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EDITORIAL

Computational models of the atrial fibrillation substrate: can they explain post-ablation recurrences and help to prevent them

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This editorial refers to 'Arrhythmogenic propensity of the fibrotic substrate after AF ablation: a longitudinal study using MRI-based atrial models' by R.L. Ali *et al.*, pp. 1757–1765.

Atrial fibrillation (AF) is an extremely common and problematic arrhythmia.[1] While treatment by catheter ablation has greatly advanced the therapeutic options, recurrences after ablation are common and clinically problematic.[2] Advances in both our understanding of the basic mechanisms underlying arrhythmia initiation and maintenance,[1] and in the technologies that can be brought to bear to address them,[2,3] are potential keys to producing significant improvements in disease management and prevention.

Computational analysis and the AF substrate

Computational models are very valuable in quantitatively integrating detailed basic information about atrial electrophysiology at the cellular[4] and tissue[5] level, making predictions about arrhythmic behaviour and providing testable higher-order hypotheses. The combination of sophisticated computational analysis and advanced imaging methods has permitted the development of personalized approaches to studying the AF maintaining substrate in individual patients.[6] The results suggest a detailed mechanistic basis for the long-recognized key role of atrial fibrosis in AF[7]: the anchoring of rotational activity in zones of moderately dense fibrosis that support conduction but provide conduction barriers that stabilize re-entrant activity.[6]

AF substrate differences between successful and unsuccessful AF-ablation cases

Ali *et al.*[8] take this approach one step further, examining the ability of personalized computational modelling to account for the recurrence of AF after apparently successful ablation procedures. The authors retrospectively analysed atrial late gadolinium enhancement–magnetic resonance imaging (LGE-MRI) data to determine the extent and distribution of left atrial (LA) fibrosis, as well as to recreate patient-specific atrial geometry. Of 30 patients with LGE-MRI acquired both before and 3–11 months after ablation, they selected 12 (seven paroxysmal AF cases and five persistent) with scans that could be used for computational modelling. All patients underwent pulmonary vein (PV) isolation (PVI); three also had an LA roof-line. The Courtemanche–Ramirez–Nattel atrial cardiomyocyte action-potential model[9] was used as the basic unit of cardiac cellular electrical activity, modified to account for changes with AF and integrated into an anatomically realistic three-dimensional model of the human atria incorporating representations of the electrophysiological consequences of atrial fibrosis, as previously described.[5,6] The authors induced AF with simulated pacing protocols in the model LAs, noted the persistence of AF and associated mechanisms.

AF could be induced in 10 of the 12 baseline models, maintained by re-entrant driver (RD) activity. For the five cases without recurrent AF on follow-up, no AF-maintaining RDs could be induced in the models based on the post-ablation follow-up MRIs (attributed by the authors to elimination by ablation of the substrate for RDs). The authors then went on to analyse the features of AF-models in the five cases with RD-maintained AF at baseline that showed recurrences after ablation. The recurrent AF cases were characterized at baseline study (compared to cases without recurrence) by more RDs and more simulated pacing-sites at which AF could be induced. In two of five recurrent cases, baseline RDs could still be induced in the follow-up models. In order to analyse the direct effects of ablation, the authors used data from CARTO maps during the initial ablation procedures to simulate the effects of ablation lesions on RDs in the recurrent AF cases: in none of these were the baseline RDs eliminated (as far as I can tell, the five cases with successful AF ablation were not studied to see whether their ablation lines eliminated baseline RDs). In addition to the persistent RDs seen on the follow-up simulation studies of two of five recurrent AF cases, all five cases showed new RDs that the authors term 'emergent RDs'. These

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emergent RDs were based on unaffected fibrotic regions, in many cases in combination with new fibrosis attributed to the consequences of ablation.

Previously studied mechanisms of AF recurrence and its prevention after catheter ablation

AF recurrences are a major factor limiting the success of catheter ablation and methods to prevent recurrence are an important consideration in contemporary clinical practice guidelines.[10] A variety of mechanisms have been implicated in post-ablation AF recurrence. The PVs have been implicated as a privileged site in maintaining AF, particularly of the paroxysmal variety,[11] and PVI is a key component of virtually all AF ablation approaches. PV reconnection is an important mechanism of AF recurrence post-ablation, particularly for paroxysmal AF, and better targeting to prevent PV reconnection significantly prevents recurrence.[12] There is also evidence that the inclusion of low-voltage atrial tissue zones, believed to represent fibrotic areas, in PVI lesions predicts recurrence- free initial ablation procedures, implicating persistent fibrosis outside ablation lesions in recurrence.[13] Finally, progression of the underlying AF substrate, due to the natural history of the underlying condition, might occur following ablation and lead to recurrence.[2,14]

Implications and limitations of the Ali study

The Ali study has a number of important findings and implications. This work is, to my knowledge, the first systematic combined imaging/computational analysis of the mechanisms underlying AF recurrence post-catheter ablation and is, for this reason alone, very important. The results suggest that patients with AF recurrence have more underlying atrial fibrosis with greater ability to host RDs. Ablation without recurrence (which the authors term 'successful PVI', but this needs to be carefully distinguished from initially successful PVI with subsequent recurrence) is characterized by loss of the ability to support RDs based on the post-ablation fibrosis distribution. The recurrence of AF was associated with two principal findings of potential mechanistic significance: (i) failure to eliminate AF-supporting RDs (in two of five cases); and (ii) the appearance of new (emergent) RDs capable of supporting AF, attributed by the authors to ablation-induced fibrosis in combination with pre-existing fibrosis, in all five. The authors also simulated the effects of ablation based on CARTO maps and noted that RD locations were preserved in all five (although analysis of the actual post-ablation images showed preservation of original RDs in only two).

This study is thought provoking and has potentially important clinical implications. It provides insights into the apparent mechanisms of post-ablation AF recurrences, identifying both failure to suppress the original RD mechanism and the emergence of new RDs post-ablation. While these ideas are not novel, this is the first time they have been described based on precise computational simulations using only anatomical/tissue-characterization imaging. If this simulation method could be used to prospectively guide lesion sets that prevent AF recurrence, the clinical utility would be enormous.

On the other hand, the work has a number of important limitations. First and foremost, the study is retrospective and there is no direct correlation with the actual mechanisms of AF recurrence in these patients, so all one can say is that the study provides plausible mechanisms that MIGHT explain recurrence; any inference about the actual mechanisms is speculative. Second, the population studied was highly selected. Only patients with both pre- and post-procedural LGE-MRIs could be included, and the authors selected 12 of the 30 'whose scans could be used for model construction' based apparently on the absence of breathing artefacts. Some potentially useful information is not provided (at least that I could find) or was not obtained. There is no indication about whether the total quantity of fibrosis increased upon follow-up, as would be expected based on the effects of ablation. While the authors used simulated ablation based on CARTO maps to show that it failed to suppress RDs in the recurrent-AF patients, the same analysis was not reported for the non-recurrent AF patients to confirm that ablation DID suppress RDs in these. The simulated ablation lesions were also somewhat unrealistic in that they were transmural and lacked any intervening gaps, a desired but elusive goal in most clinical ablations. It would have been interesting to see a correlation between ablation location and the differences in fibrous tissue distribution pre- vs. post-ablation, as has been performed previously by other groups.[15] Furthermore, it would be important to analyse the properties of applied lesion sets in relation to the outcome and baseline substrate/AF mechanisms, in order to establish how personalized computational models can be used to guide the initial ablation procedure to prevent recurrence. Finally, a number of mechanisms that might be important in AF recurrence post-ablation were either not considered or not accounted for by the simulations, including: (i) PV reconnection[12]; (ii) focal ectopic firing, believed to be particularly important in paroxysmal AF[11]; and (iii) progression of the underlying substrate due to continued atrial remodelling.[1–3,14] Despite these limitations, Ali *et al.* are to be congratulated for a careful and highly innovative study that paves the way for important future work in this area.

Conclusions

Ali *et al.* have made an important contribution to the understanding and prevention of AF recurrence after ablation procedures by showing that a sophisticated personalized computational model based on structure/tissue composition imaging can account for the mechanism of recurrence. Prospective studies including the use of personalized computational models to guide ablation so as to prevent recurrence, as well as models that incorporate mechanisms of recurrence other than those that could be examined in the present simulations, are needed in the future to move this promising approach towards practical translation.

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