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Persistent atrial fibrillation in the setting of pulmonary vein isolation – where to next?

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Clinical scenario

67 yo hypertensive overweight woman with recurrent persistent AF having undergone PVI 12 months earlier. Sinus rhythm was maintained for 6 months following PVI with 3 symptomatic recurrences despite the reintroduction of Sotalol, two of which required electrical cardioversion after 7 days duration.

An echo demonstrated normal LV systolic function with mild to moderate LA enlargement.

A repeat catheter ablation is performed in atrial fibrillation and you find that all pulmonary veins are electrically isolated. Please describe your mapping and ablation strategy.

Abstract

Catheter ablation for atrial fibrillation (AF) is indicated in symptomatic patients who are intolerant or refractory to anti-arrhythmic therapy. However, outcomes from catheter ablation remain suboptimal in patients with persistent AF. Pulmonary vein antral isolation (PVAI) is established as the cornerstone of AF ablation strategies. The landmark STAR AF II study demonstrated a lack of incremental benefit with adjunctive linear and complex fractionated electrogram ablation beyond PVAI. Randomised studies thus far have failed to consistently show favourable outcomes from other trigger/ substrate based ablation approaches over PVAI alone. In this issue of the *journal* we pose an interesting clinical scenario – of a middle aged female who presents with recurrent persistent AF but was found to have enduring PVAI on repeat electrophysiologic study. Which approach should be undertaken next? In this review article we aim to provide an overview of ablation strategies beyond PVAI. Finally in light of scant randomised data to guide decision making we have approached leading experts in the field to provide their approach to this scenario.

Manuscript

Pulmonary vein antral isolation (PVAI) is the cornerstone of AF ablation strategies, however PVAI is less effective in patients with persistent AF compared with paroxysmal AF⁽¹⁾. Meta analyses have reported a single procedure success for catheter ablation for persistent AF ranging from 43% to 66% , utilising contemporary ablation and mapping tools⁽²⁾. The most common finding in patients with AF recurrence after catheter ablation has been pulmonary vein reconnection. Achieving durable PVI has

improved substantially with increasing operator experience, contact force technology and single shot ablation tools. As a result of these advances and longer patient follow up the clinical scenario of AF recurrence in the presence of enduring PVAI is increasingly encountered.

Poorer outcomes in persistent AF are likely explained by the development of atrial substrate and potential triggers outside of the pulmonary veins. The risk factors for AF such as ageing⁽³⁾, hypertension⁽⁴⁾ and heart failure⁽⁵⁾ are associated with atrial electrical and structural remodelling. A range of ablation strategies have evolved in an attempt to modify the atrial substrate, in the hope of achieving better results. The landmark STAR AF II study randomised patients with persistent AF to PVAI alone vs PVAI plus linear ablation (roof line and mitral isthmus line), and PVAI with complex fractionated electrogram ablation (CFAE). Additional ablation beyond PVAI did not result in a significant increase in single or multi procedure freedom from AF or other atrial arrhythmia over 18 months follow up⁽⁶⁾. Subsequent multicentre randomised studies on different trigger / substrate modification techniques have been relatively few and failed to demonstrate consistent superiority of adjunct strategies beyond PVAI alone⁽⁷⁻¹⁰⁾. Hence in the 2017 Heart Rhythm Society Consensus Document on AF ablation, no additional ablation technique had received a recommendation higher than a IIb for persistent AF ablation⁽¹⁾.

There are several aspects in the management of persistent AF patients when a rhythm control strategy is desired which require further consideration. Achieving durable PVAI is an important ablation endpoint, with studies showing higher AF recurrence rates in patients with incomplete PV isolation⁽¹¹⁾. Current methods in AF ablation, including contact force sensing ablation catheters, and adenosine testing to unmask dormant PV conduction, have all helped to increase the likelihood of achieving PVAI⁽¹²⁾. Indeed a meta-analysis by Voskoboinik et al reported a success rate for PVAI alone in persistent AF patients with contemporary techniques in the range of 66%⁽²⁾. Use of novel ablation indices such as the ablation index (AI), which incorporates contact force with time and power, and minimising inter-lesional distance have likely improved ablation outcomes further⁽¹³⁾. High density mapping could potentially improve the sensitivity of detecting gaps in PVAI lines over conventional mapping catheters and further enhance the achievement of durable

PVI⁽¹²⁾. A range of single shot technologies such as the cryoballoon have reduced procedure times for PVAI at the expense of fluoroscopy times while maintaining equivalent outcomes to RF⁽¹⁴⁾. Other new technologies are currently being trialled to further improve the efficacy of performing PVAI, such as pulsed electric field (PEF) energy to create pores in cell membranes (electroporation); as well as very high power short duration (vHPSD) ablation catheter. Short term outcomes from these studies have reported 100% PVAI rates with excellent safety profiles^(15, 16) but longer term randomised trials are needed.

To further improve outcomes in atrial fibrillation, a more holistic approach is required for patient care. Risk factor treatment including hypertension, obesity, obstructive sleep apnoea (OSA), diabetes mellitus and alcohol excess form an important pillar in AF management^(17, 18). The ARREST AF study demonstrated that aggressive risk factor management incorporating smoking cessation, blood pressure management and weight loss significantly improved the long-term success of AF ablation⁽¹⁷⁾. In addition obese AF patients who achieve sustained weight loss had a significantly lower AF burden on long term follow up⁽¹⁸⁾.

As a consequence of improvements in ablation techniques and technology, the patients who do present with AF recurrence are increasingly found to have enduring PVAI. The clinical scenario which electrophysiologists are increasingly confronted by is what to do next. This conundrum arises in the context of a lack of multicentre randomised evidence to guide selection of additional ablation strategies beyond PVAI. Henceforth we aim to provide an overview of other strategies beyond PVAI while awaiting the outcome of larger randomised studies.

The first decision is whether to map and ablate in atrial fibrillation or cardiovert to sinus rhythm. Several studies including a substudy from STAR AF2 demonstrated improved outcomes when ablation is completed in sinus rhythm rather than during AF^(7, 19). Alternatively mapping and ablation to sinus rhythm without cardioversion may appear a logical endpoint in this clinical scenario. The stepwise approach which combines linear and CFAE ablation remain in the electrophysiologist's tool kit in selected patients. Achieving durable bidirectional block with linear ablation has limited the impact of this adjunctive therapy with the consequences of proarrhythmia if conduction delay develops. Randomised studies of the stepwise approach have not

demonstrated an improvement in arrhythmia free survival compared with PVAI alone⁽¹⁰⁾.

The posterior wall of the left atrium has evolved as a target for catheter ablation. It is embryologically related to the pulmonary veins and has been shown to play a role in the initiation and maintenance of persistent AF, through spontaneous trigger activity, low tissue voltage, and parasympathetic innervation. Adding isolation of the posterior wall (PWI) to PVAI had been shown in earlier studies to result in better sinus rhythm maintenance⁽²⁰⁾. A major concern with performing PWI is the risk of causing esophageal thermal injury due to the proximity of the posterior wall to the esophagus. In a recent meta-analysis on PWI, which included 17 studies and 1643 patients, acute procedural success rate for achieving PWI was 94%, with a low major complication rate of 0.1%. Single procedure success at 12month follow up was 61.9% for persistent AF patients⁽²¹⁾. Randomised studies are ongoing to determine whether the addition of PWI to PVAI is more effective than PVAI alone.

Non- pulmonary vein (PV) triggers have been well described in the persistent AF population, with the incidence ranging from 10-33%⁽²²⁾. Common sites for right sided non-PV trigger include the crista terminalis, and superior vena cava (SVC); whereas left sided non-PV trigger are commonly located at the posterior wall, coronary sinus, ligament (LOM) or vein of Marshall (VOM) and left atrial appendage (LAA). In the RASTA study, where patients were randomised to PVAI plus either: ablation of induced non-PV trigger, empirical non-PV trigger ablation, or CFAE ablation, those who underwent non-PV trigger ablation had better 1 year recurrence outcomes than the substrate modification group⁽⁹⁾. Furthermore, PVAI with non- PV trigger ablation had also been shown to result in good long term AF control even in longstanding persistent AF patients⁽²³⁾. However there are several important challenges in mapping and ablation of non -PV triggers. There is considerable variation in methods of induction of non- PV triggers and also whether atrial triggers resulting in AF or atrial ectopy alone should be targeted. Localisation of non-PV trigger can be difficult with often few ectopics to map before AF recurs. Reproducibility and a clear endpoint when non- PV triggers may be multi focal are further limitations. When triggers can be localised to a structure such as the SVC or the posterior wall then empirical isolation may be completed.

Natale and co-workers have identified the LAA as a potential target for electrical isolation to improve the outcomes of catheter ablation. In the BELIEF study, 173 patients with longstanding persistent AF who had empirical LAA isolation (in addition to conventional ablation) had significantly better freedom from recurrent AF at 1 year⁽⁸⁾. A meta-analysis which included studies utilizing different isolation techniques found significantly lower rates of AF recurrence with LAA isolation compared with standard ablation⁽²⁴⁾. However there are safety concerns with performing LAA isolation with an elevated incidence of LAA thrombus and strokes despite ongoing use of oral anticoagulation⁽²⁵⁾.

The LOM/ VOM may be a source of potential AF triggers and house parasympathetic / sympathetic innervations which contribute to AF maintenance. LOM ablation is typically performed on the endocardial site, at the left lateral ridge between the LAA and left PVs. Anatomically the VOM coincides with the location of the posterior mitral isthmus, which is often targeted in peri-mitral flutter ablation. The role of VOM ethanol infusion in persistent AF is currently being assessed in RCTs – VENUS-AF which targets patients undergoing their index ablation procedure; and MARS-AF which targets recurrent persistent AF with a prior ablation procedure⁽²⁶⁾

Advanced mapping technology, in particular multi-electrode basket catheters, had allowed for chamber-wide, simultaneous mapping of AF to detect localised drivers in the form of focal impulses and localised rotors. Focal impulse and rotor modulation (FIRM) was prospectively studied in the CONFIRM trial, where ablation at these drivers resulted in AF termination or slowing in 86% of cases. Over medium term follow up there was a significant reduction in AF recurrence in those treated with FIRM compared to conventional ablation alone⁽²⁷⁾. However the RE-AFFIRM randomised study did not demonstrate an improvement in efficacy beyond PVAI alone⁽²⁸⁾.

Last but not least, the presence of left atrial scar or fibrosis, as determined by cardiac MRI or on invasive contact mapping, is associated with increased AF recurrence post ablation⁽²⁹⁾. In non randomised studies ablation to target LVAs including box isolation and scar homogenisation may improve outcomes⁽³⁰⁾. Large scale RCTs are currently underway to further investigate the utility of left atrial voltage based scar ablation (ERASE AF), as well as MRI based scar ablation (DECAAF II). There are several

challenges, however, with a scar based approach. Imaging scar on cardiac MRI can be difficult due to the thinness of the atrial wall, and requires dedicated imaging protocols. Using the invasive voltage mapping approach, factors such as the nature of the mapping electrodes and contact force between mapping catheter and atrial myocardium affect the measured voltage. There is significant disparity in regional low voltage identified by cardiac MRI compared with endocardial voltage⁽³¹⁾. In addition, there is a lack of an accepted definition of scar or low voltage with most studies using <0.5mV as the cutoff value⁽¹²⁾.

To conclude, achieving and maintaining sinus rhythm from catheter ablation in persistent AF remains an ongoing challenge. Here we pose an interesting scenario where a patient represents with persistent AF but has enduring PVAI at electrophysiology study. We have provided an introduction to a range of current ablation strategies which are currently unsupported by large multicentre randomised trials or current guidelines. To provide some guidance we have canvassed the opinions of leading figures in the field to outline their approach to this clinical scenario.

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