**Title:** Pre-Procedure Application of Machine Learning and Mechanistic Simulations Predicts Likelihood of Paroxysmal Atrial Fibrillation Recurrence Following Pulmonary Vein Isolation

**Authors:** Julie Shade, Rheeda Ali PhD, Dante Basile, Dan Popescu, Tauseef Akhtar MD, Joseph E. Marine MD, David Spragg MD, Hugh Calkins MD FHRS, Natalia Trayanova PhD FHRS

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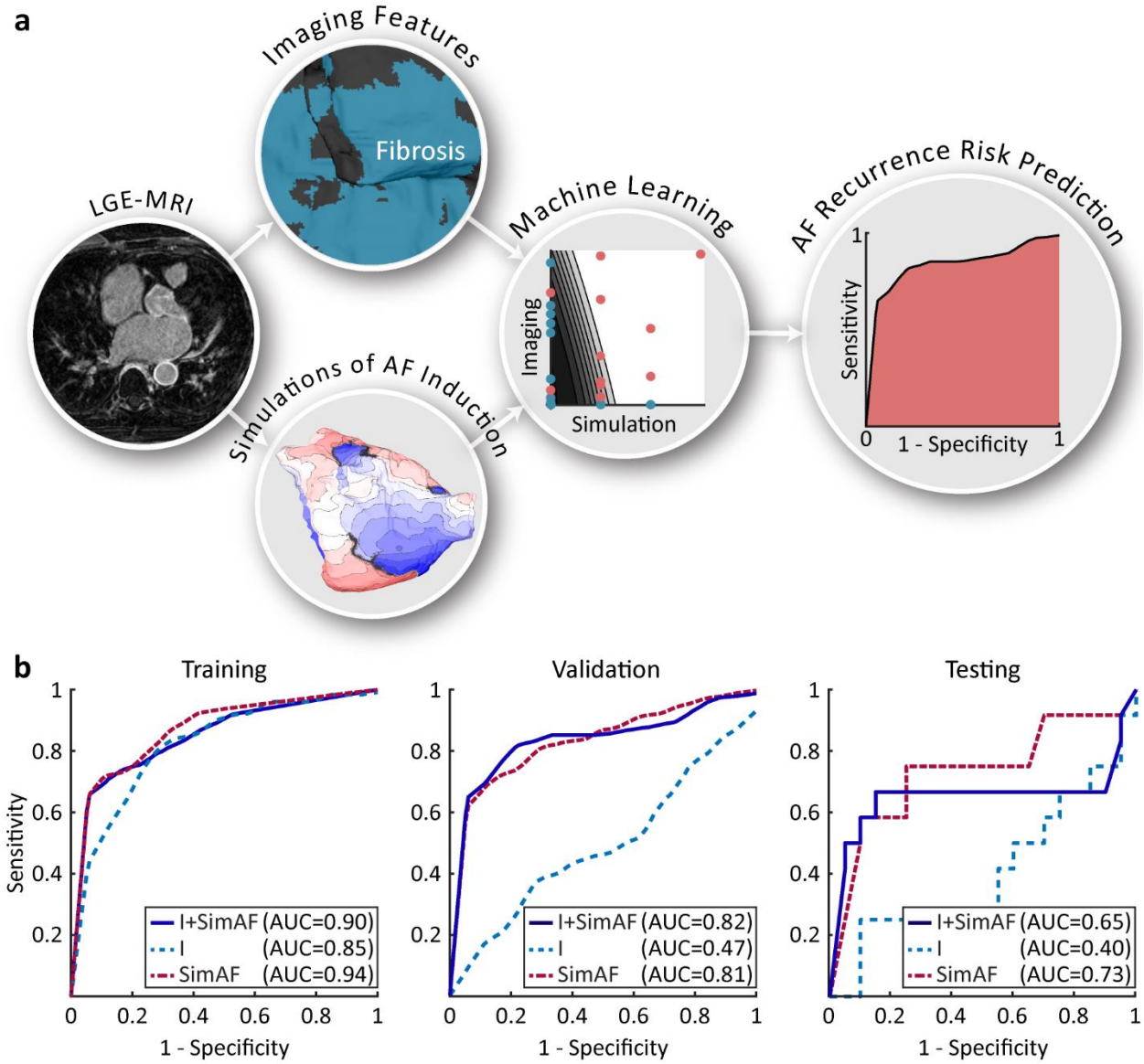
**Background**: Pulmonary vein isolation (PVI) is effective for many paroxysmal atrial fibrillation (PAF) patients, but some experience atrial fibrillation (AF) recurrence. A methodology which identifies, prior to PVI, the likelihood of AF recurrence would allow development of targeted ablation strategies for high-risk patients, reducing redo procedures.

**Objective:** To combine machine learning (ML) and mechanistic modeling to predict AF recurrence after PVI.

**Methods:** This retrospective study included 32 patients with PAF who underwent PVI and had pre-ablation late gadolinium enhanced magnetic resonance imaging (LGE-MRI). For each patient, a personalized computational model of the left atrium was constructed to simulate AF induction via rapid pacing. Features were derived from pre-procedure LGE-MRI, and from simulation results (SimAF) in 2 ways: 1) based on prior knowledge of AF dynamics, and 2) left to be chosen by the ML algorithm, unsupervised. The features with highest unbiased importance were used as input to a quadratic discriminant analysis classifier, which was optimized and tested with 10-fold nested cross validation (Fig.1A).

**Results***:* In our cohort, the ML classifier predicted probability of AF recurrence with an average validation sensitivity and specificity of 82% and 89%, respectively, and a validation AUC of 0.82 (Fig. 1B). Dissecting the relative contributions of SimAF and raw images to the predictive capability of the ML classifier, we found that when only features from SimAF were used to train the ML classifier, its performance remained similar (validation AUC=0.81). However, when only features extracted from raw images were used for training, the validation AUC significantly decreased (0.47).

**Conclusion:** ML and mechanistic atrial modeling can be used together to predict AF recurrence after PVI, even when the patient cohort is small. A classifier based solely on imaging was not generalizable when trained on this cohort and would require a much larger sample size.


a
Imaging Features
Fibrosis
LGE-MRI
Machine Learning
Imaging
Simulation
AF Recurrence Risk Prediction
Sensitivity
1 - Specificity
Simulations of AF Induction
b
Training
Validation
Testing
Sensitivity
1 - Specificity
I+SimAF (AUC=0.90)
I (AUC=0.85)
SimAF (AUC=0.94)
I+SimAF (AUC=0.82)
I (AUC=0.47)
SimAF (AUC=0.81)
I+SimAF (AUC=0.65)
I (AUC=0.40)
SimAF (AUC=0.73)