

The Blanking Period Following Pulmonary Vein Isolation – Relevance and Duration

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Abstract

Early recurrences of atrial tachyarrhythmia (ERAT) commonly occur in the initial months following catheter ablation of atrial fibrillation. Patients with ERAT are at increased risk of later recurrence, but the presence of ERAT does not necessarily indicate longer-term procedural failure. International consensus guidelines accordingly recommend a three-month 'blanking period'. Such ERAT episodes may be related to post-ablation pro-arrhythmic factors, such as inflammation, autonomic dysregulation and lesion maturation. However, studies suggest that these transient factors have a limited duration and ERAT occurring beyond this point may be more predictive of both pulmonary vein reconnection and further recurrence. This review examines the need for a blanking period and its most appropriate duration.

Keywords

Atrial fibrillation, catheter ablation, pulmonary vein isolation, blanking period, AF recurrence

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Catheter ablation has been consistently shown to provide improved freedom from atrial fibrillation (AF) compared to medical management but, nevertheless, success rates following a single procedure remain relatively poor and are significantly lower than those for ablation procedures for most other supraventricular arrhythmias.^{1,2} Recurrence of atrial tachyarrhythmias (AT; comprising AF, atrial flutter or atrial tachycardia), either symptomatic or asymptomatic, has been reported to occur in more than one in two patients in long-term follow-up after ablation.^{3,4} Outcomes for paroxysmal AF are better than for persistent AF,⁵ and although success rates have gradually increased as procedural techniques have evolved, even in contemporary studies of paroxysmal AF patients ablated using radiofrequency energy, freedom from AF at 1-year follow-up after a single procedure has only approached 70%.⁶ These disappointing success rates may contribute towards the difficulty in establishing clear prognostic benefits, such as stroke-reduction, of catheter ablation over medical therapy.

Recurrence of AT can occur at any time following catheter ablation of AF. While the majority occur in the first 6 months after ablation, first recurrences have been seen more than 4 years later.⁴ AT recurrence in the immediate aftermath of left atrial ablation is particularly common,^{7–9} and the frequency and extent of episodes can exceed those experienced prior to ablation in around 15% of patients.¹⁰ However, there remains some debate over the true relevance of such recurrences in the immediate period following AF ablation.

Early recurrence of atrial tachyarrhythmia

It has long been recognised that early recurrences of AT (ERAT) occurring soon after radiofrequency ablation may not necessarily

portend longer-term arrhythmia recurrence,^{10,11} with up to 60% of patients experiencing ERAT going on to have a successful outcome in the longer-term.¹² Accordingly, international consensus guidelines recommend a 3-month 'blanking period' following AF ablation during which AT recurrences "should not be classified as treatment failure".¹² However, data have also shown that individuals with ERAT have lower long-term success rates than those without early recurrence,^{7,13–16} and that patients with ERAT who undergo early re-ablation have improved freedom from AT at 12 months,^{17,18} suggesting that ERAT may be of clinical relevance.

The mechanisms leading to ERAT following radiofrequency ablation are not fully understood but are commonly attributed to a number of transient pro-arrhythmic factors. These include: post-ablation inflammation,^{19,20} temporary autonomic imbalance^{21,22} or the time taken for the lesion set deployed to mature.²³ Whilst pulmonary vein (PV) reconnection has been shown to be associated with long-term arrhythmia recurrence in paroxysmal AF,^{24–26} these transient factors would not be expected to lead to late AT recurrence. However, the time point at which these transient causes of ERAT give way to arrhythmia episodes related to PV reconnection has not been clearly established.

Post-ablation inflammation

Inflammation has been identified as an important cause for the initiation and maintenance of AF, including after major inflammatory insults such as cardiac surgery.^{20,27} Radiofrequency catheter ablation of cardiac tissue also stimulates a strong inflammatory response, with histological examination demonstrating infiltration of inflammatory cells into the ablated area and measurement of serum markers of inflammation

showing an increase following ablation.^{19,28,29} As the time-course of the inflammatory phase following AF ablation was unclear, a recent study set out to determine this using serum markers of inflammation and myocardial injury.³⁰ Lim and colleagues serially tested 90 patients undergoing radiofrequency AF ablation at baseline and at 1 day, 2 days, 3 days, 7 days and 1 month after ablation for serum levels of high-sensitivity C-reactive protein, Troponin T, creatine kinase-MB, as well as white cell and neutrophil counts. The authors found that the inflammatory markers (high-sensitivity C-reactive protein, white cell count and neutrophil count) all peaked by 3 days post-ablation, remained elevated compared to baseline at 7 days, but had returned to baseline levels by 1 month. For markers of myocardial injury (Troponin T and creatine kinase-MB), a peak was seen at day one post-ablation, with a return to baseline by day seven. Ablation time was identified as an independent predictor of Troponin T release, in keeping with previous studies.^{29,31} They also sought to determine the time-course of the pro-thrombotic state following AF ablation using measurement of fibrinogen and D-Dimer, and found that these markers peaked at seven days post-ablation, and although fibrinogen had returned to baseline by 1 month, D-Dimer levels remained slightly elevated at this time point.

While it should be acknowledged that serum inflammatory markers may not have the required sensitivity to detect subtle persisting inflammation, these data suggest that the inflammatory phase following AF ablation resolves within the first month. Of note, the extent to which high-sensitivity C-reactive protein was raised was the only independent predictor of ERAT in the first few days after ablation, but none of the markers of inflammation or myocardial injury were predictive of post-blanking period AT recurrence.

Autonomic imbalance

Autonomic dysregulation can be a potential trigger for AF and has therefore been mooted as a potential ablation target.^{21,32–36} However, even in the absence of specific targeting of autonomic ganglionated plexi, the autonomic nervous system is known to be affected by standard pulmonary vein isolation (PVI) ablation. Hsieh et al. examined heart rate variability changes in 37 patients with paroxysmal AF, 30 of whom underwent a PVI procedure and seven of whom had a transeptal puncture performed but no ablation.²² Heart rate variability measures included time-domain (standard deviation of RR intervals and root-mean-square of differences of adjacent RR intervals) and frequency-domain (low frequency, high frequency, and low-frequency/high-frequency ratio) parameters, and were obtained pre-ablation and 1 week, 1 month and 6 months after ablation. The authors found a significant decrease in measures of sympathetic and, particularly, parasympathetic activity, with a corresponding increase in the mean sinus rate, 1 week after ablation in patients who underwent PVI. However, these changes had resolved back to baseline by one month post-ablation. There were no changes in heart rate variability parameters in the patients who underwent transeptal puncture but no left atrial ablation. This study of the time-course of autonomic dysfunction therefore suggests that this phase resolves within 1 month.

Maturation of ablation lesions

The time-course of maturation of ablation lesions has been studied in animal models through pathological examination at various time-points after ablation. Huang and co-workers performed catheter ablation in the ventricles of dogs and undertook pathological examinations of the ablated areas 4–5 days later.³⁷ This showed that the lesions had a well-demarcated margin, and microscopic examination demonstrated

“circumscribed areas of coagulation necrosis with a peripheral zone of cellular infiltration.” Similarly, a study by Wittkamp and colleagues in another canine model identified homogeneous lesions with a distinct margin after 7 days.³⁸ Collectively, these data suggest that ablation lesions mature to their fully-developed state within approximately 1 week.

Rationale for and duration of the ‘blanking period’

From the studies described above, there are compelling reasons for the application of a blanking period. Recurrence of arrhythmia due to any of these transient factors should not lead to later recurrence, and it is therefore appropriate not to deem ERAT occurring during the time-course of these factors to be clinically relevant as this ensures that unnecessary re-interventions are avoided. Current international consensus guidelines recommend a 3-month blanking period,¹² and the rationale for this duration is based on clinical studies of the relationship between recurrence within the first 3 months and subsequent recurrence. Although such studies have shown that a significantly greater proportion of patients with ERAT in the first 3 months post-PVI go on to have later recurrence compared those without ERAT,^{7,13,15,16} the main concern regarding taking ERAT to signify later recurrence has been the poor positive predictive value of this finding. An early study by O’Donnell et al. utilising a 3-month blanking period found that 38.5% of patients experiencing ERAT were free of later recurrence.¹¹ Subsequently, a number of further studies have examined this relationship, with some finding a similar proportion in the range of 32–39%,^{8,13,39} others identifying a higher proportion in the range of 43–49%,^{7,14,40} and one study demonstrating a rate of 58.9%.⁴¹ Overall, therefore, these studies have shown that up to 60% of patients with ERAT in the first 3 months post-ablation do not experience further AT recurrence during post-blanking period follow-up, and the authors of the consensus statement have accordingly deemed 3 months to be the most appropriate duration for the blanking period.¹² However, given that some early episodes of AT post-PVI are likely to be related to transient pro-arrhythmic factors that do not cause later recurrence, this is to be expected. The primary issue, therefore, is not whether the blanking period should exist at all, but rather how long it should be.

Timing of ERAT within the blanking period and relationship with late recurrence

While several studies have examined the overall relationship between ERAT and later AT recurrence, relatively few have explored the relevance of the timing of these occurrences within the blanking period. One study that did do this, by Themistoclakis et al., included 1,298 patients undergoing PVI and classified patients with ERAT by the month of the first occurrence.⁷ Ablation was performed using point-by-point radiofrequency energy application, and antiarrhythmic drugs were stopped immediately in paroxysmal AF patients and after 2 months in those with persistent AF. The proportion of patients going on to suffer post-blanking period recurrences was 44% if the first episode of ERAT was in month one, 69% if in month two and 98% if in month three, indicating a high likelihood of later recurrence if ERAT began in months two or three.

A further study, by Bertaglia et al., again following point-by-point radiofrequency ablation and with antiarrhythmic drugs continued for at least 7 months, found that the rate of late recurrence was significantly higher in those with a first recurrence in month two or three (80%) compared to first ERAT in month one (56.7%).¹⁴ As with the study by Themistoclakis et al., the main focus was on the timing of the first recurrence, rather than the time period in which ERAT

episodes persisted. As it is entirely conceivable that an individual might have ERAT related to transient pro-arrhythmic factors in the first month post-ablation followed by ERAT related to PV reconnection in month two onwards, the timing of the last episode of ERAT would seem to be more valuable than that of the first episode. Added to this is the fact that the incidence of first AT recurrences is known to be highest in the first month, with diminishing levels in months two and three,^{7,8,14} making analysis of outcomes for these small numbers of patients difficult.

There are only three studies that have provided data regarding timing of ERAT episodes regardless of whether this was the initial episode or a subsequent recurrence. In a re-analysis of data from Bertaglia et al.,²⁹ patients had on-going ERAT in months two to three having had their first episode in month one, and five patients had their first ERAT episode in months two to three.¹⁴ Of these 34 patients with ERAT in months two to three (regardless of the timing of the first episode), 30 (88%) went on to have AT recurrence beyond the blanking period, compared to 11 of 109 (10%) patients without month two to three ERAT ($p < 0.0001$). In contrast, a study by Joshi et al. using external loop recorders for automatic detection of AF recurrences in the first 3 months following point-by-point radiofrequency ablation (divided into 2-week time periods) did not show AT recurrence in each 2-week period to be predictive of post-blanking AT recurrence up to 12 months post-PVI in a multivariate model.⁸ However, specific data on the proportion of patients with AT recurrence in each 2-week period that went on to suffer post-blanking AF was not presented and therefore cannot be analysed further. As the study only comprised a total of 72 patients and utilised narrow time-periods, such that only between 22% ($n=16$) and 54% ($n=39$) of subjects experienced ERAT within each time-period, the study may well have been underpowered to detect a difference between groups. In this study, antiarrhythmic drugs had been continued for at least 1 month and until complete freedom from AF was achieved.

More recently, a larger study of 300 AF patients undergoing point-by-point radiofrequency ablation was conducted by Liang and co-workers.⁴² Antiarrhythmic drugs were discontinued after 6 weeks in paroxysmal AF patients and after 3–6 months in those with persistent AF. In this study of the first 6 weeks following ablation, ERAT episodes were classified into 'early' (weeks one to two), 'intermediate' (weeks three to four) and 'late' (weeks five to six). The authors found that ERAT at any time in this 6-week period was predictive of treatment failure, but particularly if there were multiple episodes extending into the 'late' period. A re-analysis of these data shows that 50 of 59 (85%) patients with ERAT in weeks five to six went on to have later recurrence, compared to 82 of 241 (34%) patients with either no ERAT or ERAT confined to the first 4 weeks ($p < 0.0001$). It should be noted that there was significant variation in the duration of antiarrhythmic drug therapy given after ablation between studies, which could impact upon the incidence of ERAT. Nevertheless, the findings of Liang et al. are similar to those of Bertaglia et al., and imply that recurrences that occur beyond the first 4 weeks after point-by-point radiofrequency ablation are clinically relevant.

Other energy sources and lesion sets

While the above studies have all reported on ERAT following point-by-point radiofrequency ablation, there are also data on ERAT following cryothermal PVI. A sub-study of the Clinical Study of the Arctic Front Cryoablation Balloon for the Treatment of Paroxysmal Atrial Fibrillation (STOP-AF) trial demonstrated that ERAT during the first 3 months

after cryoballoon PVI was significantly related to later recurrence.⁴³ However, further details of the timing of ERAT episodes were not provided. Furthermore, the mechanism of tissue injury is markedly different for cryoablation, with creation of more homogeneous and clearly-defined lesions, as compared to the greater tissue necrosis and coagulation seen with radiofrequency energy.^{44,45} The role and duration of inflammation following cryoballoon PVI may therefore differ to radiofrequency ablation,^{46,47} and data pertaining to transient pro-arrhythmic factors following radiofrequency ablation cannot be assumed to be relevant to other energy sources.

The application of additional lesion sets may also impact upon ERAT. Incomplete linear lesions are prone to creating the substrate for macro re-entrant arrhythmias, and these may manifest at an early stage. A sub-study of the STAR-AF trial demonstrated that the rate of ERAT was highest with complex fractionated atrial electrogram ablation as sole strategy, followed by PVI alone, with the lowest rate seen with a combined approach.¹⁵ The reasons for this are not entirely clear, and it may have been expected that more extensive ablation would lead to greater inflammation and ERAT. However, in the STAR-AF study, the combined approach resulted in superior outcomes compared to the individual strategies,³⁹ and since a 3-month blanking period was applied, the lower rate of ERAT may simply reflect the improved success in that arm.

Relationship between ERAT and PV reconnection

While the studies detailed above have studied the relationship between ERAT and late recurrence, we have recently published an investigation into the relationship between ERAT and PV reconnection,⁴⁸ which has been clearly established as being associated with long-term arrhythmia recurrence in paroxysmal AF.^{24–26} In this study, 40 patients with paroxysmal AF underwent a protocol-mandated repeat electrophysiology study 2 months after point-by-point radiofrequency PVI, regardless of symptoms. Antiarrhythmic drugs were discontinued 4 weeks after the initial ablation. In the intervening period between the two procedures, patients were instructed to self-record a 30-second ECG each day, with additional recordings whenever they experienced symptoms, using a validated handheld ECG monitoring device.⁴⁹ Recordings were divided into those taken during the first 4 weeks ("month 1") post-PVI, and those recorded from day 29 to the date of the repeat electrophysiology study ("month 2").

ERAT was documented in 17 (42%) patients and PV reconnection was identified at repeat electrophysiology study in 25 (62%) patients, affecting a total of 41 (26%) PVs. ERAT either starting or continuing in month 2 was strongly associated with PV reconnection whereas ERAT limited to month 1 was not (85% versus 0%, $p=0.006$). In particular, month 2 ERAT was strongly associated with extensive PV reconnection (2 or more PVs) when compared to its absence (77% versus 11%, $p < 0.0001$). These data, combined with the clinical recurrence data described above, are consistent with the notion that transient pro-arrhythmic factors resolve within the first month after ablation.

Clinical implications

These data suggest that the true blanking period following radiofrequency PVI should be 1 month rather than 3, which would have significant implications for clinical practice. Currently, AF recurrence in the second and third months post-procedure are recommended to be treated as "non-clinical" and should not prompt repeat

ablation.¹² However, shortening of the blanking period would allow earlier re-intervention, a strategy that has previously been shown to improve outcomes for patients with ERAT. Lellouche and co-workers demonstrated a reduction in later AF recurrence in those with ERAT from 91% to 51% with early re-intervention,¹⁷ while Pokushalov et al. found that 80% of patients with ERAT had no later recurrence with a strategy of early re-ablation if triggers were seen (or antiarrhythmic drugs if no triggers were identified) compared to 33% without these interventions.¹⁸ Although using a different treatment modality, a similar finding has also been shown for patients with ERAT following cryoballoon therapy.⁴³ Early re-intervention may therefore reduce subsequent AF recurrence and thereby minimise some of the impact on quality-of-life associated with this.^{50,51} However, while the great majority of patients with ERAT beyond one month post-PVI appear to go on have later recurrence (>85% from available data), there remains a

minority in whom their arrhythmia subsequently settles. As suggested by a study by Liang et al.,⁴² it may be that careful monitoring of both the timing and frequency of ERAT episodes can help identify those most likely to benefit from early re-intervention.

Conclusion

The rationale for a blanking period following radiofrequency PVI is based on the presence of several transient pro-arrhythmic factors immediately following ablation and the fact that a significant proportion of patients with ERAT do not go on to develop late recurrence. However, these transient factors seem to resolve within 1 month, and studies of the timing of ERAT suggest that its occurrence beyond one month is strongly related to both late recurrence and more extensive PV reconnection. It may therefore be that the true blanking period following PVI is 1 month rather than 3 months. ■

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