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Non-Inducibility Or Termination As Endpoints Of Atrial Fibrillation Ablation: What Is Their Role?

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Abstract

Catheter ablation is widely used to treat drug-refractory, symptomatic atrial fibrillation (AF). However, beyond pulmonary vein isolation, there remains little consensus on the recommended approach to ablation both in paroxysmal or persistent AF patients. Although ancillary ablation strategies are often used, the lack of a clear endpoint for AF ablation makes it challenging to evaluate their importance. Non-inducibility and termination of AF during AF ablation have been advocated as potential endpoints. Several studies have attempted to assess their role in an AF ablation protocol. However, the data for non-inducibility and termination as endpoints are mixed. Moreover, there are a number of limitations in the studies reported and limitations of the endpoints themselves. It is likely that non-inducibility or termination of AF during AF ablation may be markers of less structural remodeling rather than true endpoints for ablation. Herein, we review the relevant literature on the topic of inducibility and termination with respect to AF ablation and attempt to draw conclusions with guidance to further investigation.

Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting between 2.7 million and 6.1 million American adults, a number that is expected to double by the year 2050.[1] Commonly, catheter-based ablation is utilized to manage the symptoms of AF. The techniques for catheter-based ablation continue to evolve, however ablation strategies that target the pulmonary vein (PV) antrum with a goal of PV isolation (PVI) remain the cornerstone of catheter ablation. Beyond PVI, there remains little consensus on approaches to ablation both in paroxysmal and persistent AF patients. The precise benefits of ancillary strategies including linear ablation, complex fractionated atrial electrogram (CFAE) ablation, ganglionated plexi ablation, and most recently focal impulse rotor modulation (FIRM) have yet to be established. Fundamentally, the goal of an AF ablation procedure is to ablate the least amount of tissue necessary to render the patient free of AF over the long-term. An optimal endpoint would therefore identify when this has been achieved, thus identifying patients who require additional ablation as well as sparing unnecessary additional ablation in patients who already would have achieved good long-term result. Non-inducibility or termination of AF have been considered for endpoints of ablation in this role.

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Mechanistic Overview Of AF: Role Of Non-inducibility Or Termination

Effects of catheter ablation of atrial fibrillation can broadly be understood with respect to the proposed pathophysiologic basis of atrial fibrillation. There are likely multiple coexistent mechanisms, which contribute to the genesis of AF in humans. These include distinct triggering events, which initiate the arrhythmia. In some, a focal rapidly-firing source serves to maintain the arrhythmia. But in most, there are abnormalities of the substrate, which serve to perpetuate AF.[2] The relative importance of triggers or substrate is unclear but likely both are critical.

Myocardial sleeves that extend from the left atrium into the pulmonary veins are the most common sources of electrical activity, which initiate atrial fibrillation.[3] However, non-pulmonary venous trigger sites, including the vein and ligament of Marshall, the posterior left atrium, the superior vena cava, the coronary sinus, and the crista terminalis may exist with varying frequency. Mapping and ablation of non-pulmonary venous triggers may have a role in catheter ablation as well, but identifying when these may be important is challenging.

The substrate allowing for maintenance of AF comes in many forms. Structural remodeling due to processes such as fibrosis or stretch provides a substrate for reentry. This structural remodeling may be due to systemic illness such as hypertension, obesity, or sleep apnea; cardiac disease such as heart failure or valvular disease; or even AF itself. Additionally, patients may develop electrical or functional remodeling, also contributing to a substrate for reentry. Ongoing high frequency atrial activity lasting longer than 24 hours leads to a process of electrophysiological remodeling which promotes sustained arrhythmia.[3] Approaches targeting substrate modification include linear ablation, CFAE ablation, ganglionated plexi ablation,

Table 1: Summary of studies evaluating non-inducibility as an endpoint of atrial fibrillation ablation.

Author	Year	N	AF Type	Induction protocol	Definition of inducibility	Follow-up	Results
Haissaguerre et al.	2004	70	AF with episode ≥ 1 hour	Decremental burst pacing (5 sec)	AF ≥ 1 min	7±3 months	87% of non-inducible patients vs. 62% of inducible patients (P=0.03) were AF-free
Oral et al.	2004	100	Paroxysmal AF	Rapid atrial pacing (≥ 15 sec @ shortest cycle length with 1:1 atrial capture)	AF > 1 min	6 months	85% of non-inducible patients after PVI vs. 67% of inducible patients after PVI vs. 86% patients who received further ablation after PVI when inducible were AF-free
Essebag et al.	2005	102	Paroxysmal and persistent AF	Burst pacing (5 sec @ 200 ms) ± isoproterenol	AF or left atrial tachycardia > 10 sec	1 year	72% of non-inducible patients vs. 53% of inducible patients (P=0.04) were AF-free
Jais et al.	2006	74	Paroxysmal AF	Decremental burst pacing (10 sec)	AF ≥ 10 min	18±4 months	91% of non-inducible patients were AF-free.
Richter et al.	2006	234	Paroxysmal (n=165) and persistent (n=69) AF	Decremental burst pacing	AF > 1 min	6 months	Non-inducibility had 46.7% sensitivity and 75% specificity for AF recurrence
Chang et al.	2007	88	Paroxysmal AF	Decremental burst pacing (5-10 sec)	AF or atrial flutter > 1 min	12±6 months	81% of non-inducible patients after PVI vs 84% of non-inducible patients after PVI plus additional ablation vs 45% of paitnets inducible after PVI plus additional ablation were AF-free
Crawford et al.	2010	112	Paroxysmal AF	Isoproterenol (up to 20 µg/min) Decremental burst pacing (10 sec)	AF up to 15 mins after infusion AF ≥ 1 min	12±5 months	84% of patients non-inducible with isoproterenol (33% sens, 97% spec), vs 76% of patients non-inducible by pacing (44% sens, 72% spec) were AF free
Satomi et al.	2008	60	Paroxysmal AF	Decremental burst pacing (10 sec)	AF > 10 mins	16±8 months	58% of non-inducible patients vs 59% of inducible patients were AF free
Leong-Sit et al.	2013	144	Paroxysmal (n=78) and persistent (n=66) AF	Decremental burst pacing (15 beats)	AF or atrial tachycardia/ flutter ≥ 2 mins	1 year	51% of non-inducible patients vs 51% of inducible patients were AF free

or FIRM ablation. Through these techniques, additional ablation at critical locations throughout the left or right atrium may be helpful in interrupting the paths of multiple wavelets or spiral re-entry in order to disrupt the maintenance of AF.

The rationale for non-inducibility with pacing as an endpoint is that a normal heart will not fibrillate longer than a certain period of time. Either the heart will not be vulnerable to fibrillation with a given pacing protocol, or that even if induced, the AF will be unstable and not sustain longer than several minutes. But patients who are destined to further AF have persistent abnormalities, which make them vulnerable to AF initiation and maintenance. The rationale for non-inducibility with high-dose isoproterenol is that potential triggers of AF such as high frequency premature atrial contractions or bursts of atrial tachycardia, which initiate AF, have been adequately eliminated.

The rationale for termination of AF as an endpoint is that it may signify the elimination of all mechanisms, which were maintaining AF. Persistent AF is maintained by initial drivers, subsequent irreversible structural remodeling, and potentially reversible electrical remodeling. Distinguishing structural remodeling from electrical remodeling, derived from electrophysiologic properties of the atrial myocardium including refractory periods and conduction velocities, is problematic. It is important to recognize that the AF substrate is a dynamic parameter. Chronicity of AF itself is known to modify the substrate. It may be also be affected by other factors including the autonomic nervous system. If a procedure continues until termination and AF persists due to temporary electrical remodeling, unnecessary ablation after elimination of all important drivers may be performed. Electrical remodeling may require a period of sinus rhythm to reverse and no amount of ablation may be adequate or necessary.

Herein, we review the relevant literature on the topic of non-inducibility and termination with respect to AF ablation and attempt to draw conclusions with guidance to further investigation.

Non- Inducibility As An Endpoint For AF Ablation

The notion behind attempting to induce AF is to reveal either a trigger or potential driver for AF. However, there are many difficulties in using non-inducibility as an endpoint: 1) inducibility may have low sensitivity or specificity for recurrent AF; 2) the methods of inducibility can vary between isoproterenol infusion or atrial pacing; 3) the methods for atrial pacing can differ; and 4) the definition of positive inducibility can vary (i.e. >1 min sustained AF, >10 min sustained AF, etc). With this background, several studies have considered non-inducibility as an endpoint of ablation with conflicting results (Table 1).

Non-Inducibility With Rapid Pacing: Studies Showing Benefit

A number of studies have suggested that non-inducibility of AF by atrial pacing after AF ablation may be associated with lower rates of AF recurrence. Presumably pacing may reveal a potential driver of AF outside of the ablated area, which could be targeted for further ablation.

Haissaguerre et al.[4] investigated the association between AF inducibility and clinical outcomes in 70 patients with drug-refractory AF. Patients were randomized to PVI with (n=35) or without (n=35) additional linear ablation. Predictors of non-inducibility were smaller left atrial size, a greater increase in AF cycle length, and termination of AF during PVI. At 7 ± 3 months of follow-up, 40 (87%) of 46 non-inducible patients remained free from arrhythmia off of antiarrhythmic drugs compared to 15 (62%) of 24 inducible patients (P=0.03).

Oral et al.[5] studied the association of inducibility with clinical outcomes in patients with paroxysmal AF undergoing PVI with possible additional linear lesions on the posterior wall and the mitral isthmus. Pulmonary vein isolation alone rendered 40 patients non-inducible (group 1). The remaining 60 patients, in whom AF was not terminated or was still inducible after initial PVI, were randomly assigned to no further ablation (group 2, n=30) or up to 60 minutes of additional ablation attempting to achieve non-inducibility (group 3, n=30). At 6 months, 85% of group 1 patients were free from AF. But 67% of group 2 compared to 86% of group 3 patients (P=0.05) were AF-free. The authors concluded that non-inducibility of AF

Table 2: Summary of studies evaluating termination as an endpoint of atrial fibrillation ablation.

Author	Year	N	AF Type	Ablation protocol	Follow-up	Results
Haïssaguerre et al.	2005	60	Persistent AF	Step-wise ablation	11±6 months	95% of patients with termination of AF during ablation were AF free
O'Neill et al.	2009	153	Persistent AF	Step-wise ablation	34 months	95% of patients with termination of AF vs 52% without termination were AF free
Rostock et al.	2011	395	Persistent AF	PVI+electrogram guided LA, CS and RA ablation and AT mapping and ablation	24 months	AF cycle length and AF termination during ablation predictors of AF free survival.
Park et al.	2012	140	Long-standing persistent AF	Step-wise ablation	18.7±7.6 months	69% of patients with termination of AF vs 45% of patients without termination were AF free (p=0.009)
Ammar et al	2013	191	Persistent AF	Step-wise ablation	12 months	42% of patients with termination to sinus vs 13% with termination to atrial tachycardia vs 25% without termination were arrhythmia free (p=0.002)
Zhou et al.	2013	200	Non-paroxysmal AF	Step-wise ablation	50.0±9.3 months	64% of patients with termination of AF vs 37% of patients without termination of AF were AF free (p<0.001)
Rostock et al	2013	110	Persistent atrial fibrillation	PVI+electrogram guided ablation +/- AT mapping	20.1±13.3 months	Those who underwent AT ablation were more likely arrhythmia free (57% vs 34%, p=0.02)
Komatsu et al.	2012	132	Persistent AF	Step-wise ablation	20±11 months	No difference in AF free survival whether or not AF terminated during ablation.
Wang et al.	2012	293	Persistent AF	Step-wise ablation	23±7 months	No difference in AF free survival whether or not AF terminated during ablation.

achieved by additional ablation may be a clinically useful endpoint.

Essebag et al.[6] studied 102 patients with paroxysmal, persistent, or permanent atrial fibrillation who underwent PVI. The authors found that paroxysmal (vs persistent or permanent) AF (OR 4.80) and non-inducibility (OR 3.84) were associated with freedom from AF at 1 year. There was no difference in freedom from AF between those inducible by burst pacing with and without isoproterenol.

In a follow-up study based on their initial findings4, Jais et al[7] enrolled 74 patients with symptomatic drug-refractory paroxysmal AF in a protocol in whom which inducibility was used as a guide for possible linear ablation in addition to PVI. Ultimately, 69 (93%) of the 74 study patients were non-inducible at the conclusion of their procedure. At 18 ± 4 months, 67 (91%) of the 74 patients were arrhythmia-free without antiarrhythmic drugs. The authors concluded that non-inducibility may be a reasonable indicator of the subset of patients who do not require additional lesions beyond PVI.

Richter et al.[8] examined the prognostic value of rapid atrial pacing induction of AF after AF ablation in 234 patients with drug-resistant paroxysmal (n=165) or persistent (n=69) AF. Atrial fibrillation was inducible in 78 of 234 (33.3%) patients after ablation.

Inducibility was found to be a significant predictor of AF recurrence by univariate (HR 2.32, CI 1.56-3.47, p<0.001) and multivariate analysis (HR 2.19, CI 1.46-3.27, p<0.001). The sensitivity and specificity of inducibility testing to predict recurrence were calculated to be 46.7% and 75%, respectively. The authors concluded that while inducibility was predictive of recurrence, it may not be a reliable procedural endpoint because of its low predictive accuracy.

Chang et al.[9] studied the utility of inducibility testing in AF ablation as well as the relationship of inducibility to atrial substrate properties in 88 patients with drug-refractory symptomatic paroxysmal AF who underwent catheter ablation. Overall, non-inducibility was associated with a higher rate of freedom from AF (82% vs. 45%, P=0.02). In addition, inducibility of AF after PVI was associated with lower left and right atrial voltages. The authors concluded that inducibility of AF after ablation was associated with AF recurrence and that left atrial substrate properties may play a role in inducibility and recurrence.

Non-Inducibility With Isoproterenol: StudiesShowing Benefit

Some advocate isoproterenol infusion to test for inducibility of AF and suggest that this may be preferable to atrial pacing. In fact, these alternate methods for inducibility may be evaluating separate mechanisms for the development of AF. While atrial pacing may test the arrhythmogenic substrate, isoproterenol may be useful to bring out potential triggers of AF. The role of isoproterenol as an induction agent has been evaluated and its use in the prognosis of AF recurrence has been compared against that of atrial pacing.

Oral et al.[10] investigated the sensitivity and specificity of isoproterenol infusion for the induction of AF in 80 patients with paroxysmal AF presenting in sinus rhythm for radiofrequency ablation. A set of control patients (n=20) with no history of AF who were undergoing paroxysmal supraventricular tachycardia ablation were also enrolled. The sensitivity of isoproterenol induction of AF was calculated as 88% with a specificity of 95%. The authors' concluded that isoproterenol inducibility should be assessed before ablation if it is to be used as an endpoint after ablation.

Crawford et al.[11] studied whether inducibility of AF with isoproterenol infusion after AF ablation is predictive of recurrence in 112 patients with paroxysmal AF. They also aimed to compare the predictive ability of isoproterenol infusion with that of atrial pacing. At 12 ± 5 months, 63 of 75 patients (84%) who were non-inducible by isoproterenol remained free from AF. Only 16 of the 36 (44%) still inducible or requiring cardioversion for termination of AF remained free from recurrence (P<0.0001). In comparison, 31 of 41 patients (76%) not inducible by rapid atrial pacing were free from AF, compared with 12 of 20 (60%) who were inducible (P=0.21). The authors concluded that isoproterenol induction testing for prediction of AF recurrence had a sensitivity of 33%, a specificity of 97%, and a diagnostic accuracy of 83%, as opposed to atrial pacing, which had a sensitivity of 44%, specificity 72%, and diagnostic accuracy 64% (P=0.03). Inducibility was suggested to be clinically useful, but isoproterenol was felt to be preferable to pacing.

Non-Inducibility Of AF After Ablation: Studies Questioning Benefit

A number of studies have questioned the use of pacing inducibility as a procedural endpoint or as a prognostic test for recurrent AF after catheter ablation. First, the specificity of pacing inducibility has been questioned in two studies, as AF can be induced by rapid pacing in patients even without clinical AF.

Huang et al.[12] investigated the inducibility of AF in 86 patients without a history of clinical AF or structural heart disease. Burst pacing induced AF in 3.5% of patients, while decremental pacing induced AF in 25.6% (with 18.6% sustained). Kumar et al.[13] also studied the inducibility of AF in 44 patients without a history of clinical AF. Kumar and colleagues found that AF was commonly inducible in patients without clinical AF or structural heart disease. Atrial fibrillation of > 10 seconds was inducible in 34 (82.7%) of 44 patients, ≥ 1 minute in 20 (49.5%) of 44, ≥ 5 minutes in 11 (29.5%) of 44, and > 10 minutes in 10 (27.8%) of 44.

Second, unlike the studies described earlier, two studies have demonstrated no prognostic value in post- ablation induced AF.

Satomi et al.[14] investigated the inducibility of atrial tachyarrhythmias and its relationship to outcomes after PVI in 60 paroxysmal AF patients. Those patients who were inducible were noted to have a significantly smaller area of isolation on electroanatomical map when compared to non-inducible patients (16.7±2.3 vs. 18.8±2.9%, P<0.05). Recurrence was similar between the non-inducible and inducible groups (42 vs. 41%) over a mean follow-up of 16.1±8.2 months. The authors concluded that inducibility is related to the area of left atrium isolated by the procedure, and that inducibility was not predictive of recurrence.

Leong-Sit et al.[15] also evaluated the prognostic significance of post-ablation induced AF in 144 patients undergoing ablation for paroxysmal (n=78) or persistent (n=66) AF. Arrhythmias were inducible in 89 (61.8%) of 144 (61.8%) patients. There was also no significant difference in outcomes of those who had been inducible and those non-inducible after ablation (49.4 vs. 49.1%, P=0.68). The only significant predictors of arrhythmia recurrence were a large left atrial size and persistent AF. The authors concluded that inducibility of atrial arrhythmias by pacing after ablation conferred no prognostic information.

Limitations Of Studies Evaluating Non-Inducibility As An Endpoint For Ablation

The evidence for non-inducibility as an endpoint for AF ablation is mixed. Moreover, there are a number of limitations in the studies using non-inducibility as an endpoint for ablation. First, induction of AF with pacing or isoproterenol may be predictive of AF recurrence, but testing by either method suffers from poor diagnostic accuracy. Pace-induced AF has a lower specificity while isoproterenol-induced has a lower sensitivity. This is highlighted by the fact that AF is frequently inducible even in patients without clinical AF. While some studies have attempted to compare isoproterenol versus pacing as an induction agent, there are no direct side-by-side comparisons of the two but rather protocols whereby one approach is followed by the other. Fundamentally, testing for inducibility of AF evaluates the presence of different mechanisms required for the genesis of AF: isoproterenol evaluates for triggers whereas pacing inducibility evaluates sustainability. Second, studies have generally been small and use a variety of ablation techniques, induction protocols, follow-up periods, and definitions of inducibility and recurrence. Clearly, more aggressive stimulation protocols and shorter duration of induced AF defined will increase sensitivity but lower specificity. Aggressiveness of pacing protocol affects vulnerability to AF and perhaps sustainability. More prolonged rapid pacing and multiple inductions may cause acute electrical remodeling which make AF more sustainable. Third, the majority of studies treated induced AF with further ablation, thereby muddling the value of inducibility as an endpoint. It is impossible to know whether inducibility would be a predictor of poor outcomes irrespective of ablation approach. Fourth, as evidenced by several studies, inducibility is a marker of other clinical parameters suggesting worsened clinical outcomes including left atrial size, atrial fibrosis, and AF cycle length. Non-inducibility may be a marker of less structural remodeling rather than an endpoint for ablation. Fifth, most of the patients in whom inducibility testing has been evaluated had paroxysmal AF. There is limited data on the utility of inducibility in ablation of persistent AF and probably a limited role. Finally, even if non-inducibility were a perfect endpoint, patients may have recurrent AF due to the failure to achieve durable ablation lesions. Without knowing whether this is the case with follow-up mapping studies, it is difficult to interpret the value of non-inducibility as an endpoint.

Termination As An Endpoint For AF Ablation

Termination of AF during ablation may result from elimination of a focal driver or adequate modification of the atrial substrate required to sustain AF. However, importantly, termination during ablation of paroxysmal AF may also be a result of fortuitous spontaneous termination. Since termination of AF with catheter ablation can be considered to be an indicator of adequate driver modification, it can potentially be used as an endpoint of ablation in persistent AF and predictor of the outcome of the ablation procedure. Of primary concern when using termination as an endpoint is that the atrial substrate may be partially reversible without the need for ablation. In attempting to terminate AF, particularly in those with a longer duration of persistent AF, more ablation may be performed than is necessary.

When considering termination as an endpoint of AF ablation, there are a number of caveats to consider: 1) In many patients, termination may be hard to achieve and patients may do well even without achieving this end-point, 2) Termination may indicate elimination of an important driver of AF at that time but does not assure elimination of all potential drivers of AF, 3) Reverse remodeling of the atrium with maintenance in sinus rhythm without achieving termination may be enough to control AF. With this background, in the following section we review the available studies assessing the importance of termination during catheter ablation in predicting long-term outcome.

Termination As An Endpoint Of Ablation: Studies ShowingBenefit

Haïssaguerre et al.[16] first reported on the benefit of termination during catheter ablation of persistent AF in a cohort of 60 patients with persistent AF undergoing a step-wise ablation procedure. Termination was achieved in 52 of the 60 patients. Repeat ablation was done for recurrent atrial tachycardia on follow-up in 23 patients. Including repeat ablation, 95% of patients were free of atrial arrhythmias at a follow-up of 11±6 months. The majority of patients undergoing a redo procedure had recurrent atrial tachycardia. The authors suggested that an extensive procedure leading to termination of AF can lead to a high medium to long term success rate. However, there was no comparison group of patients who did not have termination of AF. A and the rate of repeat ablation for atrial tachycardia was high.

O'Neill et al[17] demonstrated a high ablation success rate in a cohort of 153 patients with persistent AF at a mean follow-up of 32±11 months. Termination of AF was achieved in 85% (130) patients using

a step-wise ablation protocol advocated by the Bordeaux group. Those in whom AF was terminated had a higher rate of AF free survival (95% vs. 52%). However, it was important to note that patients in whom termination of AF was achieved had a shorter duration of AF (median duration of 12 months vs. 24 months; p=0.0022), a smaller left atrium (47±8 mm vs. 52±10 mm; p=0.030), a higher baseline AF cycle length (154±21 msec vs. 138±15 msec; p=0.0012) and required less total RF time for ablation (87±26 min vs. 97±31 min; p=0.244). Thus, ability to terminate AF during the ablation procedure appeared to be an indicator of the severity of remodeling.

Rostock et al.[18] evaluated predictors of arrhythmia free survival in 395 patients undergoing one or more catheter ablation procedures for persistent AF. At 27±7 months follow-up after the first procedure only 27% of patients remained arrhythmia free with a single procedure. However, at a median follow-up of 24 months after the index procedure, arrhythmia free survival was 79% after multiple procedures (2.3±0.6 procedures). In these patients termination of AF during the index procedure was associated with a 72% reduction in the risk of recurrence. Additionally longer baseline AF cycle length was a strong and independent predictor of outcome after the first ablation procedure.

Park et al. reported similar data from Korea in 140 patients with longstanding persistent AF undergoing a stepwise ablation protocol.[19] In this study 68% of patients had termination of AF during the ablation procedure. Patients having termination of AF during the ablation procedure had a lower recurrence rate at a follow-up of 18.7±7.6 months (45.3% vs. 68.9%, p=0.009). Interestingly, in patients undergoing re-ablation for recurrence, termination of AF during the first procedure was a predictor of termination of the arrhythmia during the second procedure and both were predictive of recurrence.

Ammar et al., studied 191 patients with persistent atrial fibrillation.[20] Patients terminating to sinus rhythm with a step-wise ablation procedure (62 patients) had a higher survival free of all atrial arrhythmia without use of any anatiarrhythmic medications at 12 months (42% in those terminating to sinus rhythm vs. 13% in those terminating to atrial tachycardia vs 25% for those without termination; p=0.002). However, there was no difference during follow-up between patients with AF termination to sinus rhythm or to AT when freedom from atrial fibrillation was considered as the endpoint.

Zhou et al.[21] similarly demonstrated a significant difference in long-term success between patients with sinus rhythm restoration with ablation vs. cardioversion (63.8% vs. 36.8%; p<0.001) in a cohort of 200 consecutive patients with nonparoxysmal AF with a single catheter ablation procedure.

Rostock et al. randomized 110 patients with persistent atrial fibrillation to two approaches.[22] Each group of 55 patients were randomized to a plan of either cardioversion or mapping and ablation of atrial tachycardia achieved after PVI and electrogram-guided ablation. Randomization to the group with the plan of mapping and ablating atrial tachycardia was the strongest predictor of arrhythmia-free survival after single ablation procedure (p-0.004).

Multiple studies have sought to evaluate whether the mode of AF termination (directly into sinus rhythm or via an atrial tachycardia) has any effect on the outcomes of ablation. Elayi et al.[23] reported on a series of 306 patients with persistent AF undergoing catheter ablation procedure. At 25±6.9 months, among 69% who maintained sinus rhythm there was no difference in the rate of recurrence between the various modes of termination of AF. However, those who organized to an atrial tachycardia with ablation were more likely to recur with AT than with AF (p=0.022). Park et al.[19] similarly found that there was no difference in arrhythmia recurrence rate whether AF terminated directly into sinus rhythm or via atrial tachycardia although patients converting to sinus rhythm via atrial tachycardia had a higher recurrence rate of atrial tachycardia (54.8% vs. 81%; p=0.016). On the other hand, Wang et al demonstrated that termination of AF directly into sinus rhythm predicted a better outcome compared with patients terminating into atrial tachycardia or patients without termination (p<0.05).[24] Miyazaki et al.[25] evaluated 135 patients who underwent a stepwise catheter ablation procedure with a mean of 1.7±0.7 procedures per patient. The mode of AF termination was an independent predictor of recurrent tachyarrhythmia after the last ablation procedure with those terminating to sinus rhythm having the best outcome and those terminating to AT having an intermediate outcome compared with those remaining in AF (AT vs. SR, HR: 1.47: 0.77-4.01; no termination vs. SR, HR: 2.38: 1.26-6.46; p=0.017). However, in a large study of 400 patients with drug refractory persistent AF conversion to sinus via atrial tachycardia predicted a higher likelihood of arrhythmia free survival compared to patients converting directly into sinus rhythm (HR 1.69, p=0.027).

Termination As An Endpoint Of Ablation: Studies Questioning Benefit

Komatsu et al.[26] reported retrospective data in 132 patients with persistent AF who were followed for a median of 3 years after undergoing catheter ablation. A stepwise ablation with PVI and substrate modification with a desired endpoint of termination of AF led to arrhythmia free survival of 68% at a follow-up of 20±11 months after one or two procedures. Duration of continuous AF was the only predictor of arrhythmia free survival in a multivariate analysis. In patients with AF duration of ≥3 years (n=67), procedural termination did not predict long-term arrhythmia free survival, however, in patients with shorter AF duration (n=65), procedural AF termination was associated with higher arrhythmia free survival (log-rank, p=0.023). The authors suggested that patients with long standing persistent AF may not benefit from extensive ablation procedure with a goal to terminate AF.

Wang et al.[24] evaluated 293 patients with persistent AF. The authors found that 45% of patients terminated to sinus rhythm during ablation while 55% required cardioversion. There was no difference in early recurrence (38.2% vs. 43.8%; p=0.328) or maintenance of sinus rhythm (67.2% vs. 59.8%; p=0.198) during 23±7 months follow-up comparing the patients who terminated to sinus rhythm with those needing cardioversion.

Termination As An Endpoint Of Ablation: Pre-Ablation Reverse Remodeling

Because atrial remodeling may be partially reversible, if maintained in sinus rhythm for a period of time prior to ablation, patients may require less ablation to terminate AF. This approach potentially allows for the more important structural components of the atrial substrate to be addressed during the ablation procedure. Rivard et al[27] reported a study comparing patients who were maintained in sinus rhythm with antiarrhythmic therapy and cardioversion prior to ablation with patients ablated without pre-ablation therapy. Patients in the reverse remodeling, sinus rhythm group required a less extensive procedure

and were more likely to terminate during ablation (95.0% vs. 77.5%; p <0.05) without affecting clinical success rates (55% vs. 45%; p=0.28 for first and 80% vs. 70%; p=0.28 for last ablation procedure over similar follow-up of 21.1±9.7 months). Pre-ablation organization of AF to unmask more critical drivers of AF by administering low-dose ibutilide before ablation of complex fractionated atrial electrograms has been proposed and a study is under way to test the efficacy of this approach.

Limitations Of Studies Evaluating Termination As An Endpoint For Ablation

Again, there are a number of limitations in studies evaluating termination as an endpoint of AF ablation. First, the probability of termination in different studies varies significantly, likely due to differences in patient populations, including the presence of structural heart disease, AF duration, etc. This makes interpretation of the benefit of termination challenging. Second, the benefit of termination reported in individual studies depends on whether only atrial fibrillation or any atrial arrhythmia (AF or atrial tachycardia) is considered a recurrence. In addition, some studies allow for repeat ablation of atrial tachycardia in demonstrating the benefit of termination. Third, it is not very clear which is a more favorable mode of termination of AF: direct conversion to sinus rhythm or conversion via atrial tachycadia. Direct conversion to sinus rhythm may suggest more favorable baseline atrial substrate, whereas, conversion via atrial tachycardia may suggest a more focused ablation of the relevant atrial tachycardia, thus reducing the recurrence of atrial tachycardia. Fourth, the ablation strategy in these studies were quite different with some studies advocating pulmonary vein isolation and complex fractionated atrial electrogram guided ablation and others including linear ablation as well. The role of ablation approach as well as procedure duration cannot be separated from termination itself as an endpoint. Fifth, it is always subjective to determine when to stop ablating with these ablation protocols and declare an inability to terminate AF. Sixth, no studies evaluate termination as an endpoint per se because the ablation strategies are guided by termination itself. Seventh, and perhaps most importantly, similar to the data on non-inducibiliy as an endpoint of ablation, termination of AF with catheter ablation may simply be an indicator of a less remodeled atrium. Lack of termination may be yet another clinical predictor of worsened outcomes such as atrial size or atrial fibrosis. Termination may be a marker of less structural remodeling rather than an endpoint for ablation.

Conclusion:

Beyond pulmonary vein isolation, there remains little consensus on the recommended approach to ablation both in paroxysmal or persistent AF patients. The lack of a clear endpoint for AF ablation contributes to this uncertainty. Non-inducibility of AF and termination of AF during AF ablation have been advocated as potential endpoints. Attempting to induce AF may have a role in identifying potential triggers outside of the pulmonary veins. Termination of AF and non-inducibility of AF may help to identify whether the substrate for maintenance of AF has been adequately modified. Unfortunately, the evidence for non-inducibility or termination as endpoints for AF ablation is mixed. Moreover, there are a number of limitations in the studies reported. It is likely that non-inducibility of AF or termination of AF during AF ablation may be markers of less structural remodeling rather than true endpoints for ablation. This may explain the finding that these endpoints have prognostic value. Further studies in which inducibility and / or termination are not used to guide AF ablation are necessary to understand the true prognostic value of these endpoints.

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