ORIGINAL ARTICLE

Prospective cross-sectional study using Poisson renewal theory to study phase singularity formation and destruction rates in atrial fibrillation (RENEWAL-AF): Study design

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Abstract

Background: Unstable functional reentrant circuits known as rotors have been consistently observed in atrial fibrillation and are mechanistically believed critical to the maintenance of the arrhythmia. Recently, using a Poisson renewal theory-based quantitative framework, we have demonstrated that rotor formation (λ_f) and destruction rates (λ_d) can be measured using in vivo electrophysiologic data. However, the association of λ_f and λ_d with clinical, electrical, and structural markers of atrial fibrillation phenotype is unknown.

Methods: RENEWAL-AF is a multicenter prospective cross-sectional study recruiting adult patients with paroxysmal or persistent atrial fibrillation undergoing clinically indicated catheter ablation. Patients will undergo intraprocedural electrophysiologic atrial fibrillation mapping, with λ_f and λ_d to be determined from 2-minute unipolar electrogram recordings acquired before ablation. The primary objective will be to determine the association of λ_f and λ_d as markers of fibrillatory dynamics with clinical, electrical, and structural markers of atrial fibrillation clinical phenotype, measured by preablation transthoracic echocardiogram and cardiac magnetic resonance imaging. An exploratory objective is the noninvasive assessment of λ_f and λ_d using surface ECG characteristics via a machine learning approach.

Results: Not applicable.

Conclusion: This pilot study will provide insight into the correlation between λ_f/λ_d with clinical, electrophysiological, and structural markers of atrial fibrillation phenotype and provide a foundation for the development of noninvasive assessment of

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1 | INTRODUCTION

Atrial fibrillation is the most common sustained cardiac arrhythmia in humans, affecting around 0.5% or 33.5 million individuals worldwide.[1] Atrial fibrillation is associated with an increased risk of stroke, heart failure, dementia, and death.[2] A critical clinical characteristic of atrial fibrillation is that it can be a progressive disease.[3] In its early stages, atrial fibrillation episodes are typically short lasting and self-terminate. Over time, atrial fibrillation episodes may progressively become more sustained, with the final evolution of the disease into long-standing persistent or permanent atrial fibrillation. The clinical evolution of the atrial fibrillation phenotype has profound consequences, including a higher risk of stroke and death.[4]

At a mechanistic level, atrial fibrillation is characterized by disorganized, aperiodic electrical wave propagation in the atrium.[5] A key feature of atrial fibrillation dynamics is the presence of unstable functional reentrant circuits known as rotors. A limitation of contemporary phenotypic classification of atrial fibrillation is that the subtypes are based on indirect subjective reports of clinical arrhythmia behavior and management interventions, rather than being based on quantifiable properties of atrial fibrillation physiology or underlying fibrillatory dynamics.[6,7]

Recently, we have demonstrated that rotational event formation and destruction rates can be accurately determined through characterization of the distributions of interformation event times and rotor lifetimes.[8] In human and experimental models of cardiac fibrillation, we have shown that these consistently show exponential distributions. The exponential distribution is significant because it is the statistical signature of a Poisson renewal process.[9] In a Poisson renewal process, the timing of individual events is independent, but the long-term event rate is fixed (Figure 1).[9]

In that study, we demonstrated the feasibility of measuring rotor formation and destruction rates by fitting the distributions of phase singularity interformation event times and phase singularity lifetimes.[8] We demonstrated these consistently followed exponential distributions in human atrial fibrillation, sheep atrial fibrillation and rat atrial fibrillation,[8] and in an extension systematic review published with our study, we demonstrated that this has been a consistent finding observable in the published data of leading investigators in the field of atrial fibrillation and ventricular fibrillation research.[8] The key implication of the exponential distribution identified in our study is that the formation and destruction of rotors occurs at relatively temporally stable rates, and in that study we demonstrated the feasibility of measuring this in both clinical and preclinical data.

The rationale for the current study is that because repetitive rotor regeneration and destruction is fundamental to the perpetuation of atrial fibrillation, the rate constants for rotor formation (λ_f) and rotor destruction (λ_d) could potentially be objective physiological markers of the underlying atrial fibrillation clinical phenotype. The study hypothesis is that clinical, electrical, and structural characteristics known to be associated with atrial fibrillation clinical phenotype will be associated with alterations in λ_f and λ_d as markers of fibrillatory dynamics. In the longer term, this will lay the foundation for λ_f and λ_d to be used as objective clinical markers of fibrillatory dynamics.

An essential practical consideration in future application of λ_f and λ_d for use as a clinical marker of atrial fibrillation electrophysiology is the development of a noninvasive approach to evaluating these measures. At present, λ_f and λ_d are measured through invasive catheter-based measurement during an electrophysiology study. As an additional secondary objective, simultaneously acquired surface ECG data will be utilized with a machine learning approach to develop a noninvasive measurement of λ_f and λ_d. This will facilitate the development of λ_f and λ_d as noninvasive measures of fibrillatory dynamics that could be used to monitor atrial fibrillation progression.

The study has the potential to lead to a significant improvement in our understanding of cardiac fibrillation. It will lay the foundation for shifting clinical determination of atrial fibrillation phenotype to the characterization of the physiological processes underpinning the atrial fibrillation mechanism. Furthermore, it will determine the link between the current clinical understanding of atrial fibrillation phenotype and progression to underlying fibrillatory dynamics. Finally, it will provide initial validation of noninvasive surface ECG measurement of λ_f and λ_d.

2 | METHODS

2.1 | Study population

RENEWAL-AF will be a nonrandomized prospective cross-sectional study analyzing the rates of rotor formation and rotor destruction preceding catheter ablation in patients with paroxysmal or persistent atrial fibrillation. Paroxysmal atrial fibrillation is defined as atrial fibrillation that terminates spontaneously or with intervention within 7 days of onset while persistent atrial fibrillation is defined as continuous atrial fibrillation that is sustained beyond 7 days.[6] Patients with atrial fibrillation who have been referred for catheter
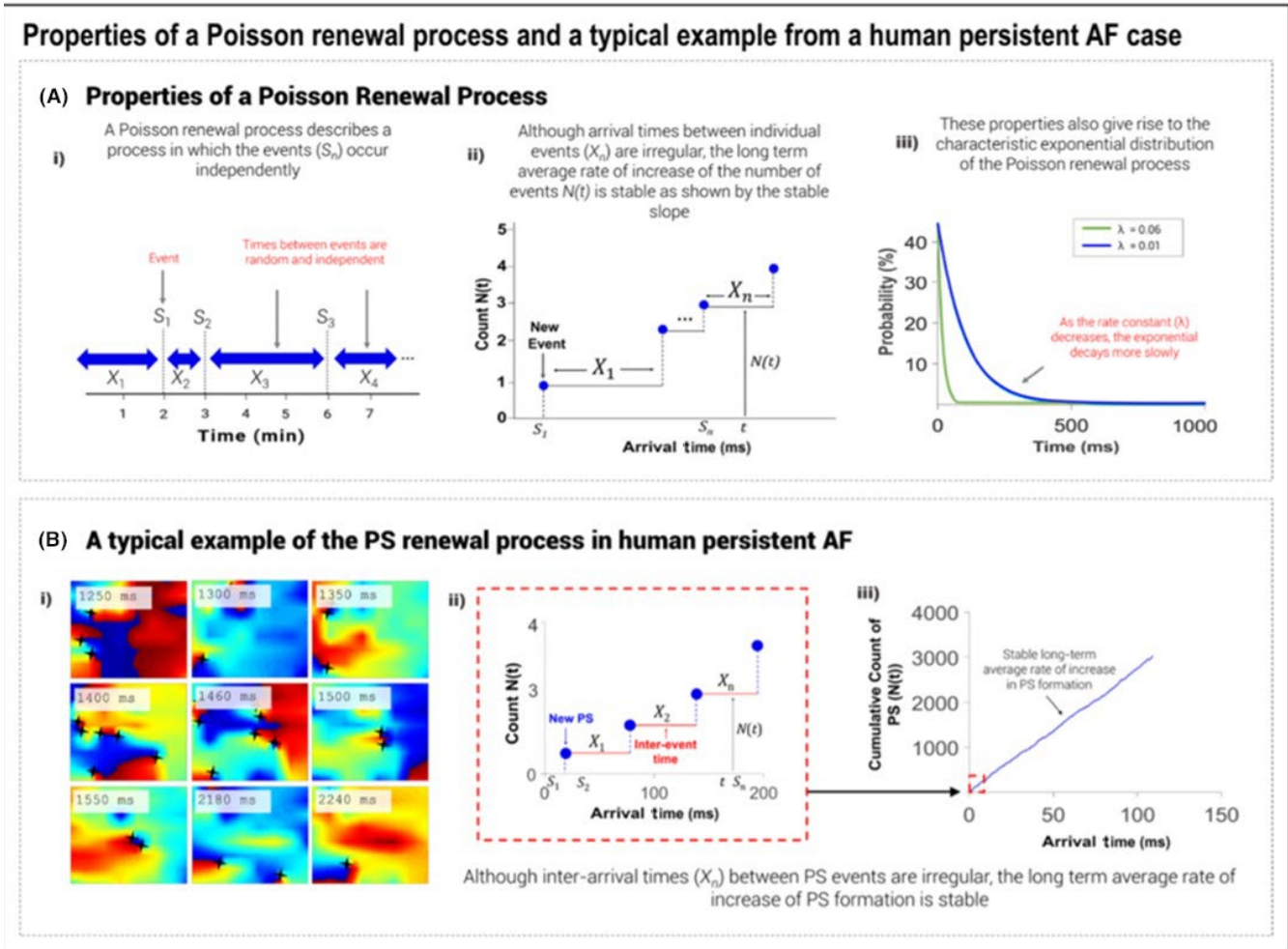
FIGURE 1 Adapted from Dharmaprani et al[8]. Properties of a Poisson renewal process and an example from a human persistent atrial fibrillation (AF) case. A, Poisson renewal process is one in which the times between events are independent but events occur at a long-term constant rate (i and ii). In the discrete case, the probability distribution function (PDF) takes the form of a geometric distribution, which converges to an exponential distribution when large numbers of phase singularity (PS) are considered. If data possess these properties, it implies that the generating process is a Poisson renewal process (iii). Examples of Poisson processes in other scientific disciplines include the timing of radioactive decay events. B, (i) Phase movie snapshots of human persistent atrial fibrillation. In the snapshots, the appearance and disappearance of several phase singularities is shown. The timing of phase singularity is tracked. It shows that phase singularity (marked with *) appear and disappear, although the time intervals between events are irregular. In (ii), we show a staircase diagram to plot the interevent (also known as interarrival) time between new-phase singularity formation events, denoted by X_n. Although the times between new-phase singularity events are irregular, the long-term average rate of increase in phase singularity formation (shown by the slope) is constant (iii)

ablation of atrial fibrillation will be recruited from cardiology outpatient's clinic by their treating physicians (Figure 2).

2.2 | Patient eligibility

2.2.1 | Inclusion criteria

1. Patients referred for clinically indicated atrial fibrillation ablation. Clinical indication for atrial fibrillation ablation will be consistent with international guidelines[6]

a. Symptomatic atrial fibrillation refractory or intolerant to at least one class 1 or class 3 antiarrhythmic medication
b. Selected symptomatic patients with heart failure with or without reduced ejection fraction (EF).

2.2.2 | Exclusion criteria

1. Patients unwilling to provide consent.
2. Presence of LA thrombus.
3. Previous ablations for atrial fibrillation.
4. Contraindications to anticoagulation therapy.
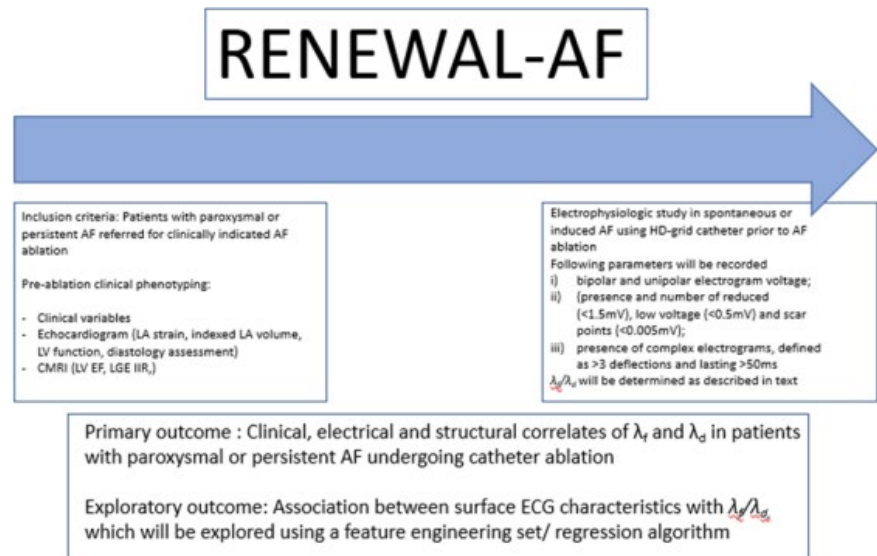
2.3 | Informed consent

Informed consent will be obtained by researchers enrolled in this study on a preset date after the clinic review, upon expression of interest. All questions raised about this study will be discussed in detail during a review in the research clinic. Patients will be assured that participation in this study is entirely voluntary, and nonparticipation in this study will not affect their planned procedures. Patients who meet all the inclusion and exclusion criteria will be enrolled after providing written informed consent. All consent forms will be kept separate from clinical information worksheet so that it will not be possible to identify the patients. Personal information of participants will be kept confidential throughout.

2.4 | Preablation clinical phenotyping

Once written, informed consent has been obtained, patients will undergo a preablation assessment to define the presence of adverse atrial substrate. This includes an initial clinical assessment to define the following clinical variables: (a) hypertension, (b) diabetes mellitus, (c) obesity, (d) obstructive sleep apnea (OSA), (e) alcohol consumption (duration and amount), and (f) atrial fibrillation pattern and clinical duration. Patients will then undergo cardiac structural assessment. This includes an echocardiogram to measure indexed left atrial volume and diameter, left atrial strain, presence and grading of diastolic dysfunction, presence of left ventricular (LV) hypertrophy, and cardiac magnetic resonance imaging to determine the degree of left atrial fibrosis and EF.[10]

2.4.1 | Electrophysiology study and ablation

Electrophysiologic studies will be performed at least five half-lives free from antiarrhythmic drugs, or in the case of patients taking amiodarone, encouraged to stop for at least 6 weeks or as long as can

be tolerated. Patients will be mapped in spontaneous or induced AF using an electroanatomic mapping with the following parameters to be determined: (a) bipolar and unipolar electrogram voltage; and (b) presence and number of reduced (<1.5 mV), low-voltage (<0.5 mV), and scar points (<0.005 mV); (c) presence of complex electrograms, defined as >3 deflections and lasting >50 milliseconds.[11] Mapping will be performed using a HD-grid catheter before ablation. The St Jude Medical Velocity electroanatomic mapping system will be utilized. Electrograms and ECG are recorded at 1000 Hz, with unipolar electrogram filter band pass set at 0.5–500 Hz. In patients presenting to the laboratory in sinus rhythm, AF will be induced using rapid atrial pacing maneuvers. Ablation will include pulmonary vein isolation with documentation of entrance and exit block. Additional lesion sets of linear ablation with or without SVC isolation will be at the discretion of the primary operator. Ablation at sites of fractionated electrograms will be avoided as a strategy for AF ablation.

2.5 | Signal acquisition and processing

Mapping will be performed using HD-grid catheter (Abbott) which is paddle-shaped, has four splines, with each spline containing four electrodes equidistant from each other. Digital 12-lead surface ECG data are recorded simultaneously to HD-grid 3-3-3-mm catheter data at 1000 Hz during the electrophysiology study and stored in Velocity 3D electroanatomic mapping system (St Jude Medical). Unipolar and bipolar electrogram recordings will be obtained in spontaneous or induced atrial fibrillation, with HD-grid catheter held in a stable position for 1 minute in locations throughout left and right atrium including the pulmonary veins, left atrial appendage, atrial septum, mitral isthmus, posterior wall, anterior wall, right atrial appendage, and right posterior wall. Electroanatomical data including electrograms, 3D data, and surface ECG will then be exported and processed using MATLAB. Signals will be filtered as previously described.[12] Phase singularity detection will be performed

with an extended topological charge-based approach.[13] A lookup table indexing onset and offset times and electrode location for each new phase singularity detection will be created to determine phase singularity lifetime and phase singularity interformation event times. Using a lookup table, computation of the histograms for phase singularity lifetimes and interformation event times will be performed. For each epoch, observed phase singularity lifetime data will be fitted using maximum likelihood and/or nonlinear least-squares regression and the phase singularity formation rate, λ_f, and destruction rate, λ_d, as previously described.[8]

2.5.1 | Cardiac magnetic resonance imaging protocol

Cardiac magnetic resonance imaging will be performed before ablation using a 1.5T magnet. In brief, the cardiac magnetic resonance imaging acquisition protocol will be as follows: Following initial localizer and scout images, a full 3D cine short-axis (SA) stack will be performed for the LV and both atria using steady-state free precession images. Contrast-enhanced three-dimensional (3D) magnetic resonance angiography images will be used to define LA and pulmonary vein anatomy. Late gadolinium-enhanced (LGE) cardiac magnetic resonance imaging scans will be acquired 20 minutes following 0.2 mmol/kg gadolinium injection (Gadovist; Bayer Healthcare Pharmaceuticals). We will utilize a 3D inversion recovery prepared fast spoiled gradient recalled respiratory sequence triggered and navigated, ECG gated, and fat suppressed (repetition time of 2.5-5.5 milliseconds, echo time of 1.52 milliseconds, flip angle at 10°, in-plane resolution of 1.3 × 1.3, slice thickness of 2.0 mm, and inversion time of 240-290 milliseconds).

2.5.2 | Cardiac magnetic resonance imaging analysis protocol

Left atrial late gadolinium enhancement quantification
The image intensity ratio (IIR), a previously described LGE-cardiac magnetic resonance imaging technique that normalizes myocardial image intensities by the mean blood pool intensity, corresponding to a bipolar voltage ≤0.3 mV will be used to identify fibrosis. For this study, we will choose a threshold of 0.3 mV to be consistent with prior studies of the extent of left atrial LGE. The methodology for calculation of the IIR and its validation against regional bipolar voltage has been previously described.[14] The mean IIR of the entire left atrial and extent of fibrosis (as a percentage of total left atrial myocardium) will be measured for all patients. Left atrial volume will be calculated based on the 3D reconstruction of the left atrial contours.

2.6 | Echocardiography protocol

Comprehensive transthoracic echocardiography will be performed before electrophysiology study and ablation by experienced sonographers using a Vivid E95 ultrasound system or equivalent equipped with an M5S 3.5 mHz for transthoracic imaging. All recordings and measurements will be made according to the American Society of Echocardiography guidelines. Patients will be scanned in the left lateral decubitus position with standard 2D images consisting of three cardiac cycles triggered to the QRS complex saved in cine-loop digital format for offline analysis. LV mitral inflow velocities will be obtained by pulsed-wave Doppler echocardiography. Septal and lateral mitral annular early myocardial relaxation velocities will be obtained using Doppler tissue imaging from the apical four-chamber view for estimates of LV filling pressure. The left atrium will be imaged from the apical 4ch, 2ch, and long-axis views with care to ensure the left atrium is within the imaging sector, and the frame rate is between 50 and 80 frames per second. 3D datasets will be acquired from the apical window capturing the entire left atrium within the dataset.

Speckle-tracking strain analysis will be performed on the left atrium from the apical four-chamber, two-chamber, and long-axis views using Q-analysis (EchoPac Version 202, GE Vingmed Ultrasound). A region of interest will be the endocardial border of the left atrium and the tracking adjusted to cover the entire left atrium throughout the cardiac cycle. Only global strain will be utilized as regional strain is not practical in the left atrium because of the pulmonary vein orifices. Studies will be deemed inadequate for analysis when any part of the tracking is unable to follow the left atrial wall adequately. Reservoir, conduit, and contractile function will be determined following the EACVI/ASE/Industry Task Force recommendations to standardize deformation imaging. Left atrial volumes and 3D speckle tracking strain will be analyzed using LAQ (EchoPac Version 202, GE Vingmed Ultrasound). LV volumes and global longitudinal strain will also be assessed.

2.7 | Follow up

Patients will be followed up at the discretion by their treating physician.

2.8 | Outcomes

2.8.1 | Primary outcome

The primary endpoints will be the association of each of the clinical, electrical, and structural characteristics with λ_f/λ_d.

2.8.2 | Exploratory outcome

An exploratory endpoint will be the association between surface ECG characteristics with λ_f/λ_d, which will be explored using a feature engineering set/regression algorithm. For example, neural network architectures such as long-/short-term memory (LSTM) has been

shown to reveal patterns from high-dimensional time series conclusively and have been applied in regression contexts for ECG data. We will explore the use of LSTMs for supervised prediction of λ_f/λ_d from surface ECG data. Furthermore, modern unsupervised clustering techniques such as dynamic time warping and nonnegative matrix factorization will be used to explore if there is a relationship between quantifiable ECG features and the contemporary classification of atrial fibrillation. This will allow a noninvasive assessment of λ_f/λ_d from available surface ECG data.

2.9 | Sample size

Power analysis for multivariate regression was performed using the method. An R^2 of the reduced model was 0.40, with the full model including four covariates including atrial fibrillation type, bipolar voltage, cardiac magnetic resonance imaging LGE IIR, and indexed left atrial volume. Using a reduced alpha of .01, with a power 1-beta of 0.80, requires n = 41 subjects to be recruited.

2.10 | Data management and statistical analysis

Baseline demographics of patients, transthoracic echo, and cardiac magnetic resonance imaging data along with data acquired from the electrophysiological study will be entered electronically by researchers enrolled in this study at Flinders Medical Centre or at participating sites where the data originated. Original study forms and reports for cardiac imaging above will be kept on file at the participating site. Patients and associated clinical information will be identified electronically in the Excel worksheet only by their date of birth. Computers used for the research project will be password protected, and hard copies will be stored in locked cabinets. If clinical data are to be used for ancillary studies, additional consent will be obtained from the patient. Data integrity will be enforced through consistency checks against data stored in database and range checks. Modifications to the data written to the database will be documented through either the date change system or an inquiry system.

Continuous variables will be presented as mean and standard deviation, and categorical variables will be presented as percentage. A t-test (if normally distributed) or nonparametric test (if not normally distributed) will be used for continuous variables when conducting baseline comparisons. A *P* value of less than .05 will be considered statistically significant. The primary endpoint will be determined using multivariate linear regression. Clinical, imaging, and electrophysiological characteristics will be entered into the model using a stepwise block entry method to predict λ_f/λ_d. Multicollinearity will be determined using a variable inflation factor analysis. Mid-term data analysis will be conducted after half the recruitment is finished, and the principal investigator will decide whether any measures need to be taken with the available

results. Flinders Medical Centre will be responsible for the data, and other researchers have access to the data only after application and permission.

3 | RESULTS

3.1 | Ethical Issues

This clinical trial has been registered on the Australian New Zealand Clinical Trials Registry (ACTRN 12619001172190p). The study protocol (version 2.0 in February 2020) has been approved by the research ethics committee of Flinders Medical Centre, Adelaide, South Australia. The research ethics committee will also be responsible for supervising all procedures of the study, including participant recruitment, conduction, and data storage. In case of any changes to the study protocol, we will submit a written application to the research ethics committee.

4 | DISCUSSION

Atrial fibrillation is characterized by aperiodic, turbulent electrical wave propagation in the atrium.[5] For over a century, the presence of unstable reentrant circuits has been a defining characteristic of atrial fibrillation.[15-20] Recently, we described a new approach based on renewal theory to enable measurement of rotor formation and destruction rates.[8]

Here, we aim to conduct a prospective nonrandomized observational cohort study to define the association of clinical, imaging, and electrophysiologic characteristics with λ_f and λ_d. A limitation of existing clinically based classification of atrial fibrillation patterns is that it has a limited quantitative resolution, and is unable to be followed longitudinally with time.[21,22] The rationale for this approach is that it will lay the foundation for utilization λ_f and λ_d as objective clinical markers of fibrillatory dynamics.

At present, the dominant clinical classification of atrial fibrillation phenotype is based on clinical symptom profiles into temporal patterns, paroxysmal, or persistent.[21,22] A limitation of this approach is that it is subjective,[21] often inaccurate,[23] and does not accurately predict progression.[21] Thus, there is a need for more objective methods to accurately phenotype atrial fibrillation that are related to the underlying properties of electrical wave propagation.

Recently, we have shown that an exponential distribution of rotor phase singularity lifetimes is a conserved feature of human and experimental atrial fibrillation and ventricular fibrillation, validated with multiple modalities including electrogram-based and optical mapping.[8] The exponential distribution is significant because it is the statistical signature of a Poisson stochastic renewal process.[9] The universality of this finding, in not only our data but observable in underlying phase singularity data from multiple other

investigators,[8,12,13,18,24,25] supports the notion that the rate constants of rotor formation and destruction are fundamental properties of atrial fibrillation pathophysiology.

In this study, we seek as an initial investigation to establish the relationship between λ_f and λ_d and known clinical markers of atrial fibrillation phenotype. The dataset will also form a clinically curated dataset to enable machine learning-based prediction of λ_f and λ_d from the surface ECG.

In the long-term, we see at least two potential clinical pathways for utilization of λ_f and λ_d measurement. Firstly, noninvasive measurement of λ_f and λ_d could be used to predict the relative likelihood for atrial fibrillation to persist or self-terminate and used longitudinally could provide an objective marker of clinical atrial fibrillation progression over time. Secondly, λ_f and λ_d measurement could also potentially be utilized intraprocedurally during atrial fibrillation ablation procedures, as markers of the likelihood of atrial fibrillation to persist and therefore to assist electrophysiologists in determining an optimized ablation strategy.

Progressive structural and electrical remodeling underlies the progression of paroxysmal atrial fibrillation to a more persistent form.[15] The hallmark of structural remodeling of the left atrium is an increase in collagen deposition in the myocardial interstitial space.[26] Using cardiac magnetic resonance imaging, Kuppahally et al. have previously shown a higher degree of left atrial fibrosis in patients with persistent atrial fibrillation compared to those with paroxysmal atrial fibrillation.[27] Left atrial strain was also predictably lower in patients with persistent atrial fibrillation.[27] In our study, the assessment of the degree of left atrial fibrosis will be performed through the use of cardiac magnetic resonance imaging LGE IIR, a method which normalizes LGE-MRI intensity of left atrial fibrosis to mean left atrial blood poor intensity that has been previously shown to correlate closely with intracardiac voltage on electroanatomic map points.[14] Evaluation of the degree of left atrial fibrosis with cardiac magnetic resonance imaging along with left atrial strain, a two-dimensional speckle tracking echocardiography (2DSTE) method to evaluate left atrial mechanics and function,[28] will be assessed preprocedurally in our patients and correlated with the measured λ_f/λ_d.

We recently observed that the interevent formation and destruction of rotors and rotor lifetime shows an exponential distribution but a constant fixed rate, consistent with these processes occurring via a Poisson renewal mechanism.[8] A greater understanding of the role of Poisson renewal mechanisms of phase singularity formation and destruction in patients with atrial fibrillation is crucial for a few reasons: (a) scientifically, it has the potential to alter the direction of research in the field, to move away from searching for 'drivers' of fibrillation, toward a model in which we seek to modulate rates of rotor destruction and formation; (b) clinically, this could provide a foundation for the development of new objective measures of atrial fibrillation progression based on the physiological parameter of rotor renewal rates. At present, clinical progression in atrial fibrillation (paroxysmal vs persistent) is assessed based on a temporal pattern and, although this is

widely accepted, yet the reliability and clinical utility of this classification of atrial fibrillation remains uncertain as it has no relationship to the underlying mechanism sustaining atrial fibrillation[21]; and (c) therapeutically, this could provide a new approach to the treatment of atrial fibrillation based on modulation of these rate constants.

5 | CONCLUSION

Development and validation of Poisson renewal theory as a tool to measure the formation and destruction of phase singularity in patients with atrial fibrillation represents a fundamental paradigm shift in the field of cardiac fibrillation. This study will provide crucial information linking conventional clinical, electrical, and structural markers of atrial fibrillation phenotype with λ_f/λ_d as a new, easily measurable markers of fibrillatory dynamics. Subsequently, validation of λ_f/λ_d from surface ECGs will allow noninvasive assessment of λ_f/λ_d in patients with atrial fibrillation not undergoing ablation, expanding the profile and utility λ_f/λ_d as an objective marker of prognosis in clinical practice.

CONFLICT OF INTEREST

Authors declare no conflict of interests for this article

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