Role of interatrial conduction in atrial fibrillation: Mechanistic insights from renewal theory–based fibrillatory dynamic analysis

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BACKGROUND Interatrial conduction has been postulated to play an important role in atrial fibrillation (AF). The pathways involved in interatrial conduction during AF remain incompletely defined.

OBJECTIVE We recently showed physiological assessment of fibrillatory dynamics could be performed using renewal theory, which determines rates of phase singularity formation (λ_f) and destruction (λ_d). Using the renewal approach, we aimed to understand the role of the interatrial septum and other electrically coupled regions during AF.

METHOD RENEWAL-AF is a prospective multicenter observational study recruiting AF ablation patients (ACTRN 12619001172190). We studied unipolar electrograms obtained from 16 biatrial locations prior to ablation using a 16-electrode Advisor HD Grid catheter. Renewal rate constants λ_f and λ_d were calculated, and the relationships between these rate constants in regions of interatrial connectivity were examined.

RESULTS Forty-one AF patients (28.5% female) were recruited. A positive linear correlation was observed between λ_f and λ_d (1) across the interatrial septum (λ_f $r^2 = 0.5$, $P < .001$, λ_d $r^2 = 0.45$, $P < .001$), (2) in regions connected by the Bachmann bundle (right atrial appendage–left atrial appendage λ_f $r^2 = 0.29$, $P = .001$; λ_d $r^2 = 0.2$, $P = .008$), and (3) across the inferior interatrial routes (cavotricuspid isthmus–left atrial septum λ_f $r^2 = 0.67$, $P < .001$; λ_d $r^2 = 0.55$, $P < .001$). Persistent AF status and left atrial volume were found to be important effect modifiers of the degree of interatrial renewal rate statistical correlation.

CONCLUSION Our findings support the role of interseptal statistically determined electrical disrelation in sustaining AF. Additionally, renewal theory identified preferential conduction through specific interatrial pathways during fibrillation. These findings may be of importance in identifying clinically significant targets for ablation in AF patients.

KEYWORDS Renewal theory; Atrial fibrillation; Interatrial conduction; Interatrial septum; Bachmann's bundle

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Introduction

A mechanistic role for interatrial connections in atrial fibrillation (AF) maintenance has been postulated.[1–4] However, to date, the precise mechanisms by which interatrial conduction plays a part in sustaining AF have not been fully defined.[2,4] A potential barrier to delineating the role

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https://doi.org/10.1016/j.hroo.2022.05.007

KEY FINDINGS

- Renewal rate constants provide a method to enable determination of areas with contiguous electrical conduction between the left and right atria during cardiac fibrillation.
- Positive linear correlations are observed between renewal rate constants in regions across the interatrial septum, the Bachmann bundle, and the inferior interatrial connecting routes.
- Atrial fibrillation (AF) progression to persistent AF and increased atrial size are associated with decreased levels of interatrial renewal rate constant correlation.

of interatrial conduction in AF perpetuation has been that it has been challenging to physiologically probe these connections during sustained AF owing to the turbulent nature of the fibrillatory process.

To date, interatrial conduction has been proposed to contribute to several divergent but important roles in sustaining AF. Mechanistically, interatrial connections have been suggested to be (1) potential sources of reentrant circuits[1,5] and (2) potential sites of conduction block that could assist in sustaining AF.[6,7] There has also been interest in a potential therapeutic effect of modifying interatrial conduction via catheter ablation, in both experimental[1,3] and computational models.[8]

In this study, we sought to extend previous research by systematic evaluation of interatrial conduction during AF in humans using a renewal theory approach. Renewal theory provides a way to measure the continuous formation and destruction of unstable reentrant circuits in AF[9–12] and ventricular fibrillation.[9] Unstable reentrant circuits, at present believed to be spiral vortices,[13,14] have been consistently observed in AF research.[1,15–19]

The repetitive creation and annihilation of spiral waves observed in AF is parallel to other turbulent systems in nature.[20–23] Theoretically, it has been proposed that in systems characterized by spatiotemporal turbulence, spiral dynamics will follow a common set of statistical laws,[12,23] namely that (1) spiral lifetimes will follow exponential distributions[23–25] and (2) spiral populations will follow a Poisson distribution.[24,26] These predictions have been independently validated in diverse physical,[21] chemical,[22] and biological systems.[20,23] In the context of fibrillation, exponential-type distributions have consistently been observed for phase singularity (PS) formation, as well as PS lifetimes in multiple laboratories.[18,19,27–29] In computational, animal, and human models of cardiac fibrillation, using the renewal theory approach,[9–12,30] we confirmed these observations and demonstrated it could allow for accurate quantification of rates of PS formation (λ_f, pronounced as "lambda f") and destruction of PS (λ_d, pronounced as "lambda d")[9,11,12,30] (Figure 1). We found that although the renewal rate constants scaled with catheter size,[30] the renewal equations for population distribution remained internally consistent,[30] in line with theoretical predictions about the effect of noise[31] and 3-dimensional character of cardiac turbulence.[32] A summary figure explaining renewal theory is provided in Figure 1.

In the current study, we build on this earlier work by aiming to determine whether renewal theory could be applied to further understand the electrophysiological relationships between the left and right atria. We hypothesized that (1) atrial regions with anatomical contiguity across the interatrial septum should have a positive correlation between respective renewal rate constants and (2) different patterns of AF could potentially have variable renewal rate constants. We further applied renewal theory to analyze fibrillatory dynamics in other locations involved in interatrial conduction, such as the Bachmann bundle and the inferior interatrial route.

Methods

Study population

RENEWAL-AF was a multicenter prospective observational study involving 4 Australian hospitals (ACTRN 12619001172190p). Paroxysmal or persistent AF patients clinically indicated for AF ablation were enrolled. Ethics approval was by the Southern Adelaide Local Health Network Ethics Committee (HREC/19/SAC/292). This research adhered to Helsinki Declaration guidelines. All patients provided informed consent.

Electrophysiology study

Baseline demographics were obtained preprocedurally and documented in an electronic clinical record form (REDCap). Electrophysiologic studies were performed 5 half-lives free of antiarrhythmic drug therapy, except for patients taking amiodarone. Patients were mapped under spontaneous or induced AF using the EnSite Precision electroanatomic mapping system (Abbott Cardiovascular, Plymouth MN). Advisor™ HD Grid mapping catheter (Abbott Cardiovascular, Plymouth, MN) was used. This catheter has 16 electrodes in a square grid (13 × 13mm^2 grid, 3 mm inter-spacing). Unipolar electrograms were recorded at 1000 Hz (bandpass filter 0.5–500 Hz). Electrograms and electrocardiogram tracings were recorded for 1 minute prior to ablation in 6 different right atrial (RA) intracardiac locations, sequentially superior vena cava (SVC)–RA junction, cavotricuspid isthmus (CTI), RA septum, RA lateral wall, RA appendage (RAA), and RA posterior; and 10 left atrial (LA) locations: left superior pulmonary vein, left inferior pulmonary vein, right superior pulmonary vein, right inferior pulmonary vein, left high posterior wall, left low posterior wall, left lateral region, LA appendage (LAA), LA anterior region, and LA septum (Figure 1).

Signal processing

Unipolar electrogram signals were processed as described.[9,11,30] QRS subtraction was performed and Butterworth filters applied.[9,11,30] Sinusoidal recomposition was

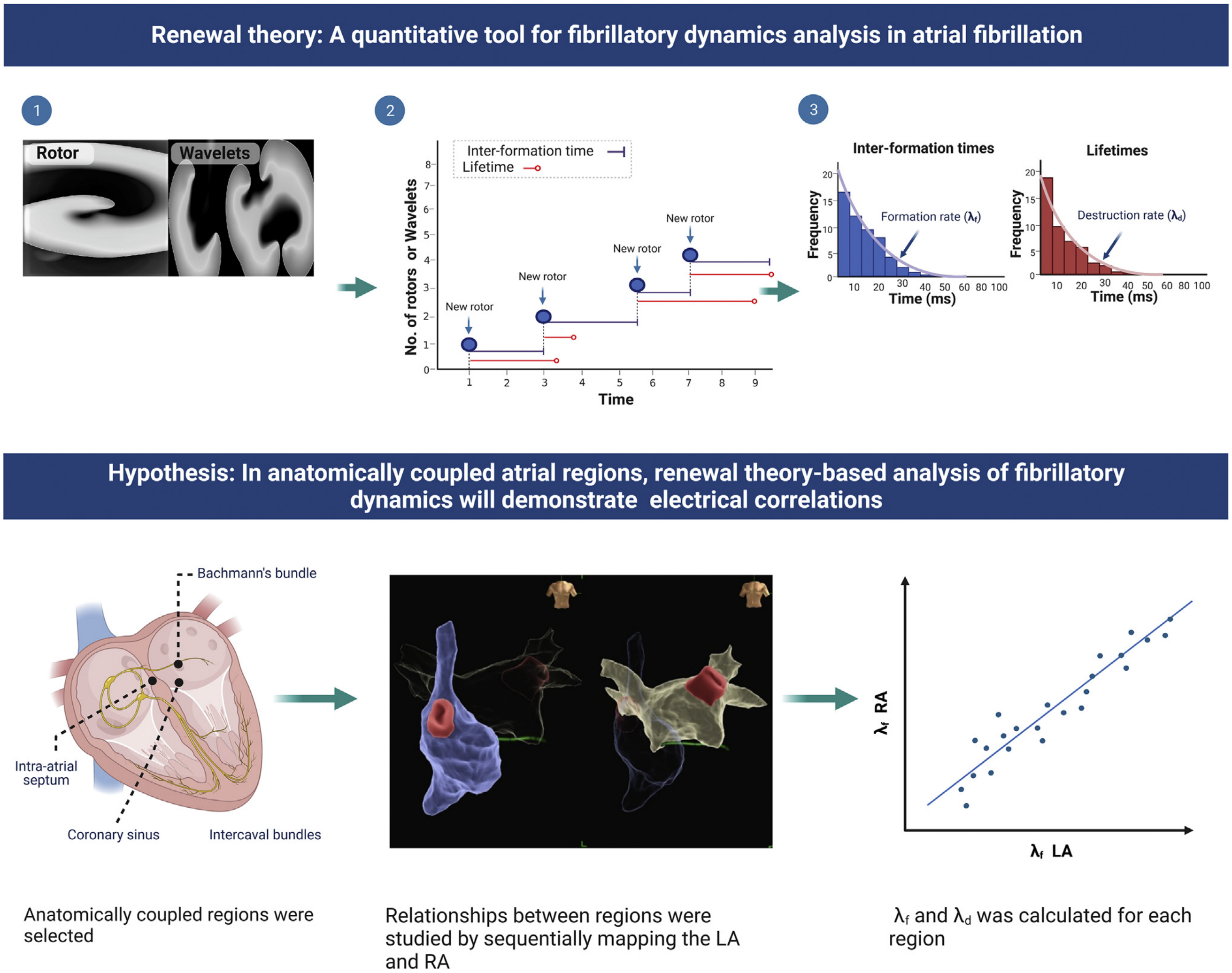

Figure 1 Introduction to renewal theory. (1) Renewal theory is based on the presence of unstable reentrant circuits, currently believed to be spiral waves in atrial fibrillation (AF). (2) The intervals between phase singularity (PS) formation events and the lifetimes of PS are measured, and distributions for these constructed. (3) These have been shown to be statistically independent and to form exponential distributions, implying a constant rate of PS formation (which we call λ_f and λ_d). The hypothesis evaluated in this study was that anatomically connected biatrial regions would show a linear correlation between λ_f and λ_d.

applied with the dominant frequency set as wavelet period and phase computed using the Hilbert transform to construct phase maps.[9,11,28,30] In each phase map, PS were detected and tracked as previously described using a convolution kernel method based on topological charge.[9,11,30] PS tracking enabled calculation of PS lifetimes and inter-formation times (times between consecutive PS formations), which also enabled construction of PS lifetime and inter-formation time distributions.[9,11,30] PS distributions were fitted using maximum likelihood fitting to estimate the rate of PS formation (denoted as λ_f) and PS destruction (λ_d) (Figure 2).[9,11,30] A description of the processing steps is provided in Figure 2.

Statistical analysis

Data were reported as the mean (standard deviation) or the median [interquartile range] for parametric and nonparametric data. Categorical variables were presented as n (%) and differences between groups were examined using the χ^2 test. Two-group comparisons were analyzed using Student *t* test. Associations between different anatomical regions were evaluated using the Pearson correlation coefficient. Statistical analysis was performed using STATA 15.1 with α at $P < .05$.

Results

Patient characteristics

Patient characteristics are described in Table 1. Data from 41 AF patients who underwent AF ablation were available for analysis. Mean age (years) of patients recruited was 59.1 ± 9.4; 28.5% were female. Mean body mass index (kg/m^2) was 31.2 ± 4.4, and 41% of patients had paroxysmal AF. Mean CHA$_2$DS$_2$-VASc score was 1.9 ± 1.5. Mean left atrial volume index (LAVi) was 42.9 ± 8.5 mL/m^2 (Table 1).

Interatrial electrical relationships

Interatrial septum

For this purpose, we compared λ_f and λ_d between RA and LA septal regions (Figure 3). Overall a positive correlation was

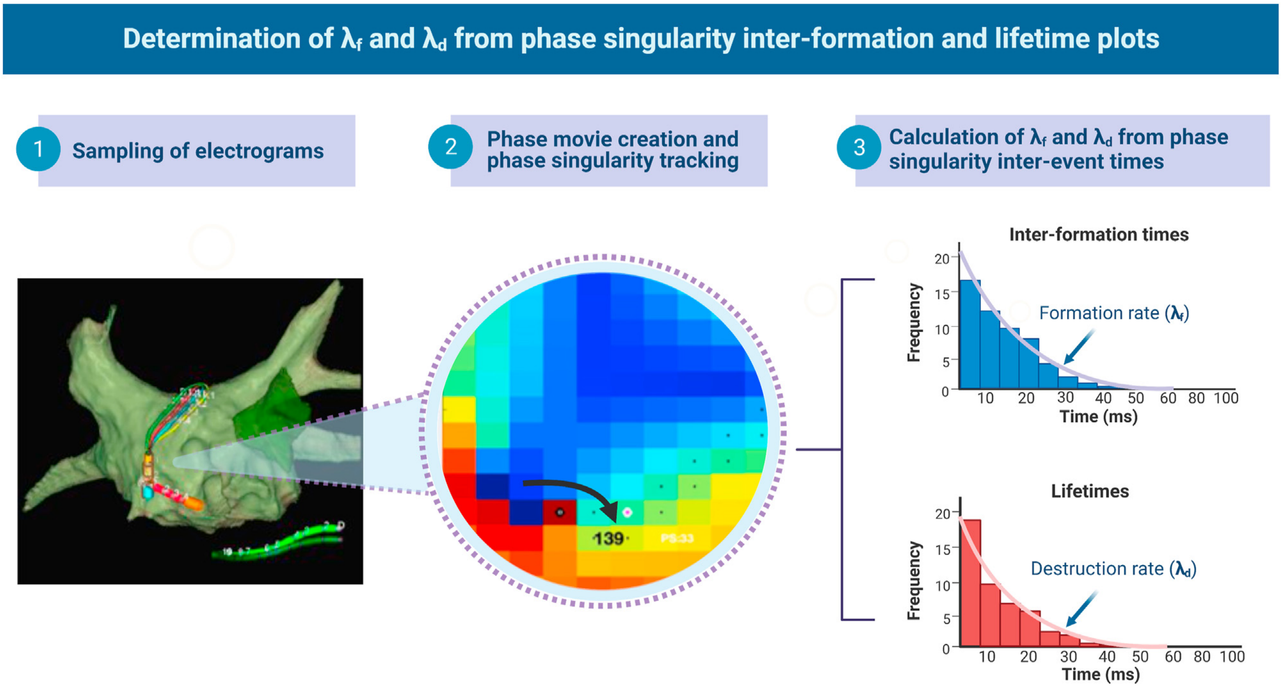

Figure 2 λ_f and λ_d were determined as follows: (1) Unipolar electrograms in atrial fibrillation were sampled preablation in 16 predefined biatrial segments (1-minute recordings) with an Advisor HD Grid catheter (Abbott Cardiovascular, Plymouth, MN). Phase movies were created (2), and renewal rate constants were calculated for formation and destruction (3).

observed between the λ_f (r^2 = 0.5, P < .001) and λ_d (r^2 = 0.45, P < .001) between both regions.

Persistent AF status and LA volume were important effect modifiers. Paroxysmal AF showed stronger correlations across the LA and RA septal region (λ_f r^2 = 0.72, P < .001; λ_d r^2 = 0.79, P < .001) than persistent AF (λ_f r^2 = 0.17, P = .08; λ_d r^2 = 0.07, P = .28). LA volume index had a comparable effect (Figure 3). For patients with LA volume index <40 mL/m^2, there was a stronger correlation than in patients with LA volume index ≥40 mL/m^2 (LAVi <40 mL/m^2: λ_f r^2 = 0.68, P < .001, λ_d r^2 = 0.68, P < .001; LAVi ≥40 mL/m^2: λ_f r^2 = 0.27, P = .03 and r^2 = 0.14, P = .14) (Figure 3).

Bachmann bundle

The Bachmann bundle is an epicardial muscular bundle that connects the left and right atrium, and the presence and the extent of conduction block in this structure has been associated with AF incidence and persistence.[6,33] The Bachmann bundle rightward arm crosses the region of the cavoatrial junction superiorly around the region of the sagittal bundle, and inferiorly around the subepicardium of the RA vestibule (area between the RA appendage [RAA] orifice and the RA atrioventricular valve annulus).[33,34] The Bachmann bundle then courses across the anterior interatrial groove and leftward to the LAA, with superficial circular muscular fiber projections around the left lateral wall.[35,36] Other studies have suggested the role of high upper septum, which has been shown to form both structural and electrical connection to the mid portion of the Bachmann bundle.[37] For this study, only endocardial mapping was performed in these patients. Hence, RAA, RA septum, and SVC-RA junction were used as surrogates for RA site attachments and LAA and LA lateral wall were used as surrogates for LA site attachments for the Bachmann bundle.

At the RAA to LAA and LA lateral wall, a modest linear correlation was observed between λ_f of the LAA and RAA (λ_f r^2 = 0.29, P = .001) and λ_d of LAA vs λ_d of RAA (r^2

Table 1 Patient baseline demographics

Baseline demographics (N = 41 patients)	Mean (SD) or n [%]
Age (years)	59.1 (9.4)
BMI (kg/m^2)	31.2 (4.4)
Sex, female	12 [28.5]
Diabetes mellitus	3 [7]
Hypertension	17 [40.5]
Vascular disease	8 [19.5]
Hyperlipidemia	13 [31]
OSA	14 [34]
Heart failure	17 [41.5]
CVA	6 [14]
Smoking history	10 [23.8]
Alcohol intake	27 [64.3]
Alcohol standard drinks/week	5.7 (11.7)
CHA_2DS_2-VASc score	1.9 (1.5)
Paroxysmal AF	17 [41]
LVEF	57.5% (10.0%)
LAVi, mL/m^2	42.9 (8.5)

Data presented as mean (standard deviation) or n [%].
AF = atrial fibrillation, BMI = body mass index; CVA = cerebrovascular accident; LAVi = left atrial volume index; LVEF = left ventricular ejection fraction; OSA = obstructive sleep apnea.

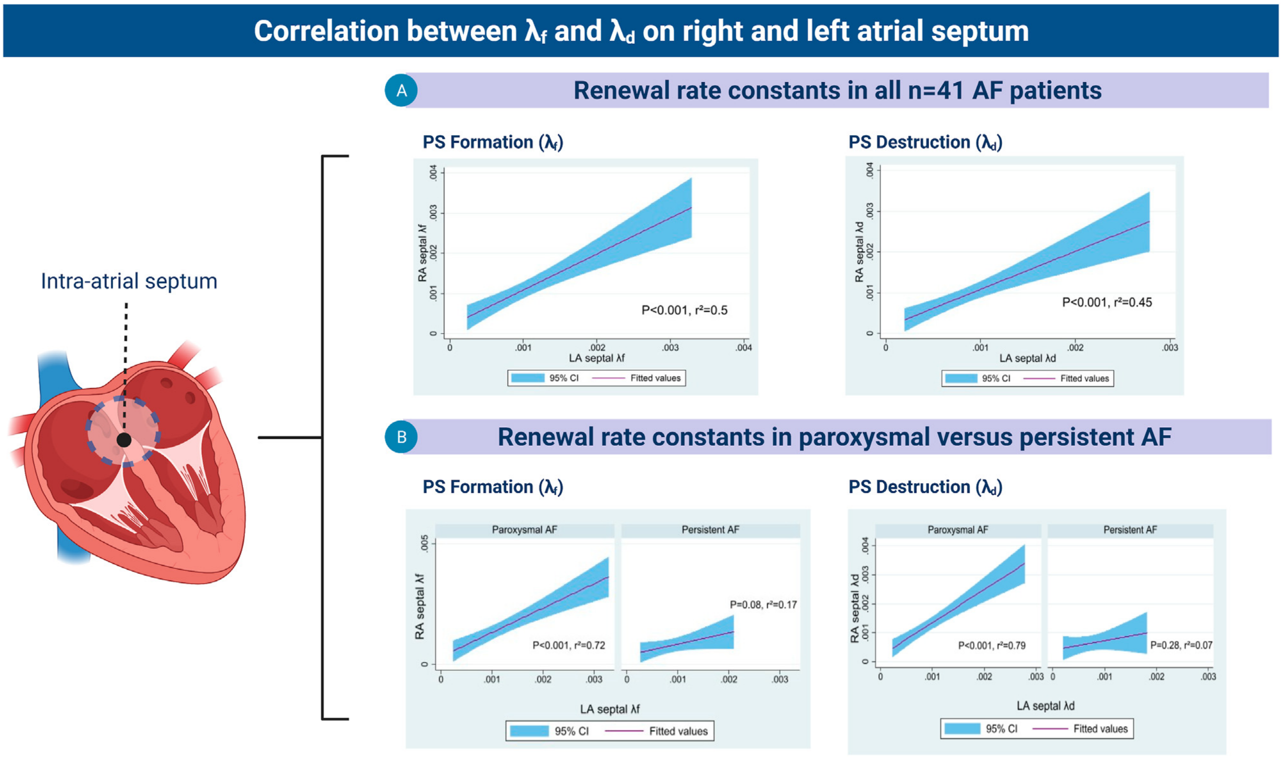

Figure 3 Interseptal conduction showed a positive linear correlation between the right and left side of the interatrial septum, an effect that was diminished in patients with persistent atrial fibrillation (AF). PS = phase singularity.

= 0.2, P = .008) (Supplemental Figure 1). A modest linear correlation was also observed between λ_f of LA lateral wall and λ_f of RAA (r^2 = 0.13, P = .05) and λ_d of LA lateral wall and λ_d of RAA (r^2 = 0.21, P = .009) (Supplemental Figure 1).

At the SVC-RA junction to LAA and LA lateral wall, a modest linear correlation was seen between λ_f of the SVC-RA junction and LAA (λ_f r^2 = 0.22, P = .003) and λ_d of LAA vs λ_d of the SVC-RA junction (r^2 = 0.23, P = .002). A modest linear correlation was also observed between λ_f of LA lateral wall and λ_f of SVC-RA junction (r^2 = 0.13, P = .05) and λ_d of LA lateral wall and λ_d of SVC-RA junction (r^2 = 0.29, P = .001).

At the RA septal to LAA and LA lateral wall, a modest linear correlation was observed between RA septal and LAA (λ_f r^2 = 0.16, P = .011) and λ_d of LAA vs λ_d of RA septal (r^2 = 0.11, P = .04). No significant relationship was observed between λ_f of LA lateral wall and λ_f of RA septal (r^2=0.02, p=0.35) in contrast with a stronger linear correlation observed between λ_d of LA lateral wall and λ_d of RAA (r^2 = 0.51, P < .0001).

Inferior interatrial connections

In this study, the cavotricuspid isthmus region was used as indicator of potential interatrial conduction in the inferior region of the RA with all 6 LA atrial regions within the LA atrial body. Positive correlations between RA CTI and a variety of LA regions (λ_f CTI-LA septum r^2 = 0.67, P < .001, CTI-LA-lateral wall r^2 = 0.53, P < .001, CTI-LA anterior wall r^2 = 0.5, P = .001, CTI-LA low posterior wall r^2 = 0.42, P = .001, CTI-LA high posterior wall r^2 = 0.28, P < .001. For λ_d, positive correlations were observed between CTI and LA anterior wall (r^2 = 0.6, P < .001), CTI–LA septum (r^2 = 0.55, P < .001), CTI–LA lateral wall (r^2 = 0.53, P = .001), CTI–LA low posterior wall (r^2 = 0.36, P < .001), and CTI–high posterior LA wall (r^2 = 0.28, P = .001) (Supplemental Figure 2).

Relationship between spatial variation of global fibrillatory process in the left atrium with the right atrium

We then analyzed the relationship of all RA atrial locations with the mean LA λ_f. Mean LA λ_f was obtained by averaging λ_f of all 10 LA locations. Mean LA λ_f showed the highest relationship with CTI region (r^2 = 0.75, P < .001),

Table 2 Degree and significance, in descending order, of correlations between λ_f of measured right atrial locations with mean left atrial λ_f

λ_f values of measured RA locations	Correlation with mean LA λ_f
CTI	r^2 = 0.75, P < .001
Septal RA	r^2 = 0.6, P < .001
Lateral RA	r^2 = 0.5, P < .001
RAA	r^2 = 0.34, P < .001
SVC-RA junction	r^2 = 0.32, P < .001
Posterior RA	r^2 = 0.11, P = .038

CTI = cavotricuspid isthmus; LA = left atrial; RA = right atrial; RAA = right atrial appendage; SVC = superior vena cava.

Table 3 Degree and significance, in descending order, of correlations between λ_d of measured right atrial locations with mean left atrial λ_d

λ_d values of measured RA locations	Correlation with mean LA λ_d
CTI	$r^2 = 0.76$, $P < .001$
Septal RA	$r^2 = 0.58$, $P < .001$
RAA	$r^2 = 0.52$, $P < .001$
SVC-RA junction	$r^2 = 0.49$, $P < .001$
Lateral RA	$r^2 = 0.45$, $P < .001$
Posterior RA	$r^2 = 0.12$, $P = .037$

CTI = cavotricuspid isthmus; LA = left atrial; RA = right atrial; RAA = right atrial appendage; SVC = superior vena cava.

followed by RA septal wall ($r^2 = 0.6$, $P < .001$), RA lateral wall ($r^2 = 0.5$, $P < .001$), RAA ($r^2 = 0.34$, $P < .001$), and SVC-RA junction ($r^2 = 0.32$, $P < .001$) and RA posterior wall ($r^2 = 0.11$, $P = .038$) (Table 2). Similar observations were made when the relationships between mean LA λ_d were analyzed with all 6 RA locations. Mean LA λ_d showed the highest relationship with CTI region ($r^2 = 0.76$, $P < .001$), followed by RA septal wall ($r^2 = 0.58$, $P < .001$), RAA ($r^2 = 0.52$, $P < .001$), SVC-RA junction ($r^2 = 0.49$, $P < .001$), RA lateral wall ($r^2 = 0.45$, $P < .001$), and RA posterior wall ($r^2 = 0.12$, $P = .037$) (Table 3).

When patients were examined according to their paroxysmal-persistent AF status, significant positive correlations were observed between mean LA λ_f and λ_f at the RA septal wall ($r^2 = 0.78$, $P < .001$) and the CTI region ($r^2 = 0.8$, $P < .001$) in patients with paroxysmal AF (Table 4). However, in those with persistent AF, only a modest correlation was observed in the CTI region ($r^2 = 0.54$, $P < .001$), followed by RAA ($r^2 = 0.38$, $P = .004$), RA posterior wall ($r^2 = 0.37$, $P = .003$), SVC-RA junction ($r^2 = 0.26$, $P = .013$), and RA septal wall ($r^2 = 0.22$, $P = .02$) (Table 4). In persistent AF patients, no significant relationships were observed between mean LA λ_f and RA lateral wall ($r^2 = 0.1$, $P = .17$) (Table 4).

Discussion

Role of interatrial conduction in atrial fibrillation

Anatomically, biatrial electrical propagation occurs via 3 main pathways: (1) the Bachmann bundle, (2) the interatrial septum, and (3) inferior interatrial connections via coronary sinus.[4] In sinus rhythm, it has been argued that the Bachmann bundle plays the dominant role in interatrial electrical conduction,[38,39] while other studies argue for the dominant role of the coronary sinus.[40,41] However, there is limited evidence to date describing the contributions of these interatrial pathways to electrical propagation during fibrillation, using high-density mapping. To the best of our knowledge, this was a study performed by Kumagai and colleagues,[1] who observed preferential conduction of fibrillation via the Bachmann bundle using sterile pericarditis canine models of AF using simultaneous electrogram recordings from 372 unipolar electrodes.

Interatrial conduction has been postulated to play a potentially important contribution in AF pathophysiology.[1,2,6,7,42] Increased thickness of the interatrial septum has been linked to the presence of AF and an increased recurrence of AF post ablation.[42,43] A highly significant contributory role for AF is as a site for critical conduction block leading to the development and perpetuation of AF, based on 185 cases mapped intraoperatively in sinus rhythm.[2,6,7] Similarly, the presence of conduction block in the Bachmann bundle has also previously been linked to the initiation and perpetuation of fibrillation in human AF.[6,7,44]

Understanding the mechanisms of fibrillatory propagation across interatrial connections is crucial to define clinically significant atrial regions that could be targeted during catheter ablation in AF.[2,4] Interatrial conduction has been suggested as a potential target for catheter ablation in AF.[2] Early experimental studies in animal models suggested that AF dynamics could be modified by ablation in the septum.[3,5] A potential mechanism for this effect was identified physiologically in more contemporary biatrial computational models, which demonstrated termination of AF with disconnection of the RA and LA in 80% of cases.[8]

Findings from RENEWAL-AF

Our study adds to the literature as the first to apply a statistical-based approach in a clinical setting to explore anatomical and electrical connections during sustained fibrillation. Renewal theory–based analysis of fibrillatory dynamics in the interatrial septum and other atrial regions involved with interatrial conductions revealed the following findings:

First, during fibrillation, statistically determined electrical disrelation between the LA and RA septum is dependent on paroxysmal-persistent status and LA size. Significant statistical electrical disrelation, measured by λ_f and λ_d, was observed in persistent AF patients compared to paroxysmal AF patients and in patients with larger LA size, suggesting interseptal statistical disrelation plays a role in AF persistence. This observation is in concordance with other studies investigating the associations between structural and electrical changes within the interatrial septum and AF presence,

Table 4 Degree and significance of correlations between λ_f of measured right atrial locations with mean left atrial λ_f, according to the paroxysmal-persistent atrial fibrillation classification

λ_f values of measured RA locations	Correlation with mean LA λ_f: paroxysmal AF (n = 18)	Correlation with mean LA λ_f: persistent AF (n=23)
CTI	$r^2 = 0.8$, $P < .001$	$r^2 = 0.54$, $P < .001$
Septal RA	$r^2 = 0.78$, $P < .001$	$r^2 = 0.22$, $P = .02$
Lateral RA	$r^2 = 0.5$, $P < .001$	$r^2 = 0.1$, $P = .17$
RAA	$r^2 = 0.3$, $P = .035$	$r^2 = 0.38$, $P = .004$
SVC-RA junction	$r^2 = 0.4$, $P = .007$	$r^2 = 0.26$, $P = .013$
Posterior RA	$r^2 = 0.04$, $P = .44$	$r^2 = 0.37$, $P = .003$

CTI = cavotricuspid isthmus; LA = left atrial; RA = right atrial; RAA = right atrial appendage; SVC = superior vena cava.

AF persistence, and known AF-related cardiac structural remodeling. Shin and colleagues[45] observed thicker interatrial adipose tissue in patients with AF, measured using cardiac computed tomography when compared with control. In AF patients, degree of thickness of interatrial adipose tissue was closely linked with both AF persistence and LA volume. In another prospective study using transesophageal echocardiogram for quantification of interatrial septal thickness, interatrial septum was observed to be significantly thicker, independent of age, weight, and height, in AF patients, compared with controls.[43] Histologically, interatrial septal biopsies obtained from AF patients have shown evidence of lymphomononuclear infiltrates, cardiomyocyte necrosis, and patchy fibrosis, when compared with patients without a history of AF.[46] When histologic analysis of interatrial septal biopsies was compared between paroxysmal and persistent AF patients, a significantly higher burden of atrial tissue C-reactive protein was observed in patients with paroxysmal AF, suggesting local atrial inflammation in the interatrial septal region plays a crucial role in early stages of AF, which may then progress to structural changes suggestive of chronicity.[46,47] Electrically, increased interatrial septal thickness has been linked with a significantly higher burden of complex fractionated electrograms and a lower procedural success rate post AF ablation.[42] This observation is crucial, as complex fractionated electrograms have previously been associated with atrial regions of conduction slowing or block and sites of wavefront collisions.[48,49]

Second, varying statistical correlations of fibrillatory processes were observed in other anatomically and electrically connected LA and RA regions, likely owing to the varying contributions of interatrial conduction to RA fibrillatory processes.

Third, highest statistical correlations between rates of PS formation and destruction between the RA and LA during fibrillation were observed in the cavotricuspid region, a surrogate for inferior interatrial conduction, followed by interatrial septum and RAA. This suggests that during fibrillation, there is either a preferential conduction through the inferior interatrial routes or presence of conduction slowing in the Bachmann bundle or interatrial septum.

Rationale for using renewal theory approach in assessing interatrial conduction

The renewal theory approach used in the current study is useful because it provides a conceptual connection between AF and other systems in nature characterized by the repetitive regeneration of PS. The repetitive generation of PS occurs in biological,[20,23] physical,[21,50] and chemical[22] systems throughout nature. Renewal theory allows the development of statistical approaches to understand the formation and destruction of PS. Importantly, the distributions identified for PS lifetimes and population distributions have been shown to be equivalent for AF and ventricular fibrillation[9,11,30] and these other natural systems, suggesting thematic similarities in terms of the underlying processes sustaining spatiotemporal turbulence in these.

Renewal theory: An alternative, statistical-based approach to demonstrate electrical dyssynchrony

The presence of electrical dyssynchrony between the endocardium and epicardium has also been observed and is hypothesized to play a crucial role in AF persistence.[51,52] In animal AF models, endo-epicardial dyssynchrony (EED) has been shown to be present in both acute and persistent forms of AF.[53] In persistent human AF models, the presence of EED has been defined either as differences of endo-epicardial activation times of $\geq$15 ms, differences in wavefront directionality or the frequency of epicardial breakthroughs.[22,52,54,55] However, a major obstacle remains in determining the optimal cutoff difference of endo-epicardial activation times to demonstrate electrical dissociation. While de Groot and colleagues[52] used a cutoff of $\geq$15 ms as a marker for dyssynchronous electrical activation, Parameswaran and colleagues[55] and Walters and colleagues[56] more recently used a stringent cutoff of $\geq$20 ms in studies involving high-density mapping of swine models and human persistent AF.[55,56] The use of renewal theory to demonstrate electrical dyssynchrony provides a robust statistical-based approach that complements currently used quantitative methods by, firstly, demonstrating the presence of statistically determined electrical disrelation between 2 atrial regions; and, secondly, in those determined to have statistically determined electrical disrelation, further quantifying the degree of electrical dissociation in this cohort. An area currently under active investigation is the application of a renewal-based approach to demonstrate EED, using simultaneous endo-epicardium HD Grid recordings in AF patients undergoing cardiac surgery (ACTRN12621000684820).

Limitations

There were a few limitations to this study. Firstly, this study involves a relatively small number of patients. However, the methodology described based on renewal theory could be applied in larger studies involving more atrial regions to improve atrial surface coverage. Secondly, sampling of the interatrial septal region was limited to the endocardium and performed sequentially. However, sequential mapping is likely to be reasonable with the renewal theory approach, as (1) the renewal rate constants are known to be temporally stable for sustained periods of time and (2) this study provides indirect evidence of temporal stability of renewal constants by showing that physiological correlations exist between anatomically connected regions. Finally, we acknowledge that all groups studying AF do not universally accept the notion of PS mapping.[57] However, PS dynamics are widely used to understand cardiac fibrillation and comparably spatiotemporally turbulent systems throughout nature.[20–23]

Conclusion

Using a renewal-based approach for fibrillatory dynamic analysis, we observed varying statistically determined electrical relationships between fibrillatory processes in RA regions to electrically and anatomically connected LA regions. Identification of atrial regions that have significant electrical disrelation could be clinically important to select a subset of AF patients who would potentially benefit from targeted ablation to these areas.

Funding Sources: National Heart Foundation Vanguard Grant 102650.

Disclosures: The authors have no conflicts to disclose.

Authorship: All authors attest they meet the current ICMJE criteria for authorship.

Patient Consent: All patients provided informed consent.

Ethics Statement: Ethics approval was by the Southern Adelaide Local Health Network Ethics Committee (HREC/19/SAC/292). This research adhered to Helsinki Declaration guidelines.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.hroo.2022.05.007.

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