Can we map atrial fibrillation?

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Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia affecting between 1.5-2% of the general population and 3.6% of those aged above 60, with prevalence increasing alongside an ageing population.(1-3) AF is associated with significant healthcare expenditure as a result of recurrent hospitalisation for symptomatic paroxysms as well as associated morbidity including stroke and heart failure. Since the key description in the late 1990s of the role of pulmonary vein ectopy in initiating AF, catheter ablation aimed at electrophysiological isolation of the pulmonary veins has been increasingly performed for patients with recurrent drug refractory symptomatic paroxysmal and persistent arrhythmia.(4-7)

In patients with paroxysmal AF, efficacy of catheter ablation approaches 80% (often requiring multiple procedures), but this figure falls significantly for those with persistent AF, especially in studies with longer follow up.(8-11) The reduced efficacy of pulmonary vein isolation (PVI) for persistent AF highlights the importance of non-pulmonary vein mechanisms in AF propagation and maintenance. These include structural atrial changes, particularly dilatation and fibrosis, referred to as the stable substrate, and electrophysiological patterns of AF propagation, referred to as the dynamic substrate.(12,13) Whilst the stable and dynamic substrates are closely related, their precise role in AF maintenance remains poorly understood.

A number of empiric ablation strategies such as linear ablation, posterior wall isolation and ablation of complex fractionated electrograms have been adopted in order to improve outcomes.(14-17) Unfortunately, randomised trials are yet to

demonstrate clear efficacy for any empirical strategy.(11) In this context, and with sights on the future era of personalised medicine, efforts have shifted towards identifying patient specific mechanisms. Here we will review a number of these strategies and their limitations.

Focal Impulse and Rotor Modulation

Conventional 3-dimensional electroanatomical mapping systems, which are now in widespread use, rely on manipulating recording electrodes around the atrial endocardial surface to undertake activation mapping, referred to as point-by-point mapping. In stable arrhythmias, this is able to create a visual model of wavefront propagation. AF however is characterised by chaotic wavefront propagation with significant variation in spatiotemporal distribution of atrial activation. This limits the ability of conventional techniques to evaluate whole chamber activation during AF and therefore their usefulness for identifying patient specific mechanisms.

Narayan et al. have pioneered a system aimed at overcoming this problem using a 64 pole basket catheter to conduct global atrial contact mapping.(18,19) Contact electrograms are processed using complex proprietary software to identify and ablate focal impulses and rotors which are thought to represent drivers of AF. This is a process referred to as focal impulse and rotor modulation (FIRM).(20) They have identified rotors in both the left and right atria, with ablation of these sites in combination with PVI resulting in improved outcomes both acutely and in longer term follow up.(20-22) However, such positive results have not always been replicated and other studies have not revealed the stable rotors described.(23,24) This may in part be due to difficulties with electrode contact. Although different size baskets are available, it is often difficult to ensure good electrode contact with the endocardium. Some studies have reported coverage of only 50% of the atrial endocardial surface with rotors falsely identified in regions without electrode contact.(25, 26)

Electrocardiographic Imaging

In contrast to invasive catheter based FIRM mapping, electrocardiographic imaging (ECGI) is a non-invasive mapping approach. Using the ECVUE System (CardioInsight, Medtronic, MN, USA), unipolar body surface potentials are recorded from the torso using a vest made up of 252 electrodes. Computed tomography is then used to generate images of electrode position and atrial anatomy. Using this data, virtual epicardial surface electrograms can be derived using a complex mathematical inverse solution to Laplace's equation. Activation maps are then computed along with further signal processing to characterise propagation patterns.(27)

This technique has been used to identify driver mechanisms that may represent targets for catheter ablation with some evidence of improved outcomes.(28,29) However, given that the mapping is performed prior to an ablation procedure and without conventional 3-dimensional electroanatomic mapping, precise localisation of driver regions for ablation can be difficult. This is compounded by a localisation error introduced by the inverse solution methodology and the fact that it is not clear whether epicardial activation also reflects endocardial activation.(30)

Phase mapping of fibrillation

Both FIRM mapping and the ECGI based system described above are based around the concept of phase mapping. Phase is a technical descriptor that facilitates the tracking of a specified region of myocardium through the action potential thereby enabling analysis of spatiotemporal changes during AF.(31) Evaluating the distribution and pattern of phase over time is used to provide insights into mechanisms of fibrillation.(31) Regions of particular interest are those identified around which phase is seen to transition through a complete cycle from $-\pi$ to $+\pi$.(31) Here, the phase is indeterminate and the propagating wave is rotating around this hinge point in an organised manner. This central region with indeterminate phase is referred to as the singularity.(31)

This method relies on computing the phase at each instant of time, known as the instantaneous phase, from recorded unipolar electograms. This is done using a mathematical approach; the Hilbert Transform. This facilitates calculation of a phase shifted signal from the original electrogram. The instantaneous phase is then computed from these 2 signals. Subsequent analysis of the phase of all the electrograms, acquired during a recording at every instant in time, facilitates identification of potential spatial organisation. Recognition of a progressive transition in space through the entire phase cycle from $-\pi$ to $+\pi$ as mentioned above suggests the presence of a rotor.(31)

This method does however possess a number of limitations. Every unipolar electrogram which form the basis of the phase analysis is obtained from the integration of electrical potential signals within a small region of myocardium.(31) Highly localised activation patterns such as local micro-reentry may not be detected. Similarly, unipolar electrograms are highly susceptible to far-field signals and noise, which may particularly be the case in regions of scar, thereby disrupting the spatial distribution of phase.(30,32) Sensitivity and specificity for rotor detection are also highly affected by inter-electrode distance, which is very sensitive to changes in basket spline position during manipulation within the atria.(32,33) Bunching of splines particularly affects the equatorial electrodes resulting in interspline distances ranging between 1.5 and 85mm.(32) Interpolation then fills the space between electrodes, with reliability falling with increasing distance from the recording electrode. Although this may not limit the sensitivity of rotor detection, it significantly reduces specificity with a high rate of false rotor detection.(30, 32-34) A similar problem is seen with signal filtering methods, of which a consistent approach is lacking. Band-pass filtering (at highest dominant frequency) can affect sensitivity and specificity of rotor detection in both invasive and non-invasive phase mapping resulting in false detection of rotors and falsely increasing both spatial and temporal stability of detected rotors.(23,34,35)

EnSite Array

An early technology aiming at facilitating global chamber mapping was the EnSite Array (Abbott/St. Jude Medical, Inc., MN, USA), which used a 64 pole balloon catheter to collect intra-cavitary non-contact unipolar signals. These are projected onto the endocardial geometry obtained through conventional contact mapping using the inverse solution in a similar way to ECGI.(36)

Although this facilitates simultaneous collection of signals from throughout the chamber, inversely calculated electrograms are only validated for regions <40 mm from the centre of the balloon, a weakness particularly in significantly dilated atria.(37) Furthermore, manipulation of an ablation catheter with the balloon within the atrium is difficult and clinical use is now limited.

Dipole density non-contact mapping

The AcQMap system (Acutus Medical, CA, USA) is a high resolution combined imaging and electrophysiological mapping system that uses catheter based ultrasound crystals to generate atrial chamber surface anatomy onto which electrical activation maps are visualised. This is a basket type catheter comprising 6 splines, each of which incorporates 8 ultrasound transducers and electrodes. When positioned in the centre of either atrium, a 3-dimensional image of the atrial surface is acquired by ultrasound through processing of up to 115,000 points per minute allowing the entire anatomy to be generated within a few minutes. The 48 electrodes are then used to record raw intracardiac unipolar signals. The entire chamber field is recorded at a rate of 150,000 samples per second. An inverse solution is applied to recreate signals on the generated endocardial surface anatomy.

Although this inverse solution methodology shares some similarities with the EnSite Array system, AcQMap uses dipole density mapping to provide more focused, high resolution visualisation of cardiac activation in comparison with voltage signals. A

dipole is a localised entity of two closely spaced oppositely charged particles. As an action potential is generated within the myocardium, facilitated by the movement of ions across the cell membrane, a small dipolar charge imbalance is created in the region of the adjacent extracellular space. The initial depolarization is followed by recruitment of adjacent cells and spreads outwards, where the dipole layer directly represents the propagating wavefront. There is then a fundamental difference between the voltage signal and dipole density, as the mere presence of these charges results in the distribution of surrounding voltages, extending beyond their localised physical boundary. Therefore, although the raw signals recorded are intra-cavitary potential signals, knowledge of the relationship between potential and charge defined by Poisson's equation, and utilization of the inverse solution enables the dipolar charge sources on the endocardial surface to be derived and displayed as an activation wavefront across the atrial surface.(38)

Additional processing allows the creation of a propagation map, which is visualised as a moving leading edge of a wavefront displayed as an isochronal map, with differing isochronal spacing representing differing conduction velocities. Interpretation of the propagation map is assisted by inbuilt AcQTrack software, which identifies regions of focal firing, rotational and irregular activation, which are thought to represent important mechanisms for the maintenance of atrial fibrillation and can then be targeted by ablation.(38) To date, this technology is limited to only a few centres in the UK as well as Europe and North America and results of the first multinational, multicenter single arm clinical trial evaluating its use (UNCOVER-AF) are awaited.

Conclusion and Future Perspectives

The limited efficacy of PVI in patients with persistent AF strongly supports the existence of non-pulmonary vein mechanisms driving or maintaining the arrhythmia. Attempts to identify these mechanisms have led to us to characterise patterns of conduction throughout the atria, in other words to map AF. As outlined above, these techniques include invasive contact and non-contact methodologies as well as non-

invasive systems, all of which have their limitations. FIRM mapping has problems with mapping the whole chamber whereas ECGI maps the epicardium only, and both suffer problems associated with the phase based analysis approach. The EnSite array appeared attractive but has practical limitations. The AcQMap system appears to be an exciting prospect but is still early in its clinical life. All of these systems could be said to 'map AF' but all in different ways and with different outputs. None is able to visualize both epicardial and endocardial activation simultaneously, which may be crucial to identifying mechanisms in an arrhythmia with significant endo-epicardial dissociation.(39)

We have intentionally not included methods of epicardial contact mapping during cardiac surgery or ex-vivo techniques using optical mapping as these are purely experimental approaches, and in the case of optical mapping is not possible in humans due to the toxicity of the voltage sensitive dyes used. This technology has submillimeter resolution, which may be crucial in identifying localised micro-reentry that is not possible with the limited resolution of the clinical systems described.(40) Whether this technique develops to be used in vivo remains to be seen.(41)

Being able to answer this question with an emphatic yes requires us to fully understand the data provided in the resultant maps. Currently the appropriate ablation strategy in response to the data provided has not been proven. Therefore, although significant progress has been made we are some way off being able to emphatically state that AF mapping is here and ready for use.

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