Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in clinical practice and is associated with significant comorbidities including increased risk of stroke, dementia, and death. Drug therapies for AF are partially efficacious with significant side effects while success rates from catheter ablation procedure remain suboptimal, despite improvement in catheter ablation and mapping techniques. Currently observed limitations of clinical success from antiarrhythmics/therapeutic procedures may be a consequence of a key pertinent issues, including: 1) opposing ideas behind mechanisms driving persistent AF (rotors versus multiple wavelets) are incompletely clearly defined; 2) temporally-based clinical classification of patients with AF may not reflect a patient's true AF pathobiology, with an improved classification of AF involving assessment of underlying structural or electrical remodeling associated with AF progression being needed to individualise therapeutic strategies for AF patients ; and 3) the relative paucity robust validated quantitative assessment tools to understand fibrillatory dynamics. Currently, available mapping techniques rely heavily on qualitative assessment and observation, which by itself, has significant limitations including electrode density, poor contact with the endocardial surface, and false positive/negative detection of rotors.

The presence of rotors in AF, both paroxysmal and persistent forms have been observed for decades. Rotors are functional re-entries, with an excitable but unexcited core. More recently, there have been several efforts developing focused approaches to target rotors in AF as they are thought to be "drivers" in persistent AF. However, clinical outcomes from this approach have been mixed. Considering these variable outcomes, we have recently shown in animal models, optical mapping data and computer simulations that the lifetime and inter-arrival times for these rotors follow an exponential curve, consistent with the notion that rotors may be able to be modelled as occurring via Poisson processes. A systematic review performed showed similar exponential curves of the rotor lifetime and inter-formation times from six previously published

studies. From a mechanistic perspective, by demonstrating rotor formation and destruction events follow a Poisson process, this has recast the mechanism of fibrillation from that of one or two dominant rotors driving fibrillation to that of a continuous, independent regeneration and degeneration of rotors in the atrium. From a therapeutic perspective, this provides us with a potentially measurable metric, referred to as λ_f/λ_d, which is given by the ratio of λ_f (rate of rotor formation) and λ_d (rate of rotor destruction). λ_f/λ_d has been shown to be individualised for different AF patients, which means it could potentially be used as a target for modulation in a drug-based intervention or catheter ablation strategy. The main purpose of this study is to therefore determine the relevance of λ_f/λ_d to known clinical, structural, and electrical correlates associated with AF progression. Additionally, we will further observe the effect of catheter ablation therapy and antiarrhythmic drug therapy during catheter ablation procedures on the metric λ_f/λ_d.

In chapter 2, we seek to understand the variation and spatiotemporal distribution of λ_f/λ_d through sampling in sixteen different locations in the atrium. The reason for this is that in AF, pulmonary vein isolation (PVI) remains the cornerstone for AF ablation, while additional ablation strategies (posterior wall isolation, roof line, superior vena cava isolation, mitral isthmus line, isolation of the left atrial appendage, targeting complex fractionated area or targeting rotors) remains at the discretion of the treating physician. By delineating the regional differences in λ_f/λ_d, it could help physicians individualise their ablation strategy, hypothetically according to zones with higher rates of λ_f/λ_d.

In chapter 3, we seek to understand the correlation between the rate of rotor formation λ_f and the rate of rotor destruction λ_d between left and right atria in atrial regions connected anatomically and electrically by interatrial pathways. Mechanistically, these interatrial pathways have been thought to contribute to the maintenance of AF. However, studies looking at the contributions of these respective interatrial pathways for fibrillatory propagation during AF have been lacking.

Clinically, while some observational studies do suggest there may be a clinical benefit of ablations targeting these interatrial pathways, no large, randomised studies have been conducted to date, partly due to difficulty defining AF patients who would benefit from these additional ablation strategies.

In Chapter 4, we seek to develop a new classification of AF by establishing AF Phenogroups using the renewal theory approach and seek to understand the correlation between λ_f and λ_d with patients' baseline clinical characteristics and clinical outcomes at 6 and 12 months. Clinical outcomes measured include the need for re-do AF ablation procedure, AF-related hospitalisations, the need for DCCV, and the need for intensification of AF therapy (increase in the dose of antiarrhythmic therapy or change to any antiarrhythmic therapy to amiodarone). The need for any type of antiarrhythmic therapy to maintain sinus rhythm will be documented. AF burden will be measured using an external Alivecor cardiac monitor for six months.

In Chapter 5, we aim to investigate the correlations between renewal theory-based fibrillatory dynamic analysis and markers of structural and functional remodeling in the left atrium, using the renewal theory approach. Structural and functional remodeling of the atria underlies AF progression, from shorter paroxysms to longer, persisting episodes. We hypothesise that AF Phenogroup, derived from the renewal theory approach, will significantly correlate with echocardiographic markers of left atrial structural and functional remodeling.

In Chapter 6, we aim to explore the mechanistic role of the right atrium in AF maintenance using renewal theory-based fibrillatory dynamic analysis. Some studies have suggested potential clinical benefits from targeted RA ablation in AF, but these results were not consistently reproducible in other studies. The inconsistent clinical benefit observed likely stems from our lack of understanding of the role of RA in AF and how this defers between individuals. It is plausible that a subset of AF patients who could benefit from targeted RA ablation exists and

characterization of this group of patients will be key to improving clinical benefits from RA ablation.

The presence of AF in patients with heart failure has been associated with adverse clinical outcomes. In Chapter 7, we aim to investigate the effects of subclinical LV systolic dysfunction, measured echocardiographically using LV global longitudinal strain (LV GLS) on LA structural and functional parameters and the spatial distribution of renewal rate constants in the LA. We hypothesise that subclinical LV systolic dysfunction will be associated with adverse LA structural and functional parameters. Additionally, we also hypothesise that a characteristic distribution of rate constants in the LA will be observed in patients with heart failure, compared to controls (patients with normal LV GLS).

In Chapter 8, we aim to investigate the relationship between renewal rate constants with dominant frequency measurement, a quantitative measure of the rate of activation of the atria. It has been hypothesised that atrial regions with the highest dominant frequency represent "drivers" in selected AF patients. However, clinical studies with ablation targeting atrial regions with the highest dominant frequency have not consistently shown improved clinical outcomes post-ablation. Furthermore, it has been recognised that there are physiologic limitations to the use of dominant frequency in the quantification of AF fibrillatory dynamics. We hypothesise that, given the intrinsic differences between the measurement of renewal rate constants and dominant frequency, there will be no correlation between these two measures.

In Chapter 9, we provide a concise summary of all the pertinent findings from earlier chapters and how these findings add to the current knowledge and potential directions for future studies.