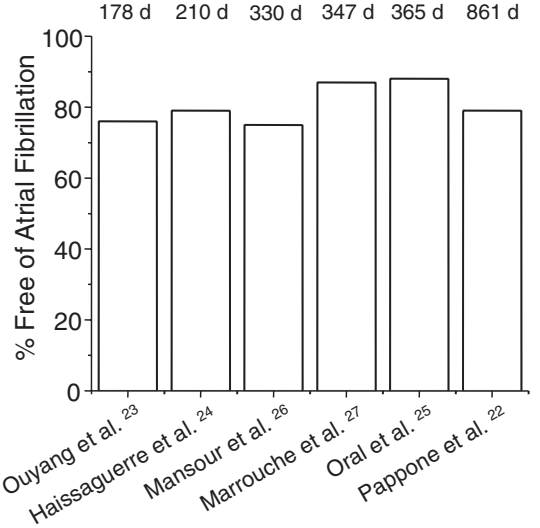

Figure 1 **Success Rates of PV-Targeted Catheter Ablation of Paroxysmal AF**

Mean duration of follow-up (days [d]) listed above each study.
AF = atrial fibrillation; PV = pulmonary vein.

although not necessarily (31), a source of AF recurrence. Last, local electrogram voltage abatement during RF application has also been used to document adequate PV isolation (32).

In addition to isolating triggers, the use of PV targeted ablations, especially antral and circumferential PV lesions, may also play a substrate-modifying role by eliminating anisotropic conduction properties at the PV-left atrial junction (33). By modifying conduction in this region, ablation at the PV-left atrial junction may hinder re-entry and perpetuation of AF (33). Additionally, PV targeted ablation has a significant impact on other markers of left atrial substrate, including dominant frequency gradient (34), fractionated electrogram distribution (35), and autonomic function (36). However, the effect of PV-targeted ablation on altering the atrial substrate remains poorly defined because currently available procedural end points are largely unable to distinguish between the trigger-isolating and substrate-modifying benefits of these various PV-targeted techniques.

Additionally, several studies have looked at the efficacy of empiric isolation of all pulmonary veins versus identification and selective isolation of arrhythmogenic veins (37,38). These studies have demonstrated shorter procedure times, less application of radiofrequency energy, and comparable efficacy with selective vein isolation. However, techniques for identifying arrhythmogenic veins vary substantially, and until this approach is more broadly validated, empiric isolation of all veins remains the most widely used technique.

Linear Lesions

In an attempt to recapitulate the early success of surgically placed linear ablation lesions, a number of catheter-based linear lesions have been advocated to improve long-term success rates. Linear lesions along the roof of the left atrium connecting the superior aspects of the left and right upper PV isolation lesions ("roof" line) and linear lesions along the region between the mitral annulus and the left inferior PV (mitral isthmus) may improve clinical outcomes (18,39,40).

In contemporary practice, much of the emphasis on performing linear lesions has focused on preventing post-ablation atypical atrial flutters. But beyond the prevention of post-ablation atrial tachyarrhythmias, linear lesions may also play a salutary role in modifying substrate and preventing AF recurrence (41,42). Although complete linear lesions may not be necessary for substrate modification (41), incomplete linear lesions may have a proarrhythmic effect (43). A number of procedural end points have been used to document bidirectional block around linear ablation lesions, including demonstration of a corridor of double potentials along the length of the ablation line during pacing and demonstration of an activation detour when pacing from either side of the line (18,40).

Electrogram-Guided Ablation

Anisotropic re-entry leading to rotors with high dominant frequency (44) has been proposed as a potential mechanism for the genesis of AF. Elimination of these rotors and AF nests may be 1 of the mechanisms by which real-time frequency analysis or complex fractionated atrial electrogram (CFAE)-guided ablation prevents AF (45,46). A number of groups have reported high success rates with tailored approaches that target drivers of AF through spectral analysis and electrogram-guided ablation during AF or sinus rhythm (16,46,47). Studies have suggested that a preponderance of CFAE sites exist in close proximity to the PVs (48) or sites of autonomic ganglionated plexi (49) and, therefore, substantial overlap may exist between CFAE-targeted lesion sets and other ablation strategies. Therefore, the relative merits of these ablation strategies and the opportunities for synergy between them remain to be defined.

Procedural end points for electrogram-guided ablation have included slowing of fractionated activity (50) or complete elimination of all complex fractionated activity (46). Other frequently used end points during electrogram-guided ablation include acute termination for patients with persistent AF and noninducibility for patients with paroxysmal AF. One of the most important questions regarding electrogram-guided ablation is whether all sites of complex fractionated activity need to be identified and isolated or whether certain electrophysiologic characteristics can be used to identify critical sites (45,50). Although the use of CFAE-guided ablation end points is still a work in progress, it represents a step forward in the quest to identify procedural markers that are reflective of the underlying atrial electrophysiologic substrate.

Autonomic Denervation

Areas rich in autonomic innervation may be a source of activity that triggers AF (51). High-frequency stimulation (HFS) around the PV-left atrial junction may identify ganglionated plexi, which serve as a source of vagal reflexes capable of inducing and perpetuating AF through spatial heterogeneity of refractoriness (52). Damage to ganglionated plexi, usually located 1 to 2 cm outside of the PV ostia, has been proposed as an effect of antral PV ablation (53).

Vagal reflexes, including bradycardia, asystole, atrioventricular block, or hypotension, may be elicited by HFS in the region of the autonomic ganglia. As a procedural end point, RF is applied in these regions until vagal reflexes are no longer elicited (52,53). However, in certain circumstances, vagal reflexes may not be elicited during application of RF energy, and specific ablation of autonomic ganglia identified by HFS is not necessarily more effective than an anatomic approach to autonomic denervation (54). Additionally, in cases where HFS is used, the importance of abolishing all sites of vagal reflex and the potential role of autonomic ganglia in other

sites (i.e., right atrium) have not been clarified. Because both sympathetic and parasympathetic elements reside in all major left atrial ganglionated plexi (55), denervation lesions may also unavoidably affect both components of the autonomic nervous system. Thus the impact of regional ablation on the components of the autonomic system cannot be easily deduced, and the clinical relevance of these observations for guiding autonomic denervation-based ablation strategies remains unclear.

Combined Approaches

In most patients, multiple mechanisms likely contribute to the initiation and perpetuation of AF. Therefore, tailored approaches combining more than 1 ablation technique have been described. Using combined approaches, the extent of left atrial ablation has been advocated as a marker of long-term success and as an adjunctive procedural end point (15). Pappone et al. (14) have suggested that a greater extent of left atrial ablation (average 30%) is associated with improved outcomes in both paroxysmal and persistent AF. This metric is based on the idea that more extensive ablation-induced damage is associated with a higher probability of modifying the atrial substrate sufficiently to prevent AF. However, given concerns that increased areas of scar with low voltage and slowed conduction in the left atrium may be proarrhythmic (56), it is unlikely that extent of ablation will evolve into an adequate procedural end point.

Acute termination of AF or slowing of the fibrillatory cycle length has also been used as a procedural end point in numerous studies (24,45,57) and has been associated with long-term freedom from AF (58). Additionally, AF inducibility after ablation has been studied prospectively as a procedural end point and as a marker to guide the need for further ablation. A number of stepwise or tailored approaches have implemented increasing ablation lesions until AF is rendered noninducible, by rapid atrial pacing and/or infusion of isoproterenol. Several studies (24,39,59) have suggested that noninducibility can be used as a procedural end point with improved short- to midterm outcomes compared with ablation procedures in which inducibility was not specifically targeted. However, in cases of long-standing persistent AF, many operators do not attempt to induce AF at the end of the procedure, thereby limiting the utility of this technique.

Novel Procedural End Points and Emerging Opportunities

Paroxysmal AF. Given the established role of PV triggers in paroxysmal AF, the development of new substrate-driven procedural end points may have a limited role in guiding ablation therapy. However, a number of reports have demonstrated important changes in the atrial substrate of patients with paroxysmal AF, including alterations in patterns of dominant frequency (60), conduction velocities/refractoriness, and sinus node dysfunction (61). Tools to identify these early changes may allow implementation of upstream therapies capable of preventing the progression from paroxysmal to persistent AF. Although the specific role of these substrate-driven markers for guiding catheter ablation of paroxysmal AF remains to be determined, these early insights suggest that substrate could play an increasingly prominent role in treating patients along the spectrum from paroxysmal to persistent.

Persistent AF. The real promise for new substrate-driven markers lies in their role as procedural end points for ablation of long-standing persistent AF. Despite the increasingly complex list of AF catheter ablation strategies, most currently available procedural end points are designed primarily to document the completeness of a particular lesion set. Few, if any, end points are capable of defining the overall impact of ablation on the propensity of an individual patient to develop recurrent AF. In some ways, the search for procedural end points has failed to keep pace with advances in other aspects of AF ablation technology.

It would be highly beneficial if the next generation of procedural end points was capable of gauging the profibrillatory potential of the atrium as a whole, rather than serving only to document the completeness of a particular lesion set. In this manner, new end points could be used to define when the arrhythmogenic potential of the underlying PVs and atrium has been sufficiently modified to prevent AF recurrence. As such, future research efforts should seek to identify electrophysiologic markers with certain specific characteristics that would allow them to serve as useful procedural end points, such as:

- The ability to measure the profibrillatory potential of the PVs and atrium in real time
- A means to gauge the impact of ablation on the underlying substrate, regardless of the specific ablation strategy or lesion set being used
- A clinically-validated threshold of change in the electrophysiologic marker that, if achieved during the course of ablation, would suggest that the arrhythmogenicity of the atrium has been sufficiently modified such that further ablation would be unnecessary and potentially harmful
- A metric to predict clinical outcome and freedom from AF recurrence

Identifying a single validated electrophysiologic marker to serve all of these purposes may be impractical. However, it is conceivable that a panel of electrophysiologic markers may be capable of meeting these needs.

A number of electrophysiologic markers have already been investigated as tools to measure properties of the electrical substrate during ablation. Many of these markers are able to provide information about the underlying atrial substrate without regard to the specific ablation strategy being used. For example, spectral analysis and dominant frequency (DF) mapping has been studied extensively as it

pertains to the effects of catheter ablation on the underlying substrate, and a number of studies have demonstrated reductions in DF after ablation at various sites (34,47,62). Additionally, at least 1 report has demonstrated that the clinical efficacy of electrogram-guided ablation in persistent AF may be associated with the degree of abatement in DF (62). Another preliminary report suggested that among patients undergoing ablation of persistent AF, a decrease in DF of ≥11.5% during ablation was associated with significantly better outcome than those who failed to achieve this threshold. Patients achieving this threshold had similar outcomes to those who achieved acute termination of AF during ablation, but with significantly shorter procedure times (63). If confirmed prospectively, observations such as these provide proof of concept that markers of the atrial substrate can be used in real time to guide ablation therapy.

As discussed above, CFAE-guided ablation also represents a significant advance in the use of substrate-driven markers. However, CFAE identification is highly dependent on operator judgment, making it difficult to develop quantitative metrics that can be used to define procedural end points. Recent reports looking at automated CFAE detection and mapping algorithms (64) may serve as a step toward quantification of CFAE-guided ablation. In this context, future studies may seek to determine whether specific thresholds such as percent or absolute reduction in CFAE sites can be identified, which would predict freedom from AF recurrence.

Prospective studies will be crucial in determining whether these or other substrate-driven markers are capable of defining an end point for ablation with a high level of safety and efficacy. Extension of these observations and identification of other novel markers of atrial arrhythmogenic substrate holds substantial promise for improving outcomes of AF catheter ablation. As such, the search for substrate-driven procedural end points represents a major step in the movement away from empiric ablation sets and toward truly customized ablation based on atrial electrophysiology.

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