

Conversion of Persistent Atrial Fibrillation After Radiofrequency Ablation by Ibutilide

Pipin Kojodjojo MD, Ph.D.

Consultant & Clinical Senior Lecturer in Cardiac Electrophysiology, Imperial College London.

Abstract

Ablation of persistent AF remains challenging with questions unanswered about what the ideal next step after pulmonary venous isolation should be. Ibutilide is a highly effective class III agent for cardioversion of acute-onset atrial flutter and fibrillation, with limited clinical use due to risks of ventricular pro-arrhythmias. However, results from the on-going MAGIC-AF trial may re-invigorate its role in clinical electrophysiology as an invaluable adjunct to facilitate controlled substrate modification during ablation of persistent AF.

Introduction

Persistent AF ablation remains challenging

Seminal work by Haissaguerre and colleagues have established the importance of pulmonary venous triggers in the initiation and perpetuation of paroxysmal atrial fibrillation (PAF).¹ Consequently, pulmonary venous isolation (PVI) on its own has been shown to be highly effective for the treatment of anti-arrhythmic drug-refractory PAF.² PAF recurrence during follow-up is associated with electrical reconnection of previously isolated PVs and repeat disconnection results in similar clinical improvement.³ However for the treatment of persistent AF, outcomes after catheter ablation are less than ideal. PVI on its own is insufficient for preventing AF recurrence.² Termination of AF into SR either directly or by transitioning through a series of organised atrial tachycardias is currently considered to be the optimal electrophysiological endpoint. Organisation of AF is associated with successive prolongation of AFCL, which can predict the likelihood of AF termination.⁴ In

the search of the ideal ablation strategy if AF persisted after PVI, two additive strategies have been studied: creation of complete lines (namely roof and mitral isthmus lines) and mapping and ablation of complex fractionated atrial electrograms (CFAE). The former is technically challenging and recurrence of conduction across lines predisposes to iatrogenic macro-entrant atrial tachycardias which are symptomatically less tolerated and necessitate additional interventions.⁵ Whilst CFAE ablation, sometimes used in isolation without PVI in persistent AF ablation, was reported to result in 76% freedom from AF after a single procedure, the same results could not be reproduced by the same authors or other high-volume units.⁶ There is also no universal definition of what constitutes a CFAE. More alarmingly, there is some evidence to show that most CFAEs represent areas of passive activation which can be spatiotemporally unstable and therefore do not form ideal ablation targets.⁷ Consistent with this, in some patients, extensive areas of the atria can be ablated but yet does not produce AF organisation or termination. In addition to lengthy procedural and fluoroscopic times,

Corresponding Address: Pipin Kojodjojo MD, Ph.D, St. Mary's Hospital, 1, Praed Street, London W2 1NY.

concerns remain about atrial contractility after such extensive ablation and the increased risks of iatrogenic atrial tachycardia by promoting re-entry through creating new unnecessary lines of block or triggered automaticity in damaged myocardium.⁸

Therefore, in patients who remain in persistent AF after PVI, the issue of “what is the best thing to do next?” remains unanswered.

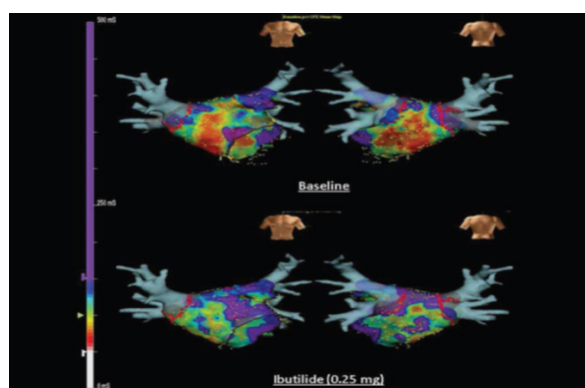
MAGIC for persistent AF?

To this end, an innovative strategy is currently being studied by investigators of the Modified Ablation Guided by Ibutilide Use in Chronic Atrial Fibrillation (MAGIC-AF).⁹ The study proposes to randomise patients undergoing their first ablation procedure for persistent AF who remain in AF after PVI to either placebo or 0.25mg ibutilide infused over 10 minutes. No further ablation would be performed if AF terminated to sinus rhythm. If AF organises into atrial tachycardias, these would be mapped using conventional activation/entrainment techniques and ablated with the desired endpoint being achieving sinus rhythm. If AF persists, CFAE ablation would be performed, guided by the mean cycle length mapping utility on Ensite NavX mapping systems. (St. Jude Medical, MN, USA) For this protocol, CFAE definition is standardised as sites with local electrogram duration in excess of 10ms, inter-electrogram separation of at least 50ms and mean cycle lengths of less than 120ms. No linear lesions are permitted unless AF converts into macro-entrant ATs which can be terminated by targeting the appropriate isthmi. In the event that AF does not organise into AT or terminate into sinus

rhythm after ibutilide and CFAE ablation, electrical or chemical cardioversion will be performed. It is left to the operator's discretion which CFAE regions should be targeted and how long to persist with CFAE ablation before performing cardioversion. The primary investigators are hopeful that this protocol will result in a greater proportion of persistent AF patients acutely achieving sinus rhythm using catheter ablation alone without the need for cardioversion. This, on its own, may have important implications. In a recent study of 232 Italian patients, termination of AF with catheter ablation alone, compared to the need for chemical or electrical cardioversion, was associated with a reduced risk of asymptomatic cerebral ischemia, as quantified by routine post-operative magnetic resonance imaging.¹⁰ The primary endpoint of the MAGIC-AF study is defined as 1 year freedom from any atrial arrhythmias greater than 30 seconds in duration after a single ablation procedure. The primary endpoint will be assessed after a 3 month blanking period at which point all anti-arrhythmic agents are stopped. Use of anti-arrhythmic agents during the 3 month blanking period is left to the discretion of the operator. Repeat catheter ablation for early arrhythmia recurrence during the blanking period is also permissible. Patients will be followed up for at least 12 months with ambulatory ECG recordings in excess of 7 day durations being performed at 3, 6 and 12 months after their procedure.

In a pilot study conducted by Singh et al. of 11 patients, administration of 0.25mg to 1mg of ibutilide terminated AF into atrial tachycardias in 3 patients.¹¹ In the remaining 8 patients, mean

Figure 1: Reduction in mean AF cycle length before (above panel) and after (below panel) ibutilide. Purple areas represent regions with mean cycle length in excess of 120ms and red areas represent areas with shortest cycle length. Note the reduction in area of CFAE, resulting in a more compact area targeted for ablation. (Adopted from Singh et al. Intraprocedural use of ibutilide to organise and guide ablation of complex fractionated atrial electrograms. *J Cardiovasc. Electrophysiol.* 201; 21(6): 608-615)



AF cycle length prolonged from 147ms to 165ms, a measure that strongly predicts eventual termination of AF during ablation.¹² After administration of ibutilide, the general location of CFAE remained similar but areas containing CFAE became smaller, allowing for lesser ablation in the atria. (Figure 1) With this protocol, AF terminated to sinus rhythm and via at least 1 atrial tachycardias in 3 and 7 patients out of 11 respectively. Only one patient required DC cardioversion for AF persisting despite biatrial CFAE ablation.

Why ibutilide?

As a tool to modify the arrhythmogenic atrial substrate and facilitate the identification of CFAE sites that are responsible for AF perpetuation rather than those created by passive activation, ibutilide seems ideal. Ibutilide, approved by the FDA since 1995, exerts class III anti-arrhythmic action via blocking potassium (IKr/HERG) channels and activating the slow delayed inward sodium current that occurs early during repolarisation. As a result, action potential duration is prolonged. It is available only for intravenous use due to extensive first pass metabolism. Onset of activity and clearance is fast. In 200 patients with either atrial flutter or AF more than 3 hours but less than 90 days in duration, intravenous ibutilide (0.015mg/kg to 0.025mg/kg) terminated atrial arrhythmias in about 45% of patients and the vast majority of termination occurred within 40 minutes.¹³ QT prolongation, which correlates with ibutilide dose, normalises within 2 to 4 hours of stopping the infusion. Its other favourable clinical attributes include the absence of haemodynamic compromise during infusion, ability to facilitate cardioversion with direct current shock and safety without increasing pro-arrhythmic adverse events in patients already treated with amiodarone.

When first introduced, ibutilide was shown to be highly effective in the cardioversion of patients presenting with acute onset atrial flutter and atrial fibrillation. In a study of 152 consecutive patients with atrial flutter or fibrillation of less than 48 hours duration, patients were randomised to infusions of amiodarone or ibutilide.¹⁴ Ibutilide was superior to amiodarone in terminating atrial flutter (87% versus 29%) and was equivalent in performance for AF. Overall, a larger proportion of ibutilide patients (80% versus 57%) were in sinus rhythm af-

ter treatment. However, for longer standing AF, the results of ibutilide therapy are less impressive with less than 50% success rates, although success rates associated with other anti-arrhythmic agents are equally disappointing.¹⁵ The main deterrent to more widespread use of ibutilide has been clinical concerns about risks of ventricular pro-arrhythmias. Similar to other class III agents, ibutilide results in QT prolongation with the risks further exacerbated in patients with severe LV impairment. The risk of torsade de pointes with ibutilide monotherapy is estimated to be 3.9% and therefore patients should be closely monitored for at least 4 to 6 hours after ibutilide infusion.¹⁶ As a result, ibutilide is currently not licensed in the European Union. This risk may be reduced in patients receiving concomitant type IC anti-arrhythmic agents such as flecainide or those reducing intravenous magnesium. Hence all patients in the MAGIC-AF study will receive 1g of magnesium to minimise chances of torsade des pointes.

Conclusions

Ibutilide is a highly effective class III agent for cardioversion of acute-onset atrial flutter and fibrillation, with limited clinical use due to risks of ventricular pro-arrhythmias. However, results from the on-going MAGIC-AF trial may re-invigorate its role in clinical electrophysiology as an adjunct to facilitate controlled substrate modification during ablation of persistent AF.

References

1. Haissaguerre M, Jais P, Shah DC et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med.* 1998;339:659-666.
2. Oral H, Knight BP, Tada H et al. Pulmonary vein isolation for paroxysmal and persistent atrial fibrillation. *Circulation.* 2002;105:1077-1081.
3. Cappato R, Negroni S, Pecora D et al. Prospective assessment of late conduction recurrence across radiofrequency lesions producing electrical disconnection at the pulmonary vein ostium in patients with atrial fibrillation. *Circulation.* 2003;108:1599-1604.
4. O'Neill MD, Wright M, Knecht S et al. Long-term follow-up of persistent atrial fibrillation ablation using termination as a procedural endpoint. *Eur Heart J.* 2009;30:1105-1112.
5. Knecht S, Hocini M, Wright M et al. Left atrial linear lesions are required for successful treatment of persistent atrial fibrillation. *Eur Heart J.* 2008;29:2359-2366.
6. Estner HL, Hessling G, Ndrepepa G et al. Electrogram-guided substrate ablation with or without pulmonary vein isolation in patients with persistent atrial fibrillation. *Europace.* 2008;10:1281-1287.
7. Habel N, Znojkwicz P, Thompson N et al. The temporal vari-

ability of dominant frequency and complex fractionated atrial electrograms constrains the validity of sequential mapping in human atrial fibrillation. *Heart Rhythm*. 2010;7:586-593.

8. Lemola K, Desjardins B, Sneider M et al. Effect of left atrial circumferential ablation for atrial fibrillation on left atrial transport function. *Heart Rhythm*. 2005;2:923-928.

9. Singh SM, D'Avila A, Kim YH et al. The Modified Ablation Guided by Ibutilide Use in Chronic Atrial Fibrillation (MAGIC-AF) Study:: Clinical Background and Study Design. *J Cardiovasc Electrophysiol*. 2011.

10. Gaita F, Caponi D, Pianelli M et al. Radiofrequency catheter ablation of atrial fibrillation: a cause of silent thromboembolism? Magnetic resonance imaging assessment of cerebral thromboembolism in patients undergoing ablation of atrial fibrillation. *Circulation*. 2010;122:1667-1673.

11. Singh SM, D'Avila A, Kim SJ et al. Intraprocedural use of ibutilide to organize and guide ablation of complex fractionated atrial electrograms: preliminary assessment of a modified step-wise approach to ablation of persistent atrial fibrillation. *J Cardiovasc*

Electrophysiol. 2010;21:608-616.

12. Rostock T, Salukhe TV, Steven D et al. Long-term single- and multiple-procedure outcome and predictors of success after catheter ablation for persistent atrial fibrillation. *Heart Rhythm*. 2011;8:1391-1397.

13. Ellenbogen KA, Stambler BS, Wood MA et al. Efficacy of intravenous ibutilide for rapid termination of atrial fibrillation and atrial flutter: a dose-response study. *J Am Coll Cardiol*. 1996;28:130-136.

14. Kafkas NV, Patsilinos SP, Mertzanos GA et al. Conversion efficacy of intravenous ibutilide compared with intravenous amiodarone in patients with recent-onset atrial fibrillation and atrial flutter. *Int J Cardiol*. 2007;118:321-325.

15. Nair M, George LK, Koshy SK. Safety and efficacy of ibutilide in cardioversion of atrial flutter and fibrillation. *J Am Board Fam Med*. 2011;24:86-92.

16. Gowda RM, Khan IA, Punukollu G et al. Female preponderance in ibutilide-induced torsade de pointes. *Int J Cardiol*. 2004;95:219-222.