A meta-analysis on adjunctive complex fractionated atrial electrogram ablation: comparing the incomparable?

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This editorial refers to ‘Efficacy of adjunctive ablation of complex fractionated atrial electrograms and pulmonary vein isolation for the treatment of atrial fibrillation: a meta-analysis of randomized controlled trials’ by M.H. Kong et al., Europace: 13(2):193–204.

Pulmonary vein (PV) isolation is a generally accepted endpoint in catheter ablation of patients with paroxysmal atrial fibrillation (AF). In long-standing persistent AF or in the presence of advanced structural heart disease, atrial substrate modification on top of PV isolation may be required. This may consist of deployment of additional linear lesions, adjunctive ablation of areas exhibiting complex fractionated atrial electrograms (CFAEs), or even a stepwise ablation strategy until conversion.

In recent years, several randomized controlled, single- and multicentre trials have been performed comparing a strategy of PV ablation only vs. PV ablation followed by additional defractionation. These studies revealed divergent results even between very experienced centres. Kong et al. performed a meta-analysis of six prospective randomized studies evaluating the additional value of defractionation beyond PV ablation including both patients with paroxysmal AF and long-standing persistent AF. This meta-analysis reveals a distinct benefit of additional defractionation on top of PV ablation with a significant overall increase in freedom of AF from 48 to 66% and a twice as high likelihood of being in sinus rhythm (odds ratio 1.98; confidence interval: 1.04–3.74). The randomized controlled trials (PubMed, clinicaltrials.gov), the primary outcome parameter (freedom of AF or atrial tachycardia with or without antiarrhythmic drug therapy after a single procedure), and the randomized-effect model were appropriately chosen, and analysis for sensitivity and heterogeneity was performed.

In spite of this, the conclusion and potential implications of this meta-analysis should be interpreted with vigilance. Analysis for publication bias and grading of the quality of the randomized clinical trials was not reported. Furthermore, there is a moderate heterogeneity in the primary outcome parameter, which itself is related to diversity in patient selection, PV ablation strategy, and defractionation approach between the incorporated studies. First, there are obvious differences in patient characteristics: three studies included patients with paroxysmal AF while three other studies included patients with high AF burden or long-standing persistent AF. This is reflected in the marked variation in success rates especially in the ‘PV ablation’ arm with freedom of AF ranging from as low as 38 up to as high as 89%. Second, the chosen PV ablation strategy varied from circumferential PV isolation without a circular mapping catheter to proven electrical PV isolation. Furthermore, follow-up duration was highly variable, ranging from 3 to 16 months. Finally, the defractionation approach was very different between the six studies at different echelons. Identification of CFAEs was performed using diverse methods varying from visual assessment to commercially available but not validated algorithms. Our group has recently reported that visual classification is highly subjective and that different commercial algorithms and cut-off values may point to different types of fractionation. Also the ablation strategy of CFAEs varied from left atrial to extensive bi-atrial defractionation with a marked difference in the pre-specified endpoint (non-inducibility of AF to extensive bi-atrial defractionation) resulting in a net increase in radiofrequency energy delivery times ranging from 14 to 33 min.

On top of the observed heterogeneity—which to some extent could be considered inherent to any meta-analysis—other limitations are present. A negative publication bias cannot be excluded (especially in outcome studies), all studies were small size (maximum 50 patients in the defractionation arm), and no single study was performed with blinded analysis and/or central adjudication of endpoints. Data extraction from the cited studies can also be criticized. Elayi et al. compared three different ablation strategies: PV ablation, PV isolation,
and PV isolation with CFAE ablation. In the meta-analysis, patients with PV ablation and PV isolation were included in the control arm whereas PV isolation was the only PV strategy in the defractionation arm. It is likely that part of the beneficial effect of additional defractionation generated in the meta-analysis was to some extent due to the superior effect of PV isolation (freedom of AF 40%) over PV ablation (freedom of AF 11%). In the study by Deisenhofer et al., CFAE ablation was only performed in patients with inducible AF after PV isolation; yet patients with non-inducible AF from this study were also included in the defractionation arm of the meta-analysis. Based on these elements, we believe that it is too early to recommend defractionation beyond PV isolation as a standard ablation strategy in patients with long-standing persistent AF or advanced structural heart disease. On the other hand, the present meta-analysis does support further research on CAFE ablation and substrate modification in general. Theoretically, ablation guided by activation mapping of fibrillatory waves with identification of the critical regions maintaining AF should be the ideal approach. However, this method is unlikely to be implemented in clinical practice because it is time consuming and requires simultaneous wave mapping and offline analysis. As an alternative, in clinical practice because it is time consuming and requires simultaneous wave mapping and offline analysis.

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References