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EDITORIAL

Rotors and breakthroughs as three-dimensional perpetuators of atrial fibrillation

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This editorial refers to 'Heterogeneous atrial wall thickness and stretch promote scroll waves anchoring during atrial fibrillation' by M. Yamazaki *et al.*, pp. 48–57, this issue.

In previous years, disruption of electrical coupling between cardiac myocytes and muscle bundles, resulting in narrower—and thus more—fibrillation waves, was identified as the main mechanism underlying enhanced stability of atrial fibrillation (AF) in structurally remodelled atria.[1] In addition, the rate of epicardial breakthrough was found to be enhanced in patients with persistent AF, which was hypothesized to be caused by more electrical dissociation between the epicardial layer and the endocardial bundle network.[2] While endo-epicardial dissociation of electrical activity and breakthrough during AF were already described many years ago,[3–5] this phenomenon was only recently demonstrated to be enhanced after several weeks to months of AF or rapid atrial pacing.[6,7] Endo-epicardial dissociation of electrical activity is regarded the *conditio sine qua non* for the occurrence of transmural conduction and epicardial breakthrough. Such a 'three-dimensional substrate' for AF is believed to significantly contribute to the stabilization of AF over time.

The study of Yamazaki *et al.*[8] adds several new aspects to the emerging concept of the three-dimensional substrate for AF. By the use of simultaneous endo-epicardial optical mapping, the authors were able to match two-dimensional high-resolution mapping data with each other and the underlying anatomical structures. This sophisticated technical approach allows new mechanistic insights in the spatio-temporal behaviour of fibrillation waves. The authors demonstrate that in persistent AF, atrial scroll waves, defined as transmural rotors around a filament spanning from the epicardial to the endocardial surface, formed the primary activation pattern. Interestingly, most of the meandering scroll wave filaments were identified in the thinner parts of the atrial wall or at the transitions to thicker areas. These results suggest that the large variability in wall thickness is an important factor for AF stabilization.

The study by Yamazaki *et al.* significantly extends insights provided by several previous publications. Schuessler *et al.*[4] had already demonstrated that endo-epicardial activation time differences were shorter in thinner regions of the atrial wall than in thicker areas. Here, it was demonstrated that this might be related to preferential stabilization of atrial scroll waves in thin parts of the atrial wall. Also, previous computer simulations had shown that the heterogeneous distribution of stretch due to the complex anatomy of the atrial wall can contribute to enhanced susceptibility of the atria for AF.[9] The experimental data as well as the computer simulations described in the study by Yamazaki *et al.* suggest that the enhanced propensity to AF in stretched atria is due to the steep gradients in thickness in the complex anatomy of the atrial wall.

On the other hand, there are some discrepancies between the present study and recent literature. The general notion of rotors being the predominant activation pattern during AF in remodelled atria is not supported by activation time mapping in patients[1,5] and also not by several studies in animal models demonstrating AF perpetuation by multiple wavelet reentry.[10,11] A detailed discussion about predisposing conditions and functional implications of spiral wave reentry vs. multiple wavelet reentry has been provided elsewhere and is beyond the scope of this editorial.[12] In the context of the three-dimensional nature of the AF substrate, other discrepancies with previous literature appear to be more relevant. For example, Yamazaki *et al.* report a lower incidence of breakthrough in the persistent AF group compared with acutely induced AF in normal atria. This finding differs from the results of earlier studies in animal models and patients where an increase in breakthrough incidence with AF duration was described.[2,7,10] Also, Yamazaki *et al.* show that in persistent AF, long-lasting atrial scroll waves occur, suggesting that the degree of endo-epicardial dissociation is lower in persistent AF than in normal hearts, where the scroll waves are often distorted by multiple breakthroughs and wavebreaks. In contrast, recent studies have demonstrated increasing dyssynchrony between endo- and epicardial activations[7] or reduced cross-correlation between endo- and epicardial electrograms in animal models of tachycardia-induced atrial remodelling.[6]

Some of these discrepancies might be due to differences in the technical approach between the studies. Yamazaki *et al.* studied Langendorff-perfused hearts by optical mapping requiring the use of blebbistatin, which might have affected the elongation of muscle

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bundles and thus the activity of stretch-activated channels. In the study showing increasing endo-epicardial dissociation with progressive structural remodelling in goats with persistent AF, fibrillating atria were investigated *in situ* by simultaneous endo-epicardial direct-contact mapping.[7] In the elegant study by Everett *et al.*,[6] endocardial non-contact mapping was combined with epicardial direct-contract mapping. It is currently unclear to what extent the experimental setting, the choice for cut-off values for conduction block, and the methods to match endo- with epicardial electrical signals have influenced the conduction pattern of fibrillation waves and the results of the data analysis in these studies.

Interestingly, Yamazaki *et al.* demonstrate that the majority of breakthroughs occurred (nearly) simultaneously in the epi- and the endocardium, suggesting ectopic focal discharges as an underlying mechanism. The incidence of the ectopic discharges, however, was much lower in persistent AF than in control. This observation is surprising as recent studies have shown that prolonged AF enhances phosphorylation[13] and open probability of the Ca^{2+} release channel of the sarcoplasmic reticulum, favouring triggered activity and ectopy during AF.[14,15] A possible explanation for this finding by Yamazaki *et al.* could be that down-regulation of Ca^{2+} influx due to AF might have prevented Ca^{2+} overload and Ca^{2+}-related triggered activity in this model.[16]

The overall implications of the perception of AF being a three-dimensional conduction process are manifold. First of all, endo-epicardial dissociation and conduction provide new reentry sites for fibrillation waves, making the fibrillatory process more stable. Secondly, simultaneous endo-epicardial recording of electrical activity during AF offers the opportunity to study the mechanism of radial spread of activation in more detail. Both transmural conduction and ectopic focal discharges have been hypothesized to underlie this frequently observed conduction pattern. These two phenomena are likely to respond differentially to antiarrhythmic drugs, which means that improving pharmacological cardioversion of AF requires better understanding of the quantitative contribution of these mechanisms to AF perpetuation. Finally, the development of realistic computer models for AF will need to implement the three-dimensional architecture of the atrial wall and conduction within this structure for the reasons explained above. In this sense, the article by Yamazaki *et al.* is important and timely and provides a valuable step towards a more comprehensive understanding of fibrillatory conduction during AF in the complex, three-dimensional structure of the atrial wall.

Conflict of interest: none declared.

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