Does targeting ibutilide-resistant CFAE improve outcomes for catheter ablation of persistent AF?

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This editorial refers to ‘The modified stepwise ablation guided by low-dose ibutilide in chronic atrial fibrillation trial (The MAGIC-AF Study)’, by S.M. Singh et al., on page 1614.

Catheter-based interventional treatment of atrial fibrillation (AF) started out with ‘local’ ablation but, today, pulmonary vein isolation (PVI) is more than ever the cornerstone of AF ablation strategies. However, the results of PVI alone for persistent AF are significantly inferior compared with those for paroxysmal AF, leading to the use of supplementary strategies including linear lesions and ablation of fractionated potentials.

While fractionated potentials have long been known to be characteristic of AF, complex fractionated atrial electrograms (CFAEs) as ablation targets were first described by Nademanee in 2004. In that single-centre series of paroxysmal and non-paroxysmal AF patients, 91% freedom from recurrent atrial tachyarrhythmias was achieved by targeting CFAEs, and achieving procedural AF termination without isolating the pulmonary veins. These results were, however, not easy to replicate, and the stepwise ablation strategy combining, progressively (until termination of AF), PVI, linear and CFAE ablations was proposed. In analogy with ablation for other supraventricular arrhythmias, this strategy is intuitively convincing, but the extensive ablation necessary to achieve termination frequently leads to multiple atrial tachycardias, typically related to atrial lesions, and multiple re-do ablations. The success rates (freedom from atrial tachyarrhythmias) have also not reached levels comparable with persistent AF.

Currently, therefore, different individualized strategies including mapping-based approaches targeting drivers, sources such as re-entries, rotors, focal impulses, high dominant frequency sites, or low voltage substrates are under evaluation for the ablation of persistent AF with the expectation of increased procedural efficiency (reduced ablation) and efficacy (better rhythm control).

In this context, Singh et al. describe the MAGIC-AF trial, evaluating the adjunctive use of ibutilide for increasing procedural efficiency, AF termination, and improving rhythm control outcomes in persistent AF.

The hypothesis of this study is that ibutilide, a class III antiarrhythmic agent, may preferentially suppress the ‘passive’ CFAEs, leaving, in the presence of continuing AF, a lesser extent of more critical and presumably active drivers of AF as remnant targets for catheter ablation. Appropriate ablation of these remnant targets would be expected to result in termination of AF at the expense of lesser ablation and overall higher rates of stable sinus rhythm maintenance during follow-up.

The study, a multicentre, international, randomized, controlled, double-blind trial, was well designed. The patient group was quite representative of the real world, with only mildly or moderately enlarged left atria, and only a minority with structural heart disease or long-standing persistent AF, all of the above suggesting a cohort likely to achieve better outcomes with catheter ablation. Also, follow-up was nearly complete, with good compliance.

What did the study actually show?

In persistent AF patients, low dose i.v. ibutilide, administered after PVI, significantly diminished the spatial extent of left atrial CFAEs compared with controls who did not receive ibutilide.

Subsequent ablation targeting these residual CFAEs resulted in significantly higher AF termination but without increasing the stable sinus rhythm maintenance rate at 1-year follow-up. There were also no differences in the generation of atrial proarrhythmia. Ergo, ibutilide, at least in the way it was used in this study, did not provide benefit.

Ibutilide

Ibutilide is a class III intravenous-only antiarrhythmic agent with significant effects on phase 2 and 3 repolarizing currents, and is FDA (Food and Drug Administration) approved for the pharmacological cardioversion of atrial flutter and fibrillation, but is not available in Europe. Ibutilide administration in animal models of AF reduces fractionation, prolongs action potential duration (APD) and cycle length (Figure 1), and terminates AF; however, clinically, ibutilide...
may be more effective at cardioverting flutter than AF. The initial description of adjunctive i.v. ibutilide administered intraprocedurally (after CFAE ablation) resulted in 32% of additional terminations of AF, and in many of the rest appeared to facilitate the appearance and subsequent ablation of organized atrial tachycardias. Moreover, patients with persistent AF on continuing amiodarone also seemed to show greater procedural AF termination during catheter ablation. In a pilot study of 11 patients, Singh et al. described a reduction in CFAE extent in the left atrium by ibutilide administered after PVI, with subsequent residual CFAE ablation resulting in good rhythm outcomes. The MAGIC-AF prospective study was in fact designed to confirm these results.

What do CFAEs signify?

Koning et al., using intra-operative right atrial epicardial unipolar mapping data, first showed that during sustained AF, complex electrograms can be produced by different activation mechanisms, such as collision, pivoting, or slowly conducting activation. Non-re-entrant foci with a nearby line of block or ‘wannabe’ re-entry, or small or micro-re-entry, may all provide an electrogram signature of complex fractionation and more so with the large bi-poles used clinically (Figure 1). Similarly, passive activation due to wavefront collision with or without associated slow conduction, curving–pivoting conduction, typically around one end of a line of block can also result in electrograms fulfilling the above definition.

For the MAGIC-AF study, CFAEs were defined automatically by the mapping system software only on the basis of a rapid cycle length (<120 ms) over a 5 s window, and only the area subtended by CFAEs was analysed. Although higher level analysis of CFAE characteristics does not appear to have been performed, this could have identified CFAE subgroups showing benefit from the ibutilide strategy. In addition to a cycle length of <120 ms, the software requires secondary thresholds of electrogram voltage and width, a ‘local refractory period’, a projection distance threshold, and an interpolation threshold. The definition based on a cycle length <120 ms has been widely used, particularly in multicentre studies, but some studies have used additional criteria in an effort to increase specificity: fractionation (continuous activity), centrifugal activation, and activation gradients, and reported higher termination and stable rhythm control rates, albeit without control groups.

The analysis of short temporal segments of 5 s may be a limitation since such a short window cannot account for temporal variability on a longer time scale. Associated spatial variability probably also went unnoticed because of the sequential nature of the mapping. Habel et al. observed a 93% likelihood of wrongly identifying the dominant frequency site with the shorter analytical window when they recorded stationary basket catheter electrograms for 300 s and then re-analysed the data in 5 s packets.

Ibutilide reduced the area of the atrial endocardium bearing CFAEs by a mean margin of 8%, less than in the pilot study, but this may be related to the higher (1 mg) dosage used in 4 of the 11 patients compared with the uniform use of 0.25 mg i.v. in this study, the lower dosage probably motivated by concerns about ventricular proarrhythmia. Despite the reduced CFAE extent, there was no corresponding reduction in the procedure duration, fluoroscopy, and, tellingly, the extent and duration of radiofrequency ablation (both overall and for the CFAEs) between the two groups. Obviously, this could in part be responsible for the lack of difference in outcomes. As pointed out by the
authors, the study was powered to detect a 40% difference and may also have lacked the sensitivity to detect a smaller advantage.

Unlike Singh et al., Nademanee et al. 1 used ibutilide after CFAE ablation, failed to terminate AF, and did not re-evaluate CFAEs after ibutilide, thus without providing electrophysiological insight into selective effects on bystander CFAEs. In a chronic AF (paced-induced) dog model, ibutilide preferentially reduced wave fronts emanating from the pulmonary veins without significant effect on non-re-entrant foci, in concordance with ibutilide’s class III effect. Any selectivity of ibutilide on ‘passive’ vs. ‘active’ CFAEs has not, however, been established. 5 Biviano et al. analysed coronary sinus electrograms in 21 patients before and after 1 mg of ibutilide, and found a reduced dominant frequency but an increased mean spectral profile, increased electrogram amplitude, and morphological variability. Interestingly, they did not find any differences between patients who did vs. those who did not terminate with ibutilide. 15

Although antiarrhythmic agents may reduce the area of CFAEs and even facilitate termination of AF, their actions could mask or conceal potentially clinically relevant residual arrhythmogenic mechanisms capable of initiating and or maintaining AF. It is possible that while ibutilide suppressed certain CFAEs, AF persisted, dominantly driven now by non-re-entrant foci. A recent randomized study comparing long-standing persistent AF patients on amiodarone vs. those without any antiarrhythmic effects showed that the amiodarone patients required lesser ablation, terminated more often, but showed fewer non-pulmonary vein triggers during provocation which correlated with a higher incidence of AF recurrence during follow-up. 16

Over and above the purely electrophysiological implications of the study, the occurrence of three deaths [one confirmed due to (ultimately) left atrio-oesophageal fistula], all in the group administered ibutilide, raises concern about the ablation parameters, lesion locations, and protective measures in this group. On the other hand, the nearly 10% incidence of post-procedural congestive heart failure were in both groups attests to the effects of extensive ablation and concomitant volume load during the 5 h plus procedures, but could have been mitigated with upfront diuretic treatment.

Ibutilide and AF termination

Animals who did not cardiovert with i.v. ibutilide had shorter cycle lengths and shorter refractory periods than those who did. 7 It is unclear if the patients who did terminate with i.v. ibutilide administration had any specific distinguishing characteristics, although the small numbers would render analysis unreliable.

Despite more frequent AF termination, the ibutilide-treated group did not show significant improvement in rhythm outcomes during follow-up, thereby raising questions about the importance of terminating AF as a procedural endpoint. The underlying mechanism(s) of termination of AF by catheter ablation have not been well studied. Termination may represent the absence, possibly temporary, of a sufficient number of wavelets or excitatory tissue. AF termination by catheter ablation may not indicate durable substrate suppression since systematic re-induction attempts after termination have not been systematically evaluated. Termination by ablation may well be a marker of a limited driving substrate or a driving source, amenable to neutralization by catheter ablation (e.g. with PVI), unlike more extensive substrate-maintained AF (e.g. long-standing persistent AF). The typically extensive ablation required to achieve termination of non-paroxysmal AF does not favour a localized or fixed driving source, whereas extensive radiofrequency ablation may electrically debulk enough atrial myocardium without leaving sufficient ‘wavelength’ to sustain fibrillation by suppressing the excitability of a large area. Of recent studies, neither STAR AFII, nor the CHASE AF study found AF termination to be associated with better arrhythmia-free survival. 17–20 As a result, AF termination as a procedural endpoint remains controversial.

Does this focused, carefully performed study add volume to the call for limiting persistent AF ablation to PVI alone?

The study certainly contributes to the current debate over optimizing ablation strategies and emphasizes the importance of understanding the electrophysiological mechanisms of persistent AF as well as of achieving effective durable PVI.

Following the publication of recent studies, 17,18 the value of CFAE ablation (and linear lesions) has been intensely questioned. However, the MAGIC-AF study did not include a control group of patients undergoing PVI alone and therefore does not allow any such conclusion to be drawn.

This well-controlled randomized trial has disproven the hypotheses suggested by single-centre uncontrolled observational studies. The authors are to be congratulated for the rigorous trial that they designed and completed, as well as the clarity of their results. As with other such trials, this one answers the specifically posed question very well but raises others which the study was not designed or intended to answer.

Since the clinical burden of persistent AF is considerable, the search for effective ablation therapies must continue. The benefits of ablation earlier in the course of the disease, before progression to persistent AF, remain to be proven. Progression is not universal, but it is unclear how to select the patient likely to progress; therefore, a blanket strategy of ablating all paroxysmal AFs seems unwarranted and likely to invite complications. It is clear that the optimal strategy for persistent AF remains to be defined. A mechanistic rather than a morphological approach to electrograms may well be fruitful. In the presence of the marked temporal and spatial variability of electrograms characteristic of AF, the limitations of sequential point by point mapping may lead to misinterpretations in activation sequences, frequency gradients, and similar analyses. A key to a better understanding of the underlying mechanisms of persistent AF may be the analysis of simultaneous, multielectrode, high-density mapping data gathered over a longer time period and from a larger field of coverage. In the interim, all additional ablation strategies beyond PVI should be carefully and scientifically evaluated.

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References