Persistent Atrial Fibrillation Catheter Ablation Outcomes Stratified by Left Atrial Posterior Wall Isolation Lesion Set Characteristics

Edward Kogan[1], Robert Knotts[1], Lior Jankelson[1], Scott Bernstein[1], David Park[1], Douglas Holmes[1], Anthony Aizer[1], Larry Chinitz[1], and Chirag Barbhaiya[1]

[1]NYU Langone Health

October 8, 2020

Abstract

Introduction: Left atrial posterior wall (LAPW) isolation is associated with favorable outcomes for catheter ablation of persistent atrial fibrillation (PEAF). Techniques for LAPW isolation include ablation at the periphery with or without high density ablation within the LAPW. The proportion of LA isolated by the lesion set also varies greatly. The optimal technique to achieve LAPW isolation is not clear. Objective: To assess impact of ablation lesion density within and dimensions of the LAPW isolation region on arrhythmia recurrence in catheter ablation of PEAF. Methods: LAPW lesion density and surface area relative to total LA surface area were calculated using electroanatomic maps of 110 consecutive patients undergoing LAPW isolation for PEAF (CARTO 3, Biosense Webster, Inc.). LAPW isolation was performed at the discretion of 5 experienced operators after voltage mapping. LAPW PV entrance and exit block were confirmed. Arrhythmia recurrence at two years was assessed by Kaplan-Meier analysis. Results: LAPW lesion density ranged from 0% - 99%. The proportion of LA surface area isolated ranged from 35% - 75%. There was no significant difference in arrhythmia-free survival stratified by median LAPW ablation density (31% vs. 27%, p=0.8) or median proportion of electrically-isolated LA surface area (31% vs. 27%, p=0.8%). Voltage map-guided LAPW isolation did not significantly decrease arrhythmia recurrence (29% vs. 28%, p=1). Conclusion: Neither the density of ablation within nor the dimensions of the LAPW isolated region predicted arrhythmia-free survival for catheter ablation of PEAF. Voltage map-guided LAPW isolation resulted in similar ablation efficacy regardless of LA scar burden.

Persistent Atrial Fibrillation Catheter Ablation Outcomes Stratified by Left Atrial Posterior Wall Isolation Lesion Set Characteristics

Brief Title: Left Atrial Posterior Wall Isolation Lesion Set Characteristics

Edward V. Kogan, MD

Robert Knotts, MD

Lior Jankelson, MD

Scott A. Bernstein, MD

David S. Park, MD, PhD

Douglas Holmes, MD

Anthony Aizer, MD, MSc

Larry A. Chinitz, MD

Chirag R. Barbhaiya, MD

Leon H. Charney Division of Cardiology. New York University Langone Health. New York, NY, USA

Disclosures: Dr. Barbhaiya has received speaking fees/honoraria from Abbott, Inc., and Medtronic, Inc., and received research support from Biotronik, Inc. Dr. Aizer has served as a consultant for Biosense Webster, Inc., received research support from Abbott Inc., and Sentreheart, Inc., and received fellowship support from Abbott, Inc., Biotronik, Inc., Boston Scientific, Inc., and Medtronic, Inc. Dr. Chinitz has received speaking fees / honoraria from Abbott, Medtronic, Biotronik, Biosense Webster and Fellowship / Research from Medtronic, Biotronik, and Biosense Webster.

Address for Correspondence:

Dr. Edward V. Kogan

Leon H. Charney Division of Cardiology

New York University School of Medicine

550 1st Avenue

New York, NY 10016, USA

Phone: 917-902-9704

Fax: 937-400-1408

E-mail address: Edward.v.kogan@gmail.com

Word Count: 1940

Abstract:

Key Words: Atrial Fibrillation, Catheter Ablation, Posterior Wall Isolation

Introduction: Left atrial posterior wall (LAPW) isolation is associated with favorable outcomes for catheter ablation of persistent atrial fibrillation (PEAF). Techniques for LAPW isolation include ablation at the periphery with or without high density ablation within the LAPW. The proportion of LA isolated by the lesion set also varies greatly. The optimal technique to achieve LAPW isolation is not clear.

Objective: To assess impact of ablation lesion density within and dimensions of the LAPW isolation region on arrhythmia recurrence in catheter ablation of PEAF.

Methods: LAPW lesion density and surface area relative to total LA surface area were calculated using electroanatomic maps of 110 consecutive patients undergoing LAPW isolation for PEAF (CARTO 3, Biosense Webster, Inc.). LAPW isolation was performed at the discretion of 5 experienced operators after voltage mapping. LAPW PV entrance and exit block were confirmed. Arrhythmia recurrence at two years was assessed by Kaplan-Meier analysis.

Results: LAPW lesion density ranged from 0% - 99%. The proportion of LA surface area isolated ranged from 35% - 75%. There was no significant difference in arrhythmia-free survival stratified by median LAPW ablation density (31% vs. 27%, p=0.8) or median proportion of electrically-isolated LA surface area (31% vs. 27%, p=0.8%). Voltage map-guided LAPW isolation did not significantly decrease arrhythmia recurrence (29% vs. 28%, p=1).

Conclusion: Neither the density of ablation within nor the dimensions of the LAPW isolated region predicted arrhythmia-free survival for catheter ablation of PEAF. Voltage map-guided LAPW isolation resulted in similar ablation efficacy regardless of LA scar burden.

Introduction:

Recent trials demonstrating a lack of benefit for adjunctive ablation beyond pulmonary vein isolation (PVI) [1] and a belief that PVI alone is insufficient for catheter ablation of persistent atrial fibrillation (AF), has resulted in left atrial posterior wall (LAPW) isolation being the preferred ablation strategy for persistent AF at many institutions. Aside from pathophysiologic and embryological rationales for this strategy, multiple randomized trials have demonstrated favorable outcomes associated with LAPW isolation[2–4]. Reported techniques for LAPW isolation include ablation at the periphery without ablation within the LAPW[5] as well as high-density ablation of all sites of electrical activity within the LAPW. Within this latter approach there are numerous potential ablation strategies including: debulking, single ring, box isolation of fibrotic areas, and varying sizes of box lesions[2,6–8]. Given that each of these disparate ablation strategies is considered "LAPW isolation," we aimed to ascertain if the benefits of more extensive ablation (i.e. atrial debulking, electrical isolation of fibrotic areas, trigger elimination, and avoidance of reconnection across linear ablation) outweigh the increased risk of more extensive ablation (i.e. esophageal injury, and prolonged procedure time). The optimal technique for LAPW isolation remains unclear.

Methods:

Patient Selection :

We evaluated 110 patients undergoing first-time catheter ablation of persistent AF at New York University (NYU) Langone Health between 8/2018-12/2018. Data collection and analysis were performed according to protocols approved by the NYU Langone Health Institutional Review Board. All authors had full access to data, take responsibility for the integrity of the data, and have agreed to the paper as written.

Electrophysiology Study :

All procedures were done under general anesthesia. Surface and intracardiac electrograms (ECGs) were digitally recorded and stored (EP Workmate, St. Jude Medical, Inc., Diamond Bar California). Non-fluoroscopic 3-dimensional electroanatomic mapping (EAM) was performed using the Carto 3 (Biosense-Webster, Inc.) mapping system. A 10- or 20-pole circumferential PV mapping catheter (Lasso, Biosense-Webster, Inc.) or a five-spline mapping catheter (PentaRay Nav, Biosense-Webster, Inc.) was utilized for left atrial mapping and recording. Left atrial three-dimensional anatomy was created with manipulation of the multi-electrode mapping catheter. Voltage mapping was performed and areas with local bipolar electrogram amplitude <0.5mV were considered to be abnormal[9].

Ablation was performed with an open-irrigated, 3.5-mm RFA catheter (ThermoCool SmartTouch, Biosense Webster Inc.). Ablation lesions were generated in a point-by-point fashion in power-controlled mode applying 20 to 35 W for 20 to 40 s per lesion during irrigation at a rate of 17 to 30-mL/min while maintaining a goal ACT of > 350 s. All electroanatomic map lesion markers were created using automated lesion annotation (VisiTag, Biosense Webster, Inc.) in the CFS group. Lesion set dimensions and degree of ablation within the LA posterior wall were at the operators' discretion. All lesion sets were rendered unexcitable utilizing a pace-ablate technique[10]. Left atrial posterior wall and pulmonary vein entrance block and exit block with pacing output > 10mA @ 2ms were confirmed after a 30-minute waiting period and infusion of adenosine.

Lesion Density Calculation :

The area of the posterior wall and total LA surface area was calculated within the EAM system. The number of RF applications within the outer boundary of the LAPW isolation lesion set was subsequently tallied using automated lesion annotation (VisiTag, Biosense Webster, Inc.). The total ablated surface area was estimated by assigning a diameter of each non-overlapping lesion as 0.5cm, resulting in an ablation area of $0.8cm^2$ per lesion. Lesion density was calculated by dividing the total RF lesion surface area by the area of the posterior wall (Figure 1). The proportion of electrically isolated LA surface area was calculated by dividing the wide antral circumferential area by the total LA surface area.

Arrhythmia Recurrence :

Patients were followed for up to 2 years after the date of their procedure. Patient follow-up was censored for the purposes of survival analyses at time of last follow up if less than 2 years after their ablation procedure. Patients were followed in clinic at 1-month post-ablation and subsequently at three-month intervals. At each visit, study assessments included a detailed medical history, physical exam, and 12-lead ECG. A 2-week mobile cardiac outpatient telemetry (MCOT) monitor was performed prior to each scheduled in-office visit in patients without implanted arrhythmia monitoring. Arrhythmia recurrence was defined as either a sustained atrial arrhythmia within the 90-day blanking period that required a repeat ablation, or an atrial arrhythmia that occurred after the 90-day blanking period and was captured on a resting 12-lead ECG or lasted longer than 30 s on an ambulatory monitor.

Statistical Analysis :

Data were reported as mean ± standard deviation for continuous variables with normal distributions and the number of events (proportion) for categorical variables. Continuous variables with non-normal distributions were reported as means ± non-parametric bootstrap standard deviation (based on 5000 replicates). The normality of data was assessed with Shapiro-Wilk testing. To assess statistical significance, the Student's t-test and analysis of variance tests were used for normal continuous variables, while Mann-Whitney U and Kruskal-Wallis testing was used for non-normal continuous variables. Chi-square or Fisher exact testing was used to assess statistical significance for categorical variables as appropriate. Multivariable Cox proportional regression analysis was performed to assess predictors of arrhythmia recurrence yielding hazard ratios with 95% confidence intervals. Predictors of AF recurrence noted in Kece et. Al. were tested in a univariate model. Subsequently variables with P values [?]0.05 were included in the multivariate analysis using the "enter" method in The R Project. P values [?]0.05 were considered significant; all are reported as 2-sided.

Survival and Event Analysis:

The Kaplan-Meier method was used to estimate the fraction of patients with event status at each follow-up interval. Survival analysis end points were arrhythmia (AF/AT) recurrence. Follow-up time was calculated from the date of AF ablation to the most recent EKG or ambulatory monitor analysis. Log-rank testing was used to compare differences in survival or in the above clinical events between patient groups. Statistical calculations were performed using The R Project 3.6.0.

Cox Proportional Regression Testing

Multivariable Cox proportional regression analysis was performed to assess predictors of arrhythmia recurrence yielding hazard ratios with 95% confidence intervals. Predictors of AF recurrence noted in Kece et. Al. were tested in a univariate model. Subsequently variables with P values [?]0.05 were included in the multivariate analysis using the "enter" method in The R Project.

Results :

Patient Characteristics :

Baseline characteristics of the analyzed patients are listed in Table 1. Within this cohort of 110 patients, 57 had complete voltage mapping of the entire LA surface area. The median LAPW lesion density was 38%. Comparison of baseline characteristics of patients stratified by median LAPW lesion density revealed no significant differences between groups (Table 1).

Lesion Density :

The method of LAPW lesion density calculation is shown in Figure 1. LAPW lesion density ranged from 0 - 99% (Figures 2-3). When the cohort was stratified by median LAPW lesion density there was no significant difference in arrhythmia recurrence between groups (31% vs. 27%, p=0.8; Figure 4a). The same was true for AT-free recurrence (20% vs. 13%, p=0.4; Figure 4b). In the 69/110 patients where complete LA voltage mapping, there was no relationship between the proportion of posterior wall scar burden and ablation lesion density within the LAPW (Figure 5).

Electrically Isolated LA Surface Area :

The proportion of electrically isolated LA surface area ranged from 35-75%. Patients with greater LA scar burden also had lesion sets with larger proportions of electrically isolated LA (Figure 10). In order to more granularly assess the effect LAPW size on arrhythmia recurrence, the cohort was stratified by median proportion of electrically isolated LA surface area, there was no significant difference in arrhythmia recurrence (31% vs. 27%, p=0.8; Figure 6). However, when the cohort was subdivided into quartiles by total LA surface area, there was significantly decreased arrhythmia-free survival in the top quartile compared to the bottom quartile (48% vs. 22%, p=0.02; Figure 7).

LA Scar Burden :

LA Scar burden ranged from 1-80% in the 57/110 patients for which it was mapped. There was no difference in arrhythmia-free survival noted between the top and bottom halves of this subgroup when sorted by median scar burden (29% vs. 28%, p=1; Figure 8). There was also no difference in arrhythmia recurrence between those patients who underwent voltage mapping and those who did not undergo voltage mapping (30% vs. 28%, respectively, p=0.5; Figure 9).

Cox Proportional Regression Analysis :

In the univariate analysis, increasing patient age, ejection fraction, and WACA area were associated with increased rates of AF/AT recurrence; increasing LA area was slightly negatively associated with AF/AT recurrence (Table 2).

Discussion:

The major findings of this study are: 1) LA PWI lesion set dimensions determined based on LA geometry, with or without voltage mapping, may attenuate the adverse ablation outcomes related to LA dilation and LA fibrosis, and 2) The extent of ablation within the LA PWI lesion set, in the presence of rigorous assessed LA PWI, does not appear to impact ablation outcomes. These conclusions are consistent with findings of prior meta-analysis of PWI ablation outcomes suggestive of benefit regardless of PWI ablation technique utilized [11].

Greater LA fibrosis as assessed by MRI or voltage mapping[12,13] has consistently been associated with worse outcomes after AF ablation. Additionally, ablation targeting LA low voltage areas has been previously associated with ablation outcomes similar to those of patients without abnormal LA voltage[14]. Outcomes of voltage map guided LA posterior wall isolation have not been previously reported. Our data suggests that the benefits of "Box Isolation of Fibrotic Areas," as described by Kottkamp, et al[14]. may be present with inclusion of low voltage areas in LA PWI, but with the added benefits of PWI, and decreased theoretical risk of creating substrate for reentrant atrial tachycardia by ablating patches of fibrosis.

Despite this outcome, the observed decrease in arrhythmia-free survival in the largest quartile of LA size implies that this cohort is grossly similar to those cited in prior studies. Similar to Kece et. al. univariate regression analysis noted several predictors of increased arrhythmia recurrence (WACA area, LA area, and ejection fraction), however none of them were significant in the follow-up multivariate analysis (Figure 11). The association of increased arrhythmia recurrence with smaller LA sizes and larger WACA areas in the univariate analyses as opposed to smaller box surface ratios in Kece et. al. may be a consequence of performing multivariate analysis with collinear variables (given that LA surface area is accounted for in both the box surface area ratio and LA volume index). It is also possible that our cohort had a larger burden of LA scar, which was not accounted for in the Kece et. al. analysis. The variables in Table 2 were also not found to be predictive of the density of posterior wall ablation in a separate multivariate regression analysis.

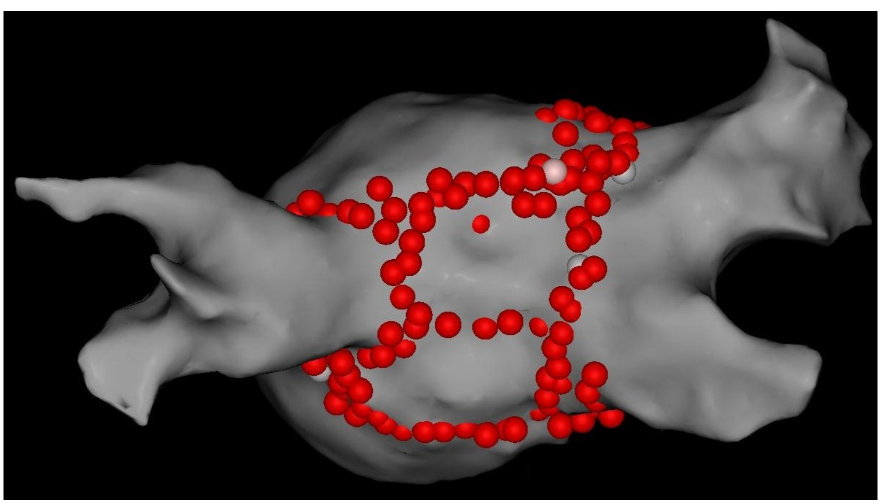
Study Limitations :

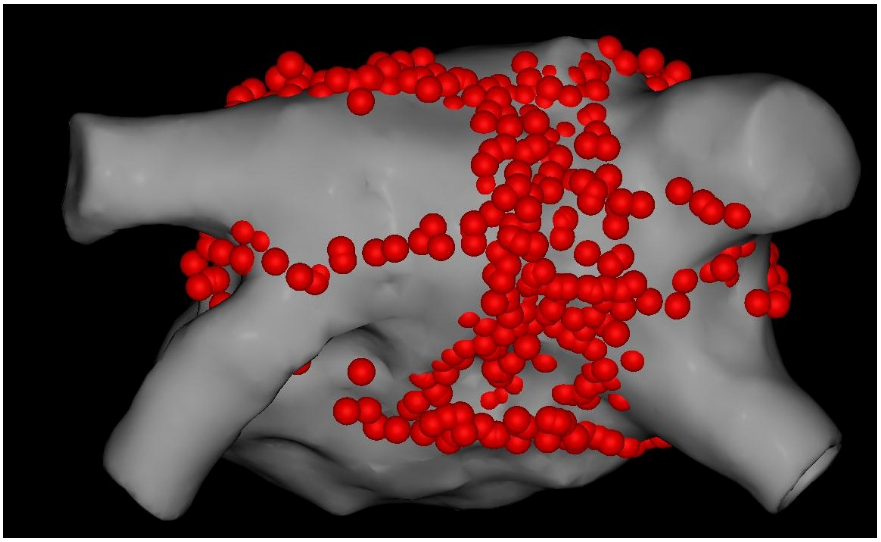
This retrospective, single-center study may have been underpowered to detect small, but clinically meaningful differences in ablation outcomes between groups. Operators were not restricted in selection of their lesion sets, thus lesion set dimensions and ablation density may have been influenced by unmeasured confounders. Additionally, LA PWI lesion sets encompassing proportions of electrically-isolated LA surface area outside the range represented in this cohort (35-75%) were not analyzed, thus outcomes associated with these lesion sets remain unknown. The same could be said of outcomes for LA scar burden proportions outside upper bound of the ranges observed in this cohort.

Conclusion:

Outcomes for rigorously confirmed LA posterior wall isolation for catheter ablation of persistent atrial fibrillation appear to be favorable regardless of the dimensions of the lesion set, or density of LA posterior wall ablation. Voltage map guided LAPW isolation may attenuate increased risk of arrhythmia recurrence associated with LA fibrosis.

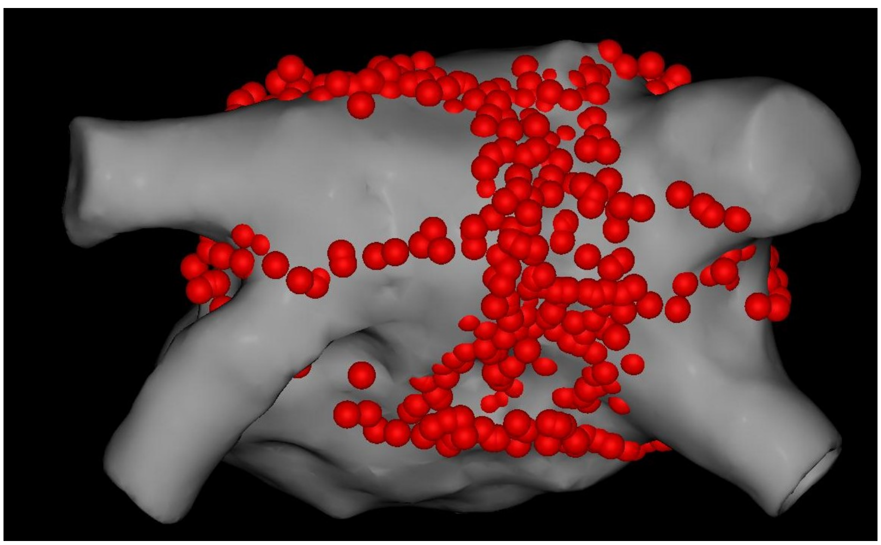
	All Patients (n=110)	**Above median (n=55)**	**Below median (n=55)**	**Median Top/Bottom LAPW Lesion Density Comparison**
LAPW Lesion Density (%)	43±26	64±20	23±11	<0.001*
Age (y)	65±10	64±11	67±9	0.2
Male (%)	78	80	76	0.8
BMI (kg/m2)	30±6	30±6	30±6	0.6
Diabetes (%)	15	18	13	0.6
Hypertension (%)	66	67	65	1
CHADSVASC	2.5±1.7	2.5±1.8	2.5±1.5	0.7
Left Atrial Size (cm)	4.4±0.6	4.3±0.6	4.5±0.7	0.3
Left Atrial Volume Index (mL/m^2)	37±12	37±13	38±11	0.4
Left Ventricular Ejection Fraction (%)	55±13	54±14	56±13	0.2

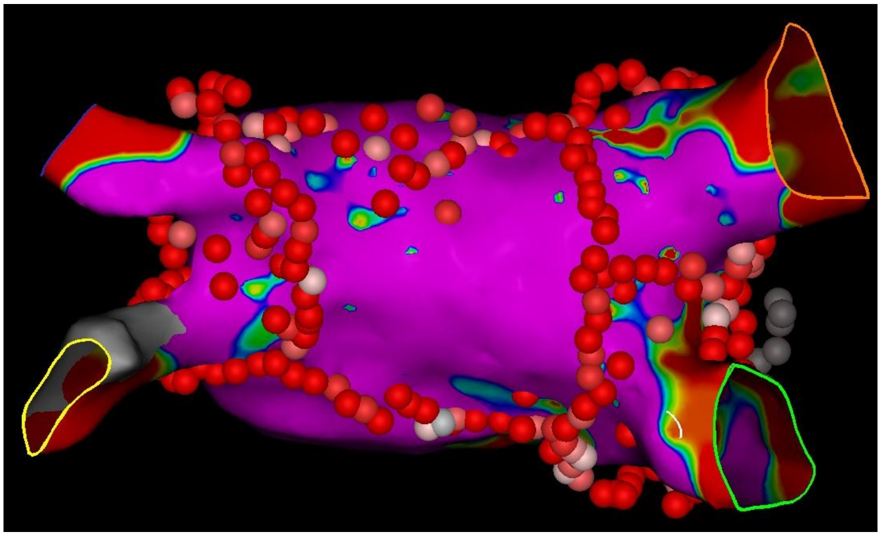


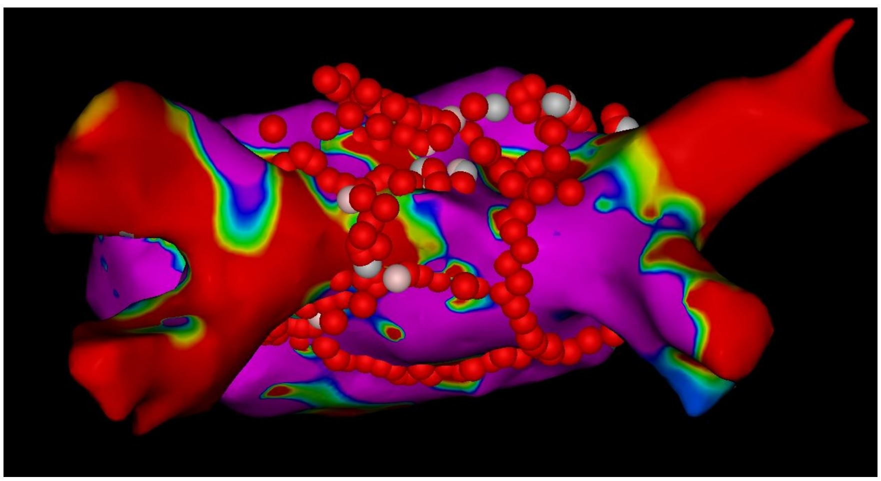


Hosted file

image3.emf available at https://authorea.com/users/365502/articles/485579-persistent-atrial-fibrillation-catheter-ablation-outcomes-stratified-by-left-atrial-posterior-wall-isolation-lesion-set-characteristics

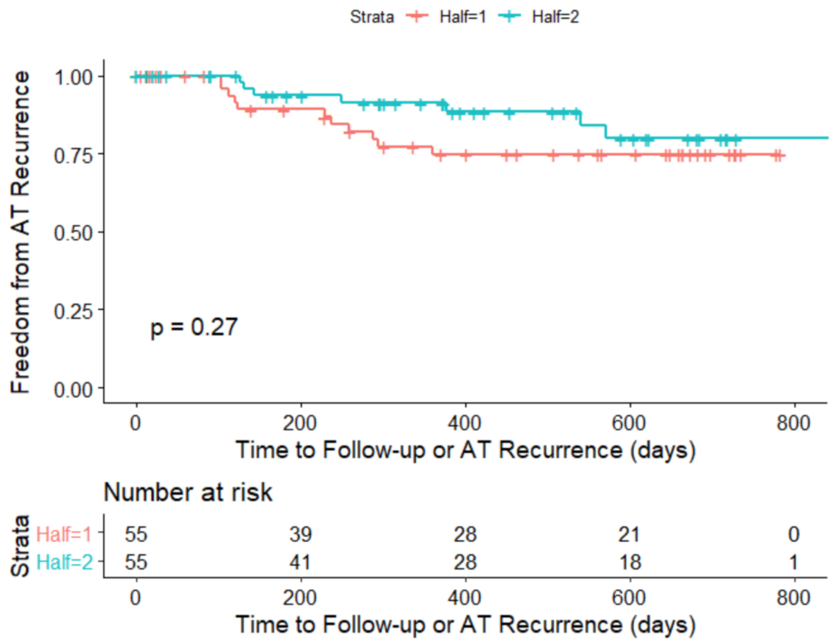


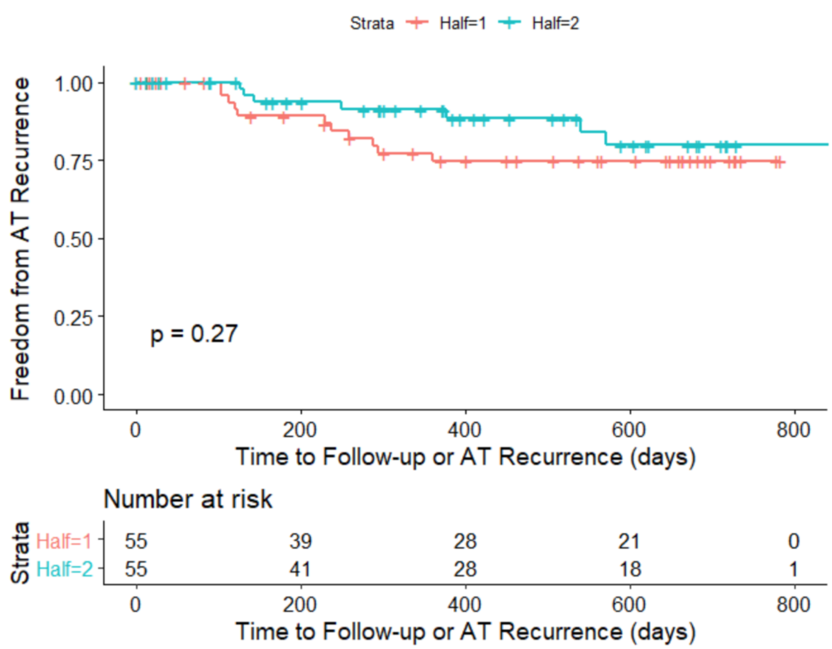


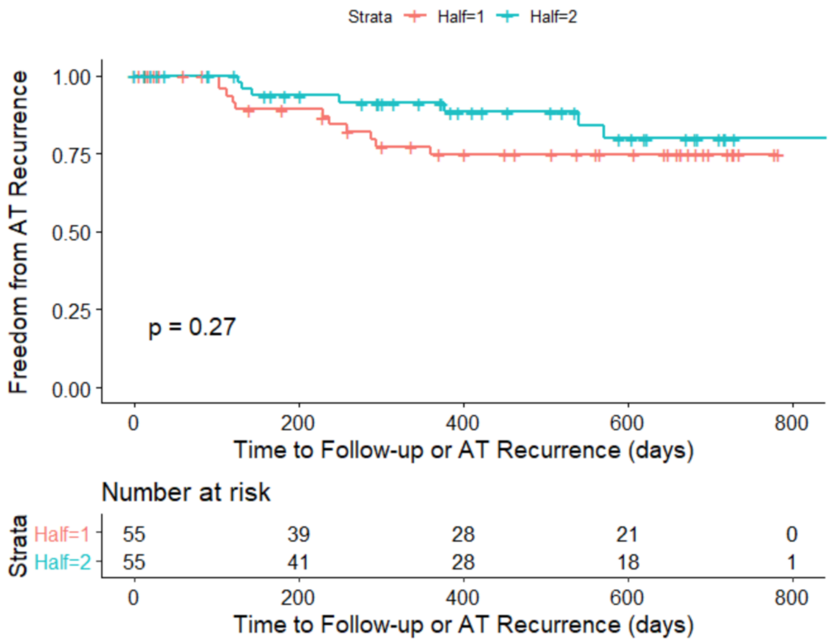


Hosted file

image6.emf available at https://authorea.com/users/365502/articles/485579-persistent-atrial-fibrillation-catheter-ablation-outcomes-stratified-by-left-atrial-posterior-wall-isolation-lesion-set-characteristics


Strata
Half=1
Half=2
Freedom from AT Recurrence
1.00
0.75
0.50
0.25
0.00
p = 0.27
0
200
400
600
800
Time to Follow-up or AT Recurrence (days)
Number at risk
Strata
Half=1 55 39 28 21 0
Half=2 55 41 28 18 1
0
200
400
600
800
Time to Follow-up or AT Recurrence (days)


Strata
Half=1
Half=2
Freedom from AT Recurrence
1.00
0.75
0.50
0.25
0.00
p = 0.27
0
200
400
600
800
Time to Follow-up or AT Recurrence (days)
Number at risk
Strata
Half=1 55 39 28 21 0
Half=2 55 41 28 18 1
0
200
400
600
800
Time to Follow-up or AT Recurrence (days)

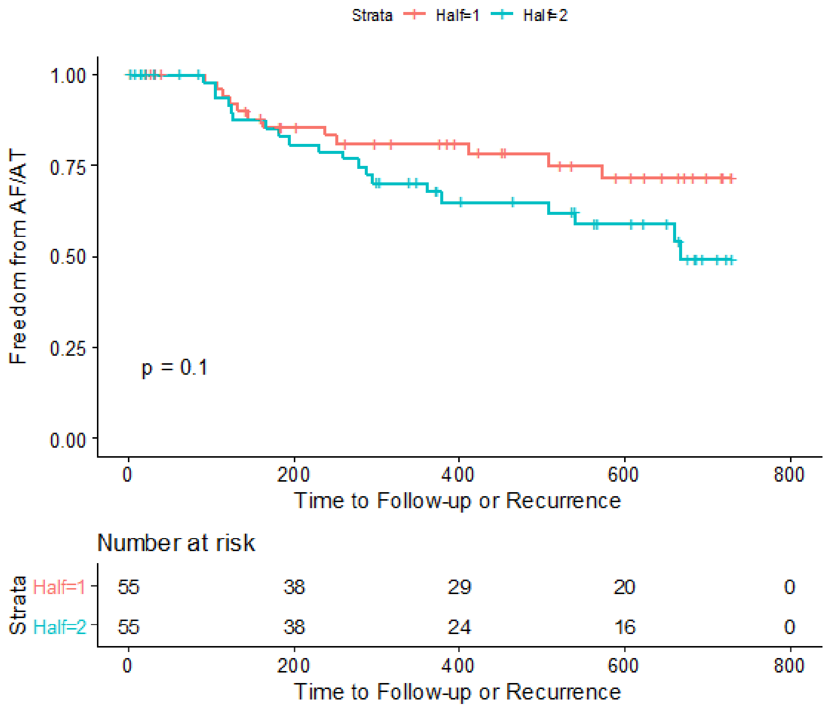


Hosted file

`image10.emf` available at https://authorea.com/users/365502/articles/485579-persistent-atrial-fibrillation-catheter-ablation-outcomes-stratified-by-left-atrial-posterior-wall-isolation-lesion-set-characteristics

Hosted file

`image11.emf` available at https://authorea.com/users/365502/articles/485579-persistent-atrial-fibrillation-catheter-ablation-outcomes-stratified-by-left-atrial-posterior-wall-isolation-lesion-set-characteristics

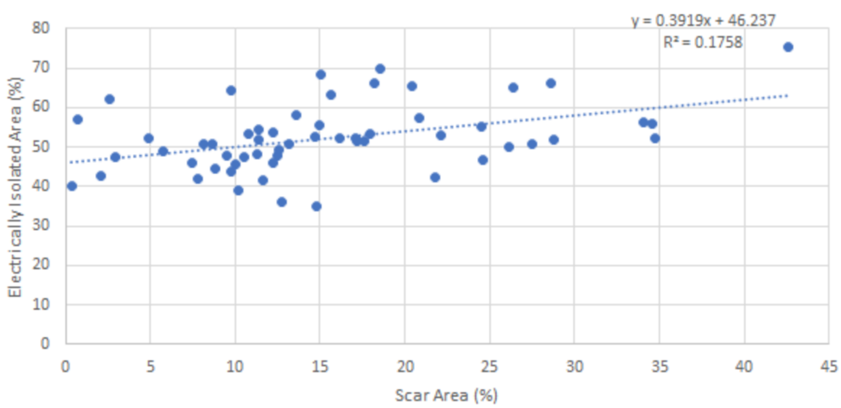


Hosted file

image13.emf available at https://authorea.com/users/365502/articles/485579-persistent-atrial-fibrillation-catheter-ablation-outcomes-stratified-by-left-atrial-posterior-wall-isolation-lesion-set-characteristics

Hosted file

image14.emf available at https://authorea.com/users/365502/articles/485579-persistent-atrial-fibrillation-catheter-ablation-outcomes-stratified-by-left-atrial-posterior-wall-isolation-lesion-set-characteristics



Variable (univariate)	HR	P-value	Variable (multivariate)	HR	P-value
Age	1.58 (1.0, 2.5)	0.052	Age	1.02 (0.98, 1.05)	0.421
Gender (Male)	7.92 (0.23, 270)	0.25			
LA Diameter	0.9 (0.82, 1.0)	0.06			
Ejection Fraction	1.22 (1.0, 1.49)	0.05	Ejection Fraction	1.0 (0.96, 1.03)	0.861
Box Scar Area	0.44 (0.18, 1.09)	0.08			
Non-WACA Scar Area	0.96 (0.84, 1.09)	0.49			
Box Area	1.25 (0.92, 1.7)	0.15			
WACA Area	1.25 (1.03, 1.53)	0.03	WACA Area	1.02 (1.0, 1.04)	0.112
LA Area	0.9 (0.82, 1.0)	0.05	LA Area	0.99 (0.98, 1.01)	0.492

References :

1. Verma A, Jiang C, Betts TR, et al. Approaches to Catheter Ablation for Persistent Atrial Fibrillation. http://dx.doi.org/10.1056/NEJMoa1408288. doi:10.1056/NEJMoa1408288

2. Bai R, Di Biase L, Mohanty P, et al. Proven isolation of the pulmonary vein antrum with or without left atrial posterior wall isolation in patients with persistent atrial fibrillation. *Heart Rhythm* . 2016;13(1):132-140. doi:10.1016/j.hrthm.2015.08.019

3. Ho Siew Yen, Cabrera José Angel, Sanchez-Quintana Damian. Left Atrial Anatomy Revisited. *Circ Arrhythm Electrophysiol* . 2012;5(1):220-228. doi:10.1161/CIRCEP.111.962720

4. Kim J-S, Shin SY, Na JO, et al. Does isolation of the left atrial posterior wall improve clinical outcomes after radiofrequency catheter ablation for persistent atrial fibrillation?: A prospective randomized clinical trial. *Int J Cardiol* . 2015;181:277-283. doi:10.1016/j.ijcard.2014.12.035

5. Tamborero David, Mont Lluís, Berruezo Antonio, et al. Left Atrial Posterior Wall Isolation Does Not Improve the Outcome of Circumferential Pulmonary Vein Ablation for Atrial Fibrillation. *Circ Arrhythm Electrophysiol* . 2009;2(1):35-40. doi:10.1161/CIRCEP.108.797944

6. Keçe F, Scholte AJ, Riva M de, et al. Impact of left atrial box surface ratio on the recurrence after ablation for persistent atrial fibrillation. *Pacing Clin Electrophysiol* . 2019;42(2):208-215. doi:10.1111/pace.13570

7. Schreiber D, Rieger A, Moser F, Kottkamp H. Catheter ablation of atrial fibrillation with box isolation of fibrotic areas: Lessons on fibrosis distribution and extent, clinical characteristics, and their impact on long-term outcome. *J Cardiovasc Electrophysiol* . 2017;28(9):971-983. doi:10.1111/jce.13278

8. Thomas SP, Lim TW, McCall R, Seow S-C, Ross DL. Electrical isolation of the posterior left atrial wall and pulmonary veins for atrial fibrillation: Feasibility of and rationale for a single-ring approach. *Heart Rhythm* . 2007;4(6):722-730. doi:10.1016/j.hrthm.2007.01.034

9. Verma A, Marrouche NF, Schweikert RA, et al. Relationship Between Successful Ablation Sites and the Scar Border Zone Defined by Substrate Mapping for Ventricular Tachycardia Post-Myocardial Infarction. *J Cardiovasc Electrophysiol* . 2005;16(5):465-471. doi:10.1046/j.1540-8167.2005.40443.x

10. Reichlin T, Lane C, Nagashima K, et al. Feasibility, Efficacy, and Safety of Radiofrequency Ablation of Atrial Fibrillation Guided by Monitoring of the Initial Impedance Decrease as a Surrogate of Catheter Contact. *J Cardiovasc Electrophysiol* . 2015;26(4):390-396. doi:10.1111/jce.12621

11. He X, Zhou Y, Chen Y, Wu L, Huang Y, He J. Left atrial posterior wall isolation reduces the recurrence of atrial fibrillation: a meta-analysis. *J Interv Card Electrophysiol* . 2016;46(3):267-274. doi:10.1007/s10840-016-0124-7

12. Marrouche NF, Wilber D, Hindricks G, et al. Association of Atrial Tissue Fibrosis Identified by Delayed Enhancement MRI and Atrial Fibrillation Catheter Ablation: The DECAAF Study. *JAMA* . 2014;311(5):498-506. doi:10.1001/jama.2014.3

13. Uijl DW den, Delgado V, Bertini M, et al. Impact of left atrial fibrosis and left atrial size on the outcome of catheter ablation for atrial fibrillation. *Heart* . 2011;97(22):1847-1851. doi:10.1136/hrt.2010.215335

14. Kottkamp H, Berg J, Bender R, Rieger A, Schreiber D. Box Isolation of Fibrotic Areas (BIFA): A Patient-Tailored Substrate Modification Approach for Ablation of Atrial Fibrillation. *J Cardiovasc Electrophysiol* . 2016;27(1):22-30. doi:10.1111/jce.12870