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Original Research
Journal of Atrial Fibrillation
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Early Recurrences During the Blanking Period after Atrial Fibrillation Ablation

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Abstract

Early recurrences of atrial arrhythmias (ERAA) after ablation are common and predict late recurrences and ablation failure. However, becausea proportion of patients with ERAA will have no subsequent arrhythmias after the blanking period, consensus guidelines recommend against immediate repeat ablation for ERAA episodes occurring during the first 3 months post-ablation. In this review, we summarize the predictors, significance, and treatment of ERAA after AF ablation.

Introduction

Catheter ablation (CA) is an increasingly utilized and effective treatment option for patients with symptomatic atrial fibrillation (AF), particularly those who have failed medical therapy with antiarrhythmic drugs (AADs). In the period immediately after AF ablation, early recurrences of atrial arrhythmias (ERAA) are common and may not necessarily imply long-term ablation failure. Therefore, guidelines recommended implementation of a "blanking period" post-ablation during which AF or OAT recurrences need not be counted against long term ablation success[1]. However, it is important to recognize that certain ERAA characteristics are more suggestive of long-term ablation failure than others. In this review, we will summarize the current literature on the topic. Specifically, we will describe predictors for ERAA development after AF ablation and discuss clinical implications of ERAA on long-term ablation success.

Early recurrences after AF ablation

Since not all patients who experience ERAA in the first few weeks after AF ablation continue to have recurrences later on, implementation of a "blanking period" makes sense, in order to better assess long-term ablation success. Previous studies have utilized a wide range of blanking periods when reporting long-term outcomes, ranging between 72 hours to 3 months post-ablation[2]. Consensus guidelines have recommended for clinical trials that a 3-month blanking period post-ablation be implemented, during which time ERAA episodes should not be classified as treatment failure[1]. This the likely reason why most electrophysiologists do not attempt repeat ablation for ERAA occurring in the first 3 months post-ablation. While the consensus statement from the Heart Rhythm Society (HRS), European Heart Rhythm Association (EHRA), and European Cardiac Arrhythmia Society (ECAS) have all selected 3 months as the blanking period of choice, this cutoff is rather arbitrary. In fact, the optimal blanking period during which early re-ablation should be avoided remains poorly studied.

The incidence of detected ERAA after AF ablation is dependent on monitoring strategies during the blanking period which, have varied from symptom-driven electrocardiograms, Holter monitors,mobile continuous outpatient telemetry monitors, and implantable loop recorders. There remains lack of consensus on the adequate monitoring strategy during the blanking period. Many providers may feel that the costs associated with monitoring outweigh the benefits of detecting asymptomatic ERAA, since these recurrences are not considered ablation failure and most patients are maintained on anticoagulation during this stage.There also remains variability in the overall incidence of ERAA during the 3-month blanking period with estimates ranging any where from 16-67%[2]. In the majority of studies,the incidence of ERAA after AF ablation with radiofrequency versus cryoablation appears to be similar, and the predictive value of ERAA on the likelihood of developing late recurrence appears to be similar between modalities[3]. However, one study by Miyazaki, et al. suggested that there may be differences in the predictive value of inflammatory responses on the incidence of ERAA post-ablation between techniques.In their study, hs-CRP levels 2 days post-ablation predicted development of ERAA in those treated with radiofrequency (HR 1.7; 95% CI [1.01-2.87]; p=0.048) but not cryoablation, suggesting that the degree of inflammatory marker elevation is more predictive of ERAA after ablation with radiofrequency energy compared with cryoablation[4].

Key Words

Atrial Fibrillation, Early Recurrence, Catheter Ablation, Pulmonary Vein Isolation.

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Table 1: Characteristics which are predictive of the development of late recurrence after AF ablation among patients with early recurrence

Clinical characteristics	Ablation procedural characteristics
Older age	Incomplete PVI
Nonparoxysmal AF type	AF inducibility
	Electrogram-based ablation
ERAA characteristics	Lack of AF termination during procedure
Later ERAA timing	
Multiple ERAA episodes	**Imaging characteristics**
Later ERAA timing	Increased left atrial size/volume

Abbreviations: AF, atrial fibrillation; ERAA, early recurrent atrial arrhythmia; PVI, pulmonary vein isolation;
*Table adapted from Andrade JG, et al. Pacing ClinElectrophysiol. 2012;35:106-16.

Predictors of ERAA

Several predictors of the development of ERAA after AF ablation have been identified and many of these are also predictors of long-term ablation failure. Baseline characteristics such as older age, male gender, presence of structural heart disease, longer AF duration, nonparoxysmal AF type, higher CHA_2DS_2-VASc scores, larger LA size, presence of LV systolic and diastolic dysfunction, and LA epicardial adipose tissue are some of the variables that have been found to predict ERAA and all these are also associated with late arrhythmia recurrence[5]-[12]. Acute procedural findings including incomplete PVI, presence of multiple AF foci, AF inducibility and lack of AF termination during ablation are also associated with ERAA[6],[13],[14]. Other ERAA predictors include markers of inflammation such as increased body temperature post-ablation, increased LA roof thickness with delayed enhancement as seen on cardiac magnetic resonance imaging at 24 hours after ablation, and increased levels of C-reactive protein and homocysteine[15]-[17].

Mechanisms of ERAA during the blanking period

It remains unclear whether the degree of elevation of inflammatory markers post-ablation is predictive of ERAA. One study compared the change in levels of inflammatory markers before ablation versus at different time points (1, 2, 3, 7 days, and 1 month) after ablation and demonstrated that the degree of elevation of hs-CRP, troponin-T, and fibrinogen were predictive of only very early recurrences (within 3 days) post-ablation[18].

Table 2: Strategies to prevent AF recurrences during the blanking period after AF ablation and long-term implications

Treatment strategy	Evidence
Antiarrhythmic drugs	Reduces ERAA episodes during blanking period
	Reduces cardioversions during blanking period
	Reduces hospitalizations during blanking period
	No effect on late recurrences after blanking period
Corticosteroids	Reduction of acute post-ablation inflammatory markers
	Possible reduction of ERAA episodes during blanking period
	No effect on late recurrences after blanking period
Colchicine	
	Reduces ERAA episodes during blanking period
	Possible reduction in late recurrences after blanking period

Das, et al. examined the association between timing of ERAA with the likelihood of PV reconnection at repeat electrophysiology study in 40 patients with nonparoxysmal AF treated with PVI[19]. In the study, the authors performed PVI in 40 patients and brought them back for repeat electrophysiology study regardless of whether they had recurrence post-ablation to assess the PVs for reconnection. A total of 17 (42%) of the patients had developed ERAA within the first 2 months after ablation, preceding the repeat electrophysiology study. Interestingly, they found a strong correlation between ERAA occurring during the second month post-ablation and PV reconnection, which was found in ≥2 PVs. On the other hand, there was no correlation between PV reconnection and ERAA when it occurred in the first month post-ablation only. Thus, their findings suggest that while early ERAA (within one month)is more likely to bedue to transient factors (i.e. inflammation, temporary autonomic imbalances, and time-course of lesion formation), ERAA which occurs later is less likely to be transient and more likely to represent PV reconnection.

In our opinion, it is difficult to differentiate whether ERAA during the immediate (up to 7 days) post-ablation period is due to transient post-ablation inflammation (and likely to resolve spontaneously in time without requiring repeat ablation) versusa more permanent issue such as inadequate PVI/PV reconnection orinadequately targeted non-PV triggers.

Andrade, et al. reported that patients from the STAR-AF trial who underwent limited ablation with PVI alone and developed ERAA (versus those without ERAA) had significantly higher rates of late recurrence[20]. However, in patients who were treated with more extensive ablation strategies including ablation of complex fractionated atrial electrograms, ERAA was less predictive of late recurrences suggesting that in this latter group, ERAA may have been more likely the result of vigorous acute inflammatory response caused by more extensive ablation.

Importance of non-PV triggers

At our center, we have generally employed a limited AF ablation strategy for patients with both paroxysmal and nonparoxysmal AF which has focused primarily on elimination of PV and non-PV triggers. We have reported non-PV triggers to occur in approximately 11% of patients[21]. We hypothesize that if non-PV triggers are not sought out and adequately ablated, they can lead to late AF recurrences. In support of this hypothesis, Gang, et al, have found that PACs detected with Holter monitors six months post-PVI (3 months after the blanking period had ended) strongly predicted late AF recurrence[22]. Alhede, et al. subsequently showed that the burden of PACs detected on 7-day Holter monitoring performed immediate after AF ablation was a predictor of late AF recurrence irrespective of AF recurrence during the blanking period or other risk factors[23]. These data would suggest that PACs from PV and non-PV sources occurring during and after the blanking period may represent inadequately targeted triggers or partial PV reconnection which are likely to result in late AF recurrence.

ERAA characteristics which predict late recurrence

Certain ERAA characteristics have been identified to be more predictive of late recurrence. Based on data from 300 patients who underwent AF ablation at our institution following a limited ablation strategy focused on PVI and elimination of non-PV triggers, we have

found that the timing and frequency ERAA is predictor of late AF recurrence.[24] Our clinical practice is to only consider the initial 6 weeks post ablation as the "blanking period". For this study, we divided the first 6 weeks post-ablation into three separate intervals (Early: weeks 1-2; Intermediate: weeks 3-4; and Late: weeks 5-6) and analyzed the predictive value of these different periods on later arrhythmia recurrence. We discovered that patients whose ERAA is limited to a single 2-week interval during the blanking period (OR 3.2 [95% CI 1.7-5.8] compared to no ERAA) are significantly less likely to experience late recurrence by 1 year post-ablation versus patients experiencing multiple ERAA episodes encompassing multiple 2-week intervals (OR 14.6 [95% CI 7.3-29.6] versus those with no ERAA). Similar results have been shown by Mugnai, et al, after AF ablation using cryoablation technology[25]. They showed in 331 consecutive patients who underwent cryoballoon AF ablation, all patients who experienced ERAA in the second half of the 3-month blanking period also developed subsequent recurrences beyond the blanking period, suggesting that later ERAA are more predictive of long term ablation failure.

The prognostic implications of ERAA may be different among patients undergoing ablation for paroxysmal versus persistent AF, as was suggested in a study by Oral, et al, which identified history of persistent AF type to be an independent predictor of late AF recurrence among patients with ERAA[26]. Furthermore, the type of ERAA (i.e. AF versus organized atrial tachycardia (OAT)) may be predictive of late recurrence, in a manner which is dependent on the initial ablation strategy. When OAT occurs in the blanking period, it may be more predictive of late recurrence since it may represent gaps in ablation lesion sets (i.e. PV connection allowing for PV AT, or gaps in linear lesions allowing for macroreentrant LA flutters) which are unlikely to resolve spontaneously over time.

Prevention and Treatment of ERAA

Several strategies to prevent ERAA after AF ablation have been tested, most notably AADs and anti-inflammatory medications. The use of AADs during the blanking period has been repeatedly shown to decrease the incidence of ERAA and is associated with reduction in hospitalizations and need for cardioversions during the post-ablation period, but reduction in ERAA with early AAD use has not translated to improved long-term ablation success. The Antiarrhythmics After Ablation of Atrial Fibrillation (5A) Study randomized 110 consecutive patients undergoing ablation for PAF to AAD vs. no AAD for 6 weeks after AF ablation and found that short-term use of AADs post-ablation significantly reduced the likelihood of early AF recurrence in the first 6 weeks (19 vs. 42%; p=0.005)[27]. However, a subsequent follow-up analysis of the 5A study showed that the use of short-term AADs after ablation does not prevent late recurrences at 6 months[28]. The AMIO-CAT trial randomized 212 patients to oral amiodarone for 8 weeks versus placebo after AF ablation and found that while short-term amiodarone use did not reduce AF recurrences at 6 months, it was effective in reducing hospitalizations and cardioversion rates during the blanking period[29]. The EAST-AF trial subsequently randomized over 2000 patients to AADs (class I or III) versus control for 3 months after AF ablation and also showed reduction of early AF recurrences during the 3 month blanking period, but no significant difference between groups at 1 year[30].

Since inflammation in the acute post-ablation period is hypothesized to contribute to the development of ERAA, corticosteroids have been used acutely after ablation in an attempt to mitigate the inflammatory process. Studies have, however, shown mixed results. For example, Koyama, et al. randomly treated 125 PAF patients post ablation with placebo versus steroids (2 mg/kg IV hydrocortisone dosed immediately post-procedure, followed by 0.5 mg/kg/day oral prednisone for 3 days) and found that while the corticosteroid group were less likely to have ERAA within the first 3 days post-ablation (7 vs. 31%), there was no difference in rates of ERAA during the remainder of the 30-day post ablation follow-up period[31]. Kim, et al. found that the use of steroids (intravenous methylprednisolone at 0.5 mg/kg for 2 days followed by 12 mg oral methylprednisolone for 4 days) was associated with lower rates of ERAA during the 3-month blanking period after ablation (23.4 vs. 48.6%, p=0.003) but did not affect rates of late recurrence at 24 months (p=0.92), suggesting that steroids (similar to AADs) are effective in reducing ERAA but do not appear to affect the likelihood of late recurrence and long-term ablation success[32]. In a recent study, Iskandar, et al. randomized 60 patients to either oral steroids (60 mg oral prednisone x 3 doses) versus placebo after AF ablation. The authors found that while steroids reduced inflammatory markers IL-6 and IL-8, there were no differences in either ERAA or late recurrence at 1 year between groups[33].

Colchicine is an agent most frequently used for treatment of gout which has also been studied in patients after AF ablation due to its anti-inflammatory effects. There have been two small randomized controlled trials from Europe which have shown benefit of colchicine in preventing both ERAA and late recurrences when used during the blanking period. In the first study, Deftereos, et al. randomized 80 paroxysmal AF patients to treatment with placebo versus colchicine (0.5 mg twice daily) for 3 months after AF ablation and found that those randomized to colchicine (versus placebo) had lower levels of inflammatory markers immediately post-ablation as well as lower rates of ERAA during the blanking period (16% vs. 33.5%; OR 0.38; 95% CI [0.18-0.8])[34]. In a larger subsequent randomized study, Deftereos, et al. showed that colchicine, when used for 3 months post-ablation, resulted in not only lower rates of ERAA during the 3-month blanking period, but also lower rates of late AF recurrence over a median follow-up of 15 months (31.1% vs. 49.5%; OR: 0.46; 95% CI [0.26-0.81])[35]. While the results from these two studies are certainly promising, additional studies are required to replicate these results before colchicine is to be widely accepted as a routine treatment to prevent AF recurrences after ablation.

How early is too early for repeat ablation? What is the optimal blanking period?

While several studies have demonstrated that early reablation in patients who experience ERAA results in superior long-term outcomes[5],[8],[36], this strategy comes at the expense of possibly performing unnecessary procedures in some patients in whom ERAA may eventually resolve spontaneously. Thus, it is important to identify patients in whom ERAA is not merely a result of transient post-ablation factors, but rather in whom it suggests recurrence of the original or development of new sustained arrhythmia mechanism(s).

Several factors may play a role in predicting long-term ablation success in patients experiencing ERAA. In an important study by Willems, et al. the authors analyzed the clinical significance of ERAA episodes occurring at different times throughout the blanking period in patients who were enrolled in the Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination (ADVICE) trial[37]. After dividing ERAA episodes based on when they occurred during the blanking period (month 1, month 2, or month 3 post-ablation), they found that ablation success rate at one year was significantly higher in patients who had no ERAA (77.2% 1-year freedom from AF), while rates of success were lower as ERAA occurred later within the blanking period. Specifically, success rates were 62.6% for those with ERAA in month 1, 36.4% for those with ERAA in month 2 and only 7.8% for those with ERAA in month 3 (hazard ratios for late recurrence: 1.84 for month 1 ERAA, 4.45 for month 2 ERAA, and 9.64 for month 3 ERAA).Using receiver operating characteristic (ROC) analysis, they found that a blanking period of 50 days yielded the greatest discriminatory potential. Their main message that 3 months may be too long of a blanking period is consistent with that of our experience. In fact, in our series, 50 of 59 (84.7%) patients with ERAA occurring between 29-42 days post-ablation suffered late recurrence[24]. Alipour, et al. recently retrospectively analyzed the prognostic impact of ERAA timing on likelihood of late recurrence in 636 patients treated with AF ablatoin. They found that among patients with ERAA, rates of late recurrence were 51% for those whose ERAA was in month 1, 76% for month 2, and 92% for month 3 (p=0.001). Compared versus those with no ERAA after ablation, those with ERAA in month 1, month 2, and month 3 were 4.22, 9.03, and 19.43 (p=0.001) times more likely to experience late recurrence. ROC analysis identified an optimal cutoff of only 23 days for the blanking period[38].

In addition to ERAA timing, we have also found that in patients with nonparoxysmal AF treated with a limited ablation strategy (antral PVI and targeting of non-PV triggers), the nature of initial AF recurrence (paroxysmal versus persistent) is a predictor of long-term arrhythmia control following an additional (≥1) ablation attempt[39]. We believe that transformation from nonparoxysmal to paroxysmal AF represents favorable changes to the underlying substrate (i.e. reverse LA electrical and structural remodeling). While yet unproven, we hypothesize that early repeat ablation during the window where patients with previously nonparoxysmal AF have transformed to paroxysmal AF (before they are allowed to progress rapidly back to persistent AF) may be associated with improved long-term ablation outcomes.

Conclusions

Early recurrences of atrial arrhythmia (ERAA) after AF ablation are common and they are associated with long term arrhythmia recurrences. However, since not all patients with ERAA will experience late recurrences, guidelines have recommended a 3-month blanking period during which arrhythmia recurrences should not be considered as ablation failure. Strategies such as AADs and steroids decrease ERAA but not late recurrence. The use of colchicine post-ablation has shown promise in improving long term ablation success, but more studies are necessary. ERAA which occurs later (>2 weeks after ablation) in the blanking period as well as the occurrence of multiple ERAA episodes throughout the blanking period are strong predictors of late arrhythmia recurrence. Thus, the current 3-month blanking period during which re-intervention is not recommended by consensus guidelines may need to be revisited. Perhaps, in certain types of ERAA, early repeat ablation may improve long term arrhythmia control. More studies in different patient populations are necessary to determine the optimal timing for repeat ablation.

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