Optimising ablation strategies to treat ventricular fibrillation

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Since the earliest documented accounts of ventricular fibrillation (VF) over 3000 years ago [1] the mechanisms responsible have been the source of on-going debate. During the early part of last century, both focal and re-entrant mechanisms were proposed, and more recently the re-entry mechanisms have polarised into the multiple wavelet and mother rotor hypotheses. The multiple wavelet hypothesis, originally put forward by [2] to explain atrial fibrillation, implies that VF is sustained by multiple circulating unstable wavelets perpetuated by a sequence of wavebreaks and self-generating re-entry. The mother rotor hypothesis [3] proposes that VF is maintained by a single rapid periodic source that is unable to sustain uniform 1:1 conduction throughout the myocardium resulting in intermittent conduction block with multiple irregular activation patterns. Early studies from several groups across a range of animal species have provided evidence in support of one or other hypothesis. A subsequent study using multi-electrode total epicardial mapping in patients undergoing routine surgical procedures showed that both mechanisms appeared to be operative during the first 20 to 40 seconds of human VF [4]. These findings are now generally accepted, although the relative contributions of focal and rotor activity are still debated. Recently, there has been a revival of interest in focal mechanisms with studies indicating a role of the Purkinje system as both a trigger and in the maintenance of VF [1,5].

These mechanistic considerations are of great importance, not only for our understanding of VF mechanisms, but also as they underpin therapeutic ablation strategies. Traditional targets include sites with structural features

that stabilise and perpetuate functional re-entry and focal sources, which can be identified using VF mapping [6]. Quantitative methods for analysing VF date back over three decades [7], with methods for identifying re-entrant activity being pioneered by Gray and colleagues [8], who used phase techniques to analyse optical maps of cardiac electrical activity during VF. Nash and colleagues [4] translated these techniques to studying VF in cardiac patients using electrocardiac mapping with arrays of contact electrodes across the entire ventricular epicardium. These techniques are now well established for studying cardiac fibrillation [9,10,11], though care must be taken over data interpretation, particularly with respect to the spatial resolution of recordings [12].

Non-invasive quantification of VF using phase analysis relies on the ability to determine the spatio-temporal electrical activity of the heart from body surface recordings. A variety of theoretical ECG imaging (ECGI) methods have been proposed to address this need by predicting epicardial potentials [13]; equivalent dipole layers [14]; or the ventricular activation sequence [15]. However, in vivo validation of these techniques has faced many challenges [16], and studies comparing ECGI predictions against directly measured cardiac electrograms have yielded mixed results. Sophisticated ECGI validation work has been performed using carefully controlled isolated perfused hearts in torso tanks [17,18], and while some in-situ validation studies have demonstrated good reproducibility (e.g. [19]), others have shown variable correlation (e.g. [20,21,22]) due to factors such as sensitivity to geometric inputs for the ECGI computations. Nevertheless, ECGI has been applied to study cardiac arrhythmias in patients (e.g. [23,24]), but there remains a paucity of data demonstrating the clinical validation of ECGI in patients with VF, primarily because of the technically challenging and demanding protocols.

In the current issue, Haïssaguerre and colleagues [25] studied 54 patients with structural heart disease presenting with VF in the absence of preceding VT. Electrophysiological mapping was used to optimise the strategy for targeted ablation therapy. The mapping techniques incorporated both endocardial and epicardial contact electrode mapping together with body surface ECGI during an initial period (mean of 16 seconds) immediately following the onset of VF. Key findings were: (i) activities during the initial period of VF arose from parts

of the structural substrate and Purkinje system prior to propagating through the ventricular mass; (ii) Purkinje arrhythmogenic activity may be elicited by programed stimulation; (iii) ablation, targeting the main sources of activation, prevented recurrence in 83% of patients over a five year follow up period.

This study is an important contribution in the management of idiopathic VF and prevention of recurrent cardiac arrest. The findings shed light on strategies to identify triggers and target the substrate - key elements enabling the development of VF - and presents a coherent case for the efficacy of combining myocardial substrate characterisation, Purkinje mapping and VF mapping to optimise ablation therapy. The use of ECGI to visualise ectopics on the ward, or during exercise testing, presents an advantage. The mapping of abnormal substrate during induced VF is an important further contribution, as this aids optimisation of ablation when ectopy is not present. Several questions arise: what specific features of these VF foci distinguish them as key source locations, or are they simply anchor sites for VF rotors in the myocardium? Moreover, can specific markers from electrograms and/or conduction-repolarisation dynamics distinguish key areas to target for ablation in idiopathic VF? Data from Brugada Syndrome and a proportion of early repolarisation idiopathic VF patients would indicate that specific depolarisation abnormalities with fractionation are important markers of 'VF substrate'. The challenge remains to ensure that bystander areas are not ablated so as to create a partial lesion that may later act as a nidus for VF. Future studies focusing on these electrophysiological characteristics would help to inform ablation strategies to standardise procedures. The main question here is which dynamic features are important? Example contenders include steep restitution slopes, specific degrees of functional block, and localised repolarisation alternans, to mention a few. Such features require detailed interrogation of the tissue, and this is becoming more accessible using high density multipolar grid catheters to streamline the techniques. Furthermore, the exact aetiology of these sites remains to be elucidated - are they due to the effect of previous micro-infarction, inflammation or somatic mutations in the tissue that can cause localised electrophysiological anomalies? Such knowledge may help inform more targeted small molecule or novel anti-arrhythmic drug strategies.

Finally, the authors should be congratulated on an outstanding contribution to clinical electrophysiology research, which adds to our understanding of VF, and will no doubt contribute to future therapeutic strategies for its management.

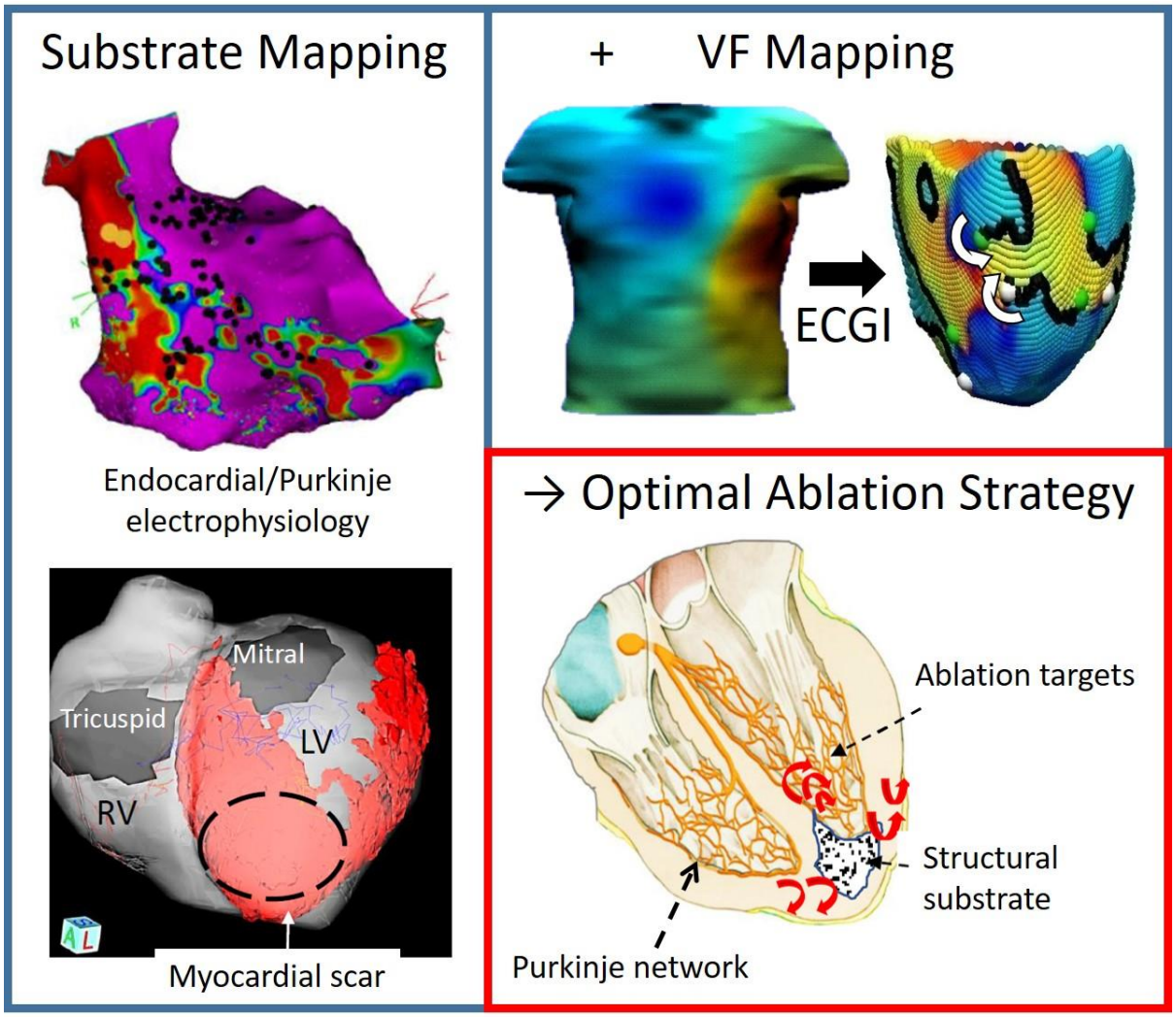

Figure: Electrophysiological/Purkinje mapping and structural imaging of the heart (left) can be used to characterise the triggers and substrate for ventricular fibrillation (VF). Combination of this myocardial substrate mapping with functional imaging of VF, via non-invasive electrocardiographic imaging (ECGI; upper right), can be used to optimise the strategy and identify targets for ablation therapy. LV/RV: left/right ventricles.

References

(1) Aras KK, Kay MW, Efimov IR. Ventricular fibrillation: Rotors or Foci ? Both ! Circ Arrhythm Electrophysiol 2017;10(12):e006011.

(2) Moe GK. On the multiple wavelet hypothesis of atrial fibrillation. Arch Int Pharmacodyn Ther 1962;140:183-188.

(3) Jalife J. Ventricular fibrillation: mechanisms of initiation and maintenance. Annu Rev Physiol 2000;62:25-50.

(4) Nash MP, Mourad A, Clayton RH, Sutton PM, Bradley CP, Hayward M. et al. Evidence for multiple mechanisms in human ventricular fibrillation. Circulation 2006;114:536-542.

(5) Haïssaguerre M, Vigmond E, Stuyvers B, Hocini M, Bernus O. Ventricular arrhythmias and the His-Purkinje system. Nat Rev Cardiol 2016;13(3):155-166.

(6) Krummen DE, Ho G, Hoffmayer KS, Schweis FN, Baykaner T, Rogers AJ, et al. Electrical substrate ablation for refractory ventricular fibrillation. Circ Arrhythm Electrophysiol 2021;14(3):e008868.

(7) Winfee AT. When Time Breaks Down: The Three-Dimensional Dynamics of Electrochemical Waves and Cardiac Arrhythmias. Princeton, NJ: Princeton University Press; 1987.

(8) Gray RA, Pertsov AM, Jalife J. Spatial and temporal organization during cardiac fibrillation. Nature, 1998;392:75-78.

(9) Umapathy K, Nair K, Masse S, Krishnan S, Rogers J, Nash MP et al. Phase mapping of cardiac fibrillation. Circ Arrhythm Electrophysiol 2010;3:105-114.

(10) Bradley CP, Clayton RH, Nash MP, Mourad A, Hayward M, Paterson DJ, et al. Human ventricular fibrillation during global ischemia and reperfusion. Paradoxical changes in activation rate and wavefront complexity. Circ. Arrhythm Electrophysiol 2011;4:684-691.

(11) Clayton RH, Nash MP. Analysis of cardiac fibrillation using phase mapping. Cardiac Electrophysiology Clinics. 2015;7(1):49-58.

(12) Kuklik P, Zeemering S, van Hunnik A, Maesen B, Pison L, Lau DH et al. Identification of rotors during human atrial fibrillation using contact mapping and phase singularity detection: technical considerations. IEEE Trans Biomed Eng 2017;64:310-318.

(13) Barr RC, Ramsey M, Spach MS. Relating epicardial to body surface potential distributions by means of transfer coefficients based on geometry measurements. IEEE Trans Biomed Eng 1977;24:1-11.

(14) van der Waal J, Meijborg V, Schuler S, Coronel R, Oostendorp T. In silico validation of electrocardiographic imaging to reconstruct the endocardial and epicardial repolarization pattern using the equivalent dipole layer source model. Med Biol Eng Comput 2020;58:1739-1749.

(15) Pullan AJ, Cheng LK, Nash MP, Bradley CP, Paterson DJ. Noninvasive electrical imaging of the heart: Theory and model development. Ann Biomed Eng 2001;29:817-836.

(16) Nash MP, Pullan AJ. Challenges facing validation of noninvasive electrical imaging of the heart. Ann Nonivasive Electrocardiol 2005;10(1):73-82.

(17) Bear LR, Cluitmans M, Abell E, Rogier J, Labrousse L, Cheng LK et al. Electrocardiographic imaging of repolarization abnormalities. J Am Heart Assoc 2021;10:e020153.

(18) van der Waal JG, Meijborg VMF, Belterman CNW, Streekstra GJ, Oostendorp T, Coronel R. Ex vivo validation of noninvasive epicardial and endocardial repolarization mapping. Front Physiol 2021:737609.

(19) Oosterhoff P, Meijborg VM, van Dam PM, van Dessel PF, Belterman CN et al. Experimental validation of noninvasive epicardial and endocardial activation imaging. Circ Arrhythm Electrophysiol 2016;9:e004104.

(20) Cluitmans MJM, Bonizzi P, Karel JMH, Das M, Kietselaer BLJH, de Jong MMJ et al. In vivo validation of electrocardiographic imaging. JACC Clin Electrophysiol 2017;3(3):232-242.

(21) Duchateau J, Sacher F, Pambrun T, Derval N, Chamorro-Servent J, et al. Performance and limitations of noninvasive cardiac activation mapping. Heart Rhythm 2019;16:435-442.

(22) Graham AJ, Orini M Zacur E, Dhillon G, Dow H, Srinivasin NT et al. Simultaneous comparison of electrocardiographic imaging and epicardial contact mapping in structural heart disease. Circ Arrhythm Electrophysiol 2019;12:e007120.
(23) Andrews CM, Srinivasan NT, Rosmini S, Bulluck H, Orini M et al. The electrical and structural substrate of arrhythmogenic right ventricular cardiomyopathy determined using noninvasive electrocardiographic imaging and late gadolinium magnetic resonance imaging. Circ Arrhythm Electrophysiol 2017;e005105.
(24) Graham AJ, Orini M, Zacur E, Dhillon G, Dow H, Srinivasin NT et al. Evaluation of ECG imaging to map haemodynamically stable and unstable ventricular arrhythmias. Circ Arrhythm Electrophysiol 2020;13:e007377.
(25) Haïssaguerre M, Cheniti G, Hocini M, Sacher F, Ramirez FD. Cochet H et al. Purkinje network and myocardial substrate at the onset of human ventricular fibrillation: implications for catheter ablation. (In this issue.)