Predicting atrial fibrillation recurrence by combining population data and virtual cohorts of patient-specific left atrial models

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Short title: AF recurrence prediction: patient-specific models

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Abstract

Background: Current ablation therapy for atrial fibrillation is sub-optimal and long-term response is challenging to predict. Clinical trials identify bedside properties that provide only modest prediction of long-term response in populations, while patient-specific models in small cohorts primarily explain acute response to ablation. We aimed to predict long-term atrial fibrillation recurrence after ablation in large cohorts, by using machine learning to complement biophysical simulations by encoding more inter-individual variability.

Methods: Patient-specific models were constructed for 100 atrial fibrillation patients (43 paroxysmal, 41 persistent, 16 long-standing persistent), undergoing first ablation. Patients were followed for 1-year using ambulatory ECG monitoring. Each patient-specific biophysical model combined differing fibrosis patterns, fibre orientation maps, electrical properties and ablation patterns to capture uncertainty in atrial properties and to test the ability of the tissue to sustain fibrillation. These simulation stress tests of different model variants were post-processed to calculate atrial fibrillation simulation metrics. Machine learning classifiers were trained to predict atrial fibrillation recurrence using features from the patient history, imaging and atrial fibrillation simulation metrics.

Results: We performed 1100 atrial fibrillation ablation simulations across 100 patient-specific models. Models based on simulation stress tests alone showed a maximum accuracy of 0.63 for predicting long-term fibrillation recurrence. Classifiers trained to history, imaging and simulation stress tests (average ten-fold cross-validation area under the curve 0.85 ± 0.09, recall 0.80 ± 0.13, precision 0.74 ± 0.13) outperformed those trained to history and imaging (area under the curve 0.66 ± 0.17), or history alone (area under the curve 0.61 ± 0.14).

Conclusion: A novel computational pipeline accurately predicted long-term atrial fibrillation recurrence in individual patients by combining outcome data with patient-specific acute

simulation response. This technique could help to personalise selection for atrial fibrillation ablation.

Keywords: Atrial Fibrillation; Machine Learning; Arrhythmias; Biophysical Simulations

Non-standard Abbreviations and Acronyms:

BB: beta-blockers

CCB: calcium channel blockers

CT: computed tomography

CV: conduction velocity

DT-MRI: diffusion tensor magnetic resonance imaging

IIR: image intensity ratio

LA-PV: left atrial – pulmonary vein

LGE-MRI: late-gadolinium enhancement magnetic resonance imaging

PS: phase singularity

PVI: pulmonary vein isolation

ROC AUC: receiver operating characteristic area under the curve

TGF-ß1: transforming growth factor beta-1

Introduction:

Radiofrequency catheter ablation therapy is recommended in symptomatic drug refractory atrial fibrillation patients. Atrial fibrillation ablation therapy ranges from pulmonary vein isolation to more extensive ablation strategies consisting of pulmonary vein isolation together with multiple additional lesions. Atrial fibrillation patients represent a diverse population

requiring a range of different treatment approaches; no single approach is right for all patients, with suboptimal success from pulmonary vein isolation of 55-75% at 1.5 years [1]. Identifying *a priori* optimal ablation approaches for individual patients has the potential to improve safety, inform patient selection, and decrease time and cost for procedures.

Large clinical trials evaluate standard ablation strategies to provide evidence on long-term treatment efficacy for the average patient in a cohort, and to derive risk scores for estimating a patient's risk of atrial fibrillation recurrence [2, 3, 4, 5]. However, such trials have provided only modest prediction using demographic information, imaging metrics [4], acute atrial fibrillation termination [6] or in multivariate regression analysis. Moreover, it is not clear how to apply these population data to an individual patient. As an emerging approach, patient-specific biophysical modelling studies enable simulation and comparison of multiple ablation approaches in a single patient [7, 8, 9] but have largely been applied to small cohorts of relatively homogeneous patients [10] and it is unclear how to generalize such models for general clinical use.

We developed a novel computational approach to predict long-term response after ablation in large cohorts, by using machine learning to combine patient-specific models of atrial fibrillation, derived metrics of atrial fibrillation physiology, clinical demographics and imaging data. We captured unknowns in patient properties such as type of fibrotic remodelling, fibre field and electrical properties by performing a series of simulation model variant stress tests to evaluate the susceptibility of the atrial substrate to sustained atrial fibrillation. In this work we aimed to (1) generate comprehensive patient-specific atrial fibrillation signatures from multiple biophysical simulation model variant stress tests for a

cohort of 100 patients, and (2) train a machine learning classifier to predict long-term ablation outcome from this patient-specific signature.

Methods

The Methods are briefly described here with full details in the **Supplemental Materials**. We have irreversibly anonymised the 100 models and made these available at https://cemrg.com/models.html.

Patient cohort

Cardiac magnetic resonance imaging data were processed for 43 paroxysmal atrial fibrillation, 41 persistent atrial fibrillation and 16 long-standing persistent atrial fibrillation patients undergoing imaging at St Thomas' Hospital to create a total of 100 patient-specific models. Ethical approval was granted by the regional ethics committee (17/LO/0150 and 15/LO/1803) and subjects gave informed consent. The inclusion criteria for this study were first time atrial fibrillation ablation patients with no previous left atrial ablation who had LGE-MRI performed at the clinician's discretion for pre-procedural planning. At St Thomas' Hospital, ablation treatment is indicated for patients with symptoms of atrial fibrillation who have failed a single anti-arrhythmic agent. These patients underwent first-time catheter ablation therapy for atrial fibrillation, which consisted of pulmonary vein isolation alone, or with the addition of ablation lines (mitral or roof) and/or posterior box isolation ablation [11]. Patients were followed up for 1 year after their ablation procedure as per routine assessment at our institution. This consisted of 2-4 appointments over the year with AF symptom assessment, 12-lead ECG recordings and ambulatory monitoring on the basis of patient symptoms. Atrial fibrillation recurrence was assessed following a three-month blanking

period. **Table 1** details patient demographics, ablation therapy approach and anti-arrhythmic drug therapy, analysed by atrial fibrillation recurrence.

The schematic in **Figure 1** shows an overview of the methodology used for predicting clinical outcome by combining patient-specific biophysical simulation stress tests and population data through machine learning techniques.

Simulated atrial fibrillation model variant stress tests

Models were constructed using the steps given in the **Supplemental Materials** (in Sections: *Construction of patient specific models; Fibrotic remodelling methodology; Atrial fibrillation induction protocols; Modelling of ablation lesion sets; Post-processing atrial fibrillation simulations and calculating structural and electrical metrics).* Simulation model variant stress tests were designed to probe the uncertainty in atrial properties and test the ability of the substrate to sustain atrial fibrillation before and after varying ablation lesion sets. Acute response to simulated ablation was tested for eleven different simulation set-ups shown in **Figure 2**. The baseline set-up - shown in the light blue box and numbered (1) in **Figure 2** - included combination fibrotic remodelling (interstitial fibrosis with conductivity and ionic changes) together with the baseline choice for the following properties: DT-MRI fibre field, pulmonary vein isolation lesion set, atrial fibrillation initiation map, and effective refractory period. To evaluate the effects of uncertainty in each component of the atrial substrate separately, we varied the properties of the baseline atrial model individually, while leaving the other properties of the model fixed at the baseline values. The properties we varied were the type of fibrotic remodelling (tests 1-4); the DTMRI fibre map (5-6); the ablation lesion size (7); the initiation protocol (8-9); the electrical properties (10-11). Pre-ablation arrhythmia simulations (15s) were analysed for set-ups (1-4); post-ablation arrhythmia simulations (2s)

were analysed for set-ups (1-11). More details on each set-up are given in the **Supplemental Materials** (in Section: *Simulated atrial fibrillation model variant stress tests).*

Machine learning classifiers to predict atrial fibrillation recurrence on long-term follow up

Machine learning classifiers were trained to map clinical data to long-term outcome. Specifically, classifiers were trained to predict binary clinical atrial fibrillation recurrence for three clinical datasets: (a) simulation, imaging and patient history, (b) imaging and patient history, (c) patient history alone. Further details on the metrics included in each classifier are given in the **Supplemental Methods**.

Statistical Analysis

For each dataset (a)-(c), the following machine learning classifiers were compared: K nearest neighbours, support vector machine, random forest and logistic regression. Each classifier was trained to each dataset either with or without principal component analysis pre-processing, with the number of components chosen to retain 95% of the variance. The accuracy, recall, precision and receiver operating characteristic area under the curve values were compared for each combination of dataset and classifier, with and without principal component analysis. For each dataset (a)-(c), the classifier with the largest receiver operating characteristic area under the curve value was selected. Further details are given in the **Supplemental Methods**.

Results:

Cohort properties

Follow-up data were available for 99 of the 100 cases. AF recurred in the first year after ablation (following a three-month blanking period) for 34 of the patients, with a mean recurrence time of 189 ± 95 days. None of the clinical metrics considered were significantly different between cases with or without arrhythmia recurrence (see **Table 1**).

Imaging metrics related to atrial fibrillation recurrence

The average visual fibrosis score was higher for the atrial fibrillation recurrence group, but this did not reach significance (p=0.169). **Figure 3** shows that, when defining fibrotic regions with an image intensity ratio threshold of 1.22, the calculated imaging metrics were not significantly different between the groups with and without atrial fibrillation recurrence. These include: (A) total atrial surface area (152.0 ± 30.5 vs 154.8 ± 27.2 cm^2, p=0.55), (B) pulmonary vein surface area (27.8 ± 8.6 vs 28.2 ± 7.0 cm^2, p=0.58), (C) fibrosis surface area (32.4 ± 24.2 vs 31.9 ± 22.0cm^2, p=0.94), (D) area of fibrosis in the pulmonary veins (8.6 ± 6.3 vs 6.3 ± 6.6cm^2, p=0.72). The median fibrosis surface areas by visual fibrosis category were as follows: healthy 23.7cm^2, mild 18.2cm^2, moderate 33.1cm^2 and severe 41.6cm^2.

Relating acute atrial fibrillation termination by simulated ablation to long-term recurrence

Prediction accuracy of the single acute simulation stress tests for predicting long-term clinical atrial fibrillation recurrence was in the range: 0.38 – 0.63 (using a threshold dominant frequency of 4.7Hz to define simulations with atrial fibrillation). **Figure 4** shows transmembrane potential maps 2 seconds after pulmonary vein isolation ablation for the interstitial fibrosis set-up (simulation stress test set-up number 3): 40/65 cases of no clinical

recurrence were classified correctly, and 20/34 cases of clinical recurrence were classified correctly using the acute simulation outcome.

In general, acute simulation outcome stress tests did not differentiate between clinical outcomes. **Supplemental Table I** gives all the simulation metrics by group (without or with clinical atrial fibrillation recurrence). The table first lists properties of the 15s atrial fibrillation simulations before pulmonary vein isolation was applied for the different fibrosis type set-ups 1-4, as follows: mean number of phase singularities, phase singularity area and pulmonary vein phase singularity area. These are followed by the outcome variables given as dominant frequency (atrial rate) for the simulations in the 2 seconds after pulmonary vein isolation was applied for set-ups 1-11. For dominant frequency, there was a trend between groups without and with atrial fibrillation recurrence for simulations including interstitial fibrosis (set-up number 3: 2.6±2.5Hz vs 3.4±2.3Hz, p=0.11) and no fibrotic remodelling (set-up number 4: 3.2±2.5Hz vs 4.1±2.1Hz, p=0.095). Other simulation metrics were not significantly different.

Prediction of atrial fibrillation recurrence by combining population data and patient-specific modelling

Figure 5 shows receiver operating characteristic curves for optimal classifiers constructed from (A) simulation, imaging and patient history data, (B) imaging and patient history data, (C) patient history data.

For the simulation, imaging and patient history classifier (**Figure 5 (A)**), the optimal classifier was support vector machine with principal component analysis: ROC AUC 0.85 ± 0.09, accuracy 0.74 ± 0.13, recall 0.80 ± 0.12, and precision 0.72 ± 0.15. Other classifiers

ROC AUC values were as follows: K nearest neighbour 0.85 ± 0.09, random forest 0.77 ± 0.14, and logistic regression 0.59 ± 0.12.

Conversely, less inclusive classifiers were less predictive. **Figure 5B** shows results for the imaging and patient history classifier; the optimal classifier in this case was K nearest neighbour with principal component analysis: ROC AUC 0.66 ± 0.17, accuracy 0.68 ± 0.07, recall 0.57 ± 0.34, and precision 0.58 ± 0.38. For the patient history classifier shown in **Figure 5 (C)**, the random forest classifier was optimal: ROC AUC 0.61 ± 0.14, accuracy 0.64 ± 0.14, recall 0.46 ± 0.24, and precision 0.46 ± 0.28.

Discussion

Main findings

We present a novel personalized digital approach that predicted response to atrial fibrillation ablation in individual patients when patient-specific geometry and simulations were combined with clinical data. The foundation for this approach demonstrates a novel computational pipeline which can be tuned to individual patient features, which takes into account likely physiological interactions between clinical demographics and the natural history of atrial fibrillation post ablation, and which can be readily scaled to personalize therapy. Notably, we found that predicting atrial fibrillation ablation response was suboptimal based on patient history or imaging data alone. Adding patient-specific simulations significantly improved prediction accuracy. This is the largest atrial fibrillation simulation study to date, demonstrating that patient specific simulation can be scaled to generate virtual cohorts that can predict patient-level outcomes, and could potentially be used to design optimal procedures for each individual *a priori*.

Comparison with other imaging predictors of atrial fibrillation recurrence

Translating from average results to predictions for individual patients using standard risk scores is challenging. Previous studies have assessed the utility of anatomical and imaging metrics calculated from populations of images for predicting atrial fibrillation recurrence. For example, the Delayed-Enhancement MRI Determinant of Successful Radiofrequency Catheter Ablation of Atrial Fibrillation (DECAAF) clinical trial indicated that the degree of atrial late gadolinium enhancement was independently associated with atrial fibrillation recurrence following catheter ablation in a cohort of 260 patients [12]. We did not find this in our study; however, we used a smaller cohort with both paroxysmal and persistent atrial fibrillation patients. For anatomical metric analysis, Varela et al analysed left atrial anatomy from MRI across a cohort of 144 patients to predict atrial fibrillation recurrence using vertical asymmetry together with left atrial sphericity to give an area under the ROC curve of 0.71 [2]. Bratt et al demonstrated that atrial volume is a good predictor of atrial fibrillation recurrence, with an ROC AUC of 0.77 [3]. They automatically segmented the left atrial body from CT scans using deep learning and showed that atrial volume is an independent predictor of atrial fibrillation, with an age-adjusted relative risk of 2.9 [3]. Costa et al. showed that left atrial volume is more important than atrial fibrillation type for predicting atrial fibrillation recurrence following pulmonary vein isolation [4]. In contrast to these studies, Ebersberger et al showed no association between pulmonary vein properties or left atrial anatomical or functional properties measured on CT and early atrial fibrillation recurrence at 3-4 months post-ablation [13]. Our study also found that simple imaging metrics are not predictive of atrial fibrillation recurrence. However, we did not include vertical asymmetry or volume in this assessment, and we used MRI rather than CT data [14].

CT data also provides information on epicardial adipose tissue content, which may affect atrial fibrillation maintenance. Nalliah et al investigated the mechanisms for how epicardial adipose tissue affects atrial fibrillation, showing that higher adipose tissue is associated with slower conduction, higher degrees of electrogram fractionation, increased fibrosis and increased lateralisation of connexin40 gap junctional protein [15]. Further to this, El Mahdiui and Simon et al found that posterior left atrial adipose tissue attenuation is predictive of atrial fibrillation recurrence post ablation [5].

Comparison with other simulation predictors of atrial fibrillation recurrence

Shade et al combined modelling and machine learning to predict atrial fibrillation recurrence in a cohort of 32 paroxysmal atrial fibrillation patients [10]. This study extends their elegant work by testing a range of unknowns in the substrate, enabling a greater degree of personalization through a simulation stress test approach, and by testing the effects of ablation approach, in a larger cohort of less homogeneous paroxysmal and persistent atrial fibrillation patients. The simulation stress test approach used in our study is analogous to a rigorous clinical test of post pulmonary vein isolation atrial fibrillation inducibility, which provided high specificity for atrial fibrillation recurrence in a large meta-analysis [16] although it is difficult to apply due to practical constraints. We used a technique of initiating re-entry through seeding phase singularities in multiple different locations. We applied this technique to initiate atrial fibrillation in set-ups 1-4 before ablation, and also to test inducibility after pulmonary vein isolation for set-ups 1-11. This technique is more computationally efficient but may be less clinically realistic than the initiation technique of rapid pacing from multiple locations performed by Boyle et al [9] . Recently, Azzolin et al. proposed a technique that paces at the end of the effective refractory period to initiate atrial fibrillation and compared this to rapid pacing or using a phase distribution method to show that their method induced a

larger variety of re-entry scenarios, with a marginal increase in simulation time [17]. More extensive inducibility testing protocols, such as those proposed by Boyle et al. and Azzolin et al., could be used to identify further re-entry areas and as additional features for the classifiers, which may increase the predictive accuracy [9,17].

Limitations

There are multiple factors we did not include in the simulation model including the effects of ectopic beats on arrhythmia recurrence. We did not model the pulmonary vein isolation ablation lesions applied clinically, but rather simulated these lesions as wide area circumferential ablation at a fixed distance from the left atrial/ pulmonary vein junctions. Further, these lesion sets may be incomplete with gaps of surviving or recovered tissue, which would affect acute simulation outcome. We only simulated pulmonary vein isolation and did not include patient-specific lesion sets. We considered follow-up data for one-year post ablation only. The choice of image intensity threshold used for modelling scar will influence the imaging and simulation metrics. We used rule-based calibration of conduction velocity based on image intensities, but there is uncertainty associated with this prediction. We do not have validation of this rule-based inclusion of patient-specific electrophysiology across the dataset used in the current study[18]. We only included the left atrium in our simulations; however, performing biatrial simulations [19–21] may improve the predictive accuracy of the classifier. Adding features derived from the 12-lead ECG provides additional information on the atria and could further improve the classifier [7]. Overall, further work is required to choose the optimal simulation stress test set-up. The optimal classifier properties for screening for likely atrial fibrillation recurrence will be considered in future studies.

Conclusion

We present a novel computational pipeline that accurately predicted atrial fibrillation recurrence following ablation therapy in individual patients by combining outcome data with patient-specific acute simulation response. This technique could help to personalise selection for atrial fibrillation ablation and could be evaluated through a prospective clinical trial.

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Supplemental Materials:

Supplemental Methods

Supplemental Tables I

Supplemental Videos I-II

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Table:

Grouped by AF recurrence		No AF recurrence	AF recurs	P-Value
n		65	34	
BMI		29.1 (4.6)	28.2 (4.9)	0.391
LVEF		59.7 (7.2)	57.0 (8.4)	0.116
Age at ablation		61.3 (9.0)	58.8 (13.1)	0.315
CHA_2DS_2-VASc		1.4 (1.4)	1.2 (1.3)	0.638
Female gender		21 (32.3)	7 (20.6)	0.320
Congestive Heart Failure		8 (12.3)	3 (8.8)	0.744
Hypertension		19 (29.2)	13 (38.2)	0.494
Diabetes		5 (7.7)	1 (2.9)	0.661
History of Stroke/TIA		3 (4.6)	2 (5.9)	0.445
Coronary Disease		6 (9.2)	4 (11.8)	0.733
AF type	paroxysmal	29 (44.6)	13 (38.2)	0.712
	persistent	25 (38.5)	16 (47.1)	
	long-standing	11 (16.9)	5 (14.7)	
Ablation type	PVI only	41 (63.1)	15 (44.1)	0.212
	PVI + lines	3 (4.6)	1 (2.9)	
	PVI + box	17 (26.2)	16 (47.1)	
	PVI + box + lines	4 (6.2)	2 (5.9)	
Rhythm Control	Amiodarone	13 (20.0)	7 (20.6)	0.511
	Flecainide	8 (12.3)	7 (20.6)	
	Sotalol	2 (3.1)	3 (8.8)	
	None	29 (44.6)	13 (38.2)	
	Unknown	13 (20.0)	4 (11.8)	
Rate Control	Beta-blockers	23 (35.4)	17 (50.0)	0.556
	Calcium Channel Blockers	5 (7.7)	1 (2.9)	
	Digoxin	2 (3.1)		
	BB + CCB	3 (4.6)	1 (2.9)	
	BB + Digoxin	2 (3.1)		
	CCB + Digoxin	1 (1.5)		
	None	16 (24.6)	11 (32.4)	
	Unknown	13 (20.0)	4 (11.8)	

Table 1: Clinical metrics analysed by atrial fibrillation recurrence. *Results are given as the mean with the standard deviation in brackets (BMI – CHA_2DS_2-VASc), or number with the percentage in brackets (female gender – rate control). Abbreviations are as follows: PVI:*

pulmonary vein isolation; BB: beta-blockers; CCB: calcium channel blockers. P-values refer to t-test or chi-squared test results.

Figure Legends:

Figure 1: Schematic methodology for using machine learning to combine biophysical simulation stress tests for acute simulation responses with population data to predict long-term atrial fibrillation recurrence.

Clinical imaging data were used to construct a cohort of patient-specific models. Biophysical simulation stress tests with different types of fibrosis, fibre maps, atrial fibrillation induction protocols, effective refractory period (ERP) values and pulmonary vein isolation (PVI) sizes were used to test atrial fibrillation inducibility. These simulation stress test metrics were combined with imaging and patient history metrics to produce a patient-specific signature. This was repeated to produce a population of models. Machine learning classifiers were trained across this population to predict clinical outcome from patient-specific signature. Classifiers used either (A) simulation, imaging and patient history metrics, (B) imaging and patient history metrics or (C) patient history metrics.

Figure 2: Simulation model variant stress tests.

The choices indicated by the light blue background represent the baseline model. Other set-ups include the baseline model set-up with a variation in one of the following model features: (set-ups: 2-4) fibrosis type, (5-6) DT-MRI fibre maps, (7) pulmonary vein isolation size, (8-9) atrial fibrillation initiation map, (10-11) effective refractory period (ERP) values.

Figure 3: Simple imaging metrics do not vary with atrial fibrillation recurrence.

(A) Total surface area (p=0.55).

(B) Pulmonary vein surface area (p=0.58).

(C) Total fibrosis surface area (thresholded at image intensity ratio >1.22, p=0.94).

(D) Total fibrosis surface area in the pulmonary vein regions (p=0.72).

Figure 4: Acute response to pulmonary vein isolation ablation for simulations incorporating interstitial fibrosis grouped by clinical atrial fibrillation recurrence. *Transmembrane potential plots are shown 2 seconds after pulmonary vein isolation ablation for the interstitial fibrosis simulation set-up. The first 65 cases had no clinical atrial fibrillation recurrence, while the bottom 34 had atrial fibrillation recurrence. The background colour indicates whether acute simulation response was considered successful (termination to sinus rhythm or organised non-fibrillatory rhythms) in white, or atrial fibrillation is sustained in grey.*

Figure 5: Receiver operating characteristic curves for simulation, imaging and patient history classifiers. *Receiver operating characteristic curves for classifiers constructed from: (A) simulation, imaging and patient history data (support vector machine classifier), (B) imaging and patient history data (K nearest neighbour classifier), (C) patient history data alone (random forest classifier). The grey area indicates ± 1 standard deviation calculated from ten-fold cross validation.*