Abstract

Atrial fibrillation requires a trigger that initiates the arrhythmia and substrate that favors perpetuation. Cardiac mapping is necessary to locate triggers and substrate so that an ablation strategy can be optimized. The most commonly used cardiac mapping approach is isochronal or activation mapping, which aims to create a spatial model of electrical wavefront propagation. Historically, activation mapping has been successful for mapping point source and single or double wave reentrant arrhythmias, while mapping multiple wavelets or driving sources that underlie most episodes of atrial fibrillation remains challenging. In the multiple wavelet model of AF there is no particular area critical to sustain atrial fibrillation, and a “critical mass” of atrium is required to maintain AF. Recent studies suggest endocardial and epicardial dissociation may play an important role. Investigation of driving sources that sustain AF has focused on the presence of rotors. Rotors in human AF have now been observed using multiple imaging modalities, however ablation strategies targeting rotors remain of unproven benefit. In addition, substrate mapping of AF is now feasible. Increasing degrees of atrial fibrosis on delayed enhancement magnetic resonance imaging (DE-MRI) has been shown to correlate with poor procedural outcomes for AF ablation, which suggests the increased burden of scar promotes more complex and extensive arrhythmia substrate. Atrial fibrosis is also identifiable using electrogram voltage tagging in an electro-anatomic mapping system. Patient-specific ablation strategies targeting areas of fibrosis are currently under investigation. Recent technological advances have facilitated greater understanding of the potential role for AF mapping and has allowed initiation of clinical studies to evaluate the effectiveness of mapping-based intervention. Multi-modality mapping is likely to play an increasingly important role in AF ablation, but is currently limited by the inability to simultaneously record and interpret electrical signals from both atria and from both the epicardium and endocardium.

Introduction

Atrial fibrillation requires a trigger that initiates the arrhythmia and substrate that favors its perpetuation. The majority of ectopic discharges initiating atrial fibrillation (AF) emerge from the pulmonary vein sleeves. Rapid activity from the PVs may be due to new impulses generated due to automaticity, triggered activity or from micro-reentry due to abnormalities in PV tissue. These impulses propagate into the posterior LA wall where highly heterogeneous and anisotropic fiber bundle arrangements and abrupt changes in thickness provide an ideal substrate for sink-to-source mismatch, wave-break, and reentry formation. Theoretically, catheter ablation for AF may be aimed at destroying the trigger mechanism or altering the perpetuating substrate or both.

Subjects with AF represent a spectrum of patients with arrhythmia episodes varying in duration, frequency, pattern of onset, triggers and mode of termination. Persistent and permanent forms of AF incorporate more complex electrical and structural remodeling forming the necessary substrate for AF maintenance. In these patients, persistence of AF depends on an “arrhythmogenic substrate.” Structural changes are part of the progression of atrial disease and contribute to AF being permanent. Structural remodeling caused by the arrhythmia itself and/or progression of underlying structural heart disease. Progressively longer duration AF is observed after repeated AF induction (either via burst stimulation or rapid atrial pacing) in both the goat and canine models of AF, a concept referred to as “AF begets AF”. The increased AF stability is associated with a decrease in atrial effective refractory periods (ERPs), increased spatial heterogeneity of ERP and loss of normal ERP rate adaptation. Until recently there has been relatively limited data characterizing wavefront patterns in human persistent AF due to the spatial-temporal complexities and technical challenges. Improved understanding of the underlying mechanism of AF is critical for developing treatment modalities for AF.
Theoretically, catheter ablation for AF may be aimed at destroying the trigger mechanism or altering the perpetuating substrate or both. However, a selective ablation approach requires knowledge of the underlying mechanism. The success of PVI in eliminating AF episodes can be attributed to a number of factors such as:
1. Isolation of the trigger(s),
2. Modification of the arrhythmogenic substrate located in the pulmonary veins and left atrial posterior wall,
3. Interruption of crucial pathways of conduction,
4. Atrial debulking or
5. Atrial denervation. Reported success rates for AF ablation vary widely in the published literature ranging from 40% to 70% and suggest a need for better patient selection criteria. Cardiac mapping may be a suitable tool to acquire knowledge of the arrhythmogenic substrate necessary for selection of the optimal ablation strategy.

**Activation Mapping**

The most commonly used cardiac mapping approach is isochronal or activation mapping, which creates a spatial model of the wavefront excitation sequence. The crucial element in cardiac activation mapping is correct interpretation of the electrogram morphology and timing consistent with local activation. Mapping of AF is particularly challenging as there is a considerable beat-to-beat variability in the morphology, timing and duration of fibrillation potentials; as AF persists for longer duration a greater number of prolonged and fractionated potentials are seen. These complex and variable recordings hamper appropriate determination of the local activation times. There is no question that AF is disorganized, but whether that disorganization results from organized sources or whether it is the primary driver of AF has been debated for years. Decades of simulation, animal, and human studies have lead to the development of two schools of mechanistic thought: multiple wavelets vs. small number of driving sources.

**Multiple Wavelets**

Factors such as shortened ERP, ERP heterogeneity, slowed conduction, increased tissue mass increase the stability of AF in the multiple wavelet model in which no particular area is critical to sustain AF. Multiple studies have provided evidence that suggest that AF requires a ‘critical mass’ of tissue. Perpetuation of AF is determined by the number of simultaneously wandering wavelets. Thus, a larger atrial mass can accommodate more wavelets, thereby stabilizing AF and reduction of atrial mass may therefore be anti-fibrillatory. Although, one may observe fibrillatory conduction confined within PVs isolated in a wide circumferential fashion, it rarely persists (figure). It is thought that PVI efficacy may be in part related to diminishing atrial mass as a significant amount of atrial myocardium may be replaced by scar tissue.

Evidence is accumulating that persistent AF in patients with structural heart disease is a complex 3-dimensional problem. A recent study of high-density, segmental, biaxial mapping of acute and persistent AF during cardiac surgery has provided evidence for a variation of the multiple wavelet concept in which the substrate of persistent AF is the result of progressive endo-epicardial dissociation, transforming the atria into an electrical double layer of dissociated waves that constantly ‘feed’ each other. In patients with long-standing AF, endo-epicardial breakthroughs were found to generate >400 fibrillation waves per second, and 35% of the fibrillation waves have been shown to arise from a focal point on the epicardium, distributed over the entire atrial surface. Progressive uncoupling of cardiac myocytes and muscle bundles was identified as the main mechanism of enhanced AF stability (“longitudinal dissociation”). Epicardial breakthrough was enhanced in persistent AF patients, hypothesized to be due to more electrical dissociation between the epicardial layer and endocardial bundle network. In a goat model, progressively longer duration of AF was associated with pronounced dissociation of electrical activity between the epicardial layer and the endocardial bundle network owing to progressive electrical uncoupling between these layers, leading to increasing stability and complexity of the AF substrate. Additional studies with simultaneous bi-atrial mapping and simultaneous endo-epicardial mapping are required to better characterize the role of endo-epicardial dissociation in the maintenance of AF and to understand any possible implications for the interventional management of AF. Clearly, our current ablation procedures routinely map the endocardium alone, which limits our field of view. Perhaps body surface mapping techniques or pericardial access may be necessary to get a complete picture as mapping techniques are refined.

**Driving Sources**

Specific sources that have been hypothesized to drive AF include stable reentry circuits known as “mother waves”, which are unstable re-entry circuits which can sustain AF as long as at least one is always present, and rotors that can be fixed or wandering through the atria. Studies postulate that these rotational waves are the major organizing centers of AF with a hierarchical distribution of local excitation frequencies, mostly originating from the left atrium (LA), in particular the posterior LA.

Identification of driving sources remains a clinical challenge. Complex fractionated atrial electrograms (CFAE) sites may represent critical areas responsible for the maintenance of AF. When used in combination with pulmonary vein isolation (PVI), CFAE site ablation has been shown to result in acute AF slowing and termination and long-term freedom from AF recurrence. Although CFAE sites are purported to represent critical sites crucial to AF perpetuation, some CFAE may represent sites of passive wavefront collision, which are not important to the maintenance of AF. Recent studies have shown increased incidence of AT following CFAE site ablation without improvement in overall arrhythmia-free survival, and thus the role of CFAE mapping and ablation in AF ablation remains unclear.

An important property of the bipolar EGM is the direct relationship between wavefront direction and EGM amplitude. Changing wavefront direction near the rotor pivot has been hypothesized to lead to changes in EGM morphology and information content, while bipoles located at the periphery of rotating waves should have relatively stable EGM morphology because of consistency of wavefront direction approaching these locations. Shannon entropy is a statistical measure based on the distribution of amplitude values within the signal histogram that may identify areas of wavefront pivot that correspond with rotors. Increased Shannon entropy was noted at wavefront pivot points in a study of multiple models of AF, however, in the same study there was no association between CFAE regions and wavefront pivot points.

Clinical evidence supporting the presence of localized sources of AF includes the presence of stable frequency gradients between and within the atria, the presence of consistent and reproducible
using contact-force sensing ablation catheters, or assessing pace-
during ablation, means of improving PVI efficacy such as monitoring of impedance
conventional ablation did not necessarily include currently accepted
especially, why patients might remain free of AF recurrences despite
the PVs). Rotor ablation, in addition to conventional ablation, resulted in an
in 98 of 101 patients with sustained AF
rotors may be a key
driving source of AF.

Rotors have been defined using three key characteristics:
1. Extreme wavefront curvature at the core in which head meets
tail,
2. An excitable and precessing core,
3. A highly variable reentrant wavelength, with an often-
undetectable excitable gap. These criteria distinguish rotors from other rotational arrhythmia mechanisms such as classical reentry, in which electrical activity around a fixed obstacle occurs with a fixed wavelength and an excitable gap, and leading circle reentry, in which reentrant circuits surround a functionally inexcitable core that remains in a stable position. Investigators have proposed that these differences, particularly the precessing core, made rotors undetectable in-vivo until novel mapping approaches were developed to allow a greater field of view of atrial electrical activity.

Rotors were first demonstrated in human AF using a system in which filtering and digital processing of intracavitary signals obtained using 64-pole atrial basket catheters (eight splines of eight electrodes; Constellation, Boston Scientific, Natick, MA, USA) and analyzed using a proprietary algorithm (Topera Inc.) that produces a video of the computed activation processes of the right and left atria during AF. A mapping and ablation strategy, targeting Focal Impulse and Rotor Modulation (FIRM), successfully identified an electrical rotor somewhere in the right or left atrium in 98 of 101 patients with sustained AF and RF energy delivered at the center of the rotor terminated AF in 31 of 36 patients (86%). Rotor ablation, in addition to conventional ablation, resulted in an almost doubling of the long-term success rate. After a median of 273 days, 82.4% vs. 44.9% of patients were reported to be free from AF, although some of these patients had AT as a recurrent arrhythmia or perhaps higher density mapping may miss rotors because it is too focused on the details at the expense of the “big picture.” High density, simultaneous mapping of the entirety of both atria during surgery has recently been shown to be feasible and may provide both the large field of view and high electrode density required to address this question. Given that multiple groups now report rotors in AF using different techniques, the debate regarding rotors is shifting towards clinical trials that will define the best approach toward identification and ablation of rotor sites using various novel technologies and whether this substrate approach improves the success of ablation compared with conventional anatomically based ablation. The reproducibility of individual patient maps over time, the duration of AF mapping required to capture all potential sources, the role of epi-endocardial dissociation, and necessary spatial mapping resolution all require further investigation.

Substrate Mapping

Studies have demonstrated that AF is associated with electric,
contractile, and structural remodeling in the LA that contributes to the persistence and sustainability of the arrhythmia.\textsuperscript{47} Atrial structural remodeling promotes atrial tissue fibrosis, which perturbs the continuous cable-like arrangement of atrial cardiomyocytes and slows atrial conduction.\textsuperscript{49} In contrast to electrical remodeling, which reverses after resumption of sinus rhythm, the structural changes seen in the atria take longer to recover and recovery is incomplete.\textsuperscript{50,51} The degree of voltage reduction may help grade the severity of tissue pathology underlying AF, and preliminary results suggest that the success of pulmonary vein isolation is reduced when substantial low-voltage tissue or preexisting scar is present.\textsuperscript{52} Whether fibrotic transformation of atrial myocardium is a cause or consequence of AF in patients with cardiovascular disease remains unclear.

There is now increasing evidence that even in patients with “lone” or idiopathic AF, the AF is an arrhythmic manifestation of a structural atrial disease which has recently been defined and described as fibrotic atrial cardiomyopathy (FACM).\textsuperscript{53,54} This may explain AF recurrence following a period of stable sinus rhythm after ablation with durable PVI. Such progression is seen with other substrate-based arrhythmias (e.g., ventricular tachycardia in ischemic or nonischemic ventricular cardiomyopathy), in which remodeling of the substrate after an initially successful ablation may lead to new arrhythmias.

Electroanatomic bipolar voltage mapping has been described to define the relationship between anatomic and electrophysiological abnormalities in an experimental model\textsuperscript{55} and is now used in clinical electrophysiological studies for substrate description in atrial arrhythmias. Low bipolar endocardial voltage can be identified and localized using an electroanatomic mapping system. It is unclear at this time if this information is beneficial for guiding catheter ablation. Investigators have reported anecdotal success with a new patient-tailored ablation strategy – box isolation of fibrotic areas,\textsuperscript{56} however these findings require further evaluation.

Alternatively, delayed-enhancement magnetic resonance imaging (DE-MRI) is an established method for visualizing tissue necrosis and scarring in cardiac disease processes, including myocardial infarction and myocarditis.\textsuperscript{57,58} Contrast enhancement occurs as a result of altered washout kinetics of gadolinium relative to normal surrounding tissue, which may reflect increased fibrosis or tissue remodeling of the myocardium.\textsuperscript{57} Using DE-MRI, atrial fibrosis has been categorized into four stages (Utah I – IV) with higher grades corresponding to greater fibrosis.\textsuperscript{59,60} The feasibility of DE-MRI to provide a noninvasive means of assessing left atrial myocardial tissue in AF patients has recently been demonstrated, and patients with a greater extent of delayed enhancement in the LA wall have been shown to suffer much higher recurrence rates after PVI for AF.\textsuperscript{59,60,61} The role of targeting areas of DE-MRI identified atrial fibrosis during catheter ablation remains unclear and is currently under investigation.

The relationship between fibrosis on substrate maps and drivers on activation maps has yet to be defined. Of note, a recent study demonstrated that extensive MRI-based atrial fibrosis was associated with a lower prevalence of fractionated electrograms.\textsuperscript{62} These findings suggest that drivers of AF may localize independently of substrate for AF, however.

Conclusions

After decades of investigation and debate, recent technological advancements have brought the field of AF mapping to an inflection point, and understanding of the fundamental nature of AF now seems within reach. While greater understanding of AF activation patterns and AF substrate have occurred in parallel, the relationship, if any, between activation patterns and substrate remain unknown. Future studies will be aimed at development of tailored ablation strategies based on integration of anatomical and electrophysiological characteristics. After over 50 years of investigation, AF mapping is just beginning to move into the realm of clinical practice.

References

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