

Study Title: Investigator Initiated Randomized Controlled Trial Comparing Two Radiofrequency Ablation Strategies in Patients with Persistent Atrial Fibrillation

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1.0 ABSTRACT

This is an investigator initiated randomized controlled trial (RCT) of two ablation protocols that are currently done in our EP lab, but have not been studied prospectively to identify which, if either, is superior for patients with persistent atrial fibrillation. Specifically, we would like to perform a RCT of 100 patients who will be consecutively enrolled and randomized to either *Arm 1* (PVI) or *Arm 2* (PVI+PI). PVI=pulmonary vein isolation. PI=posterior wall isolation.

Expected Outcomes

Primary study outcome is the percentage of patients free from atrial arrhythmias and off AADs at 1 year after single ablation procedures.

2.0 BACKGROUND/RATIONALE

Background

Atrial fibrillation (AF), the most common type of arrhythmia in clinical practice, affects approximately 2.7 million US adults. This number is expected to double over the next 25 years. AF accounts for 500,000 hospitalizations and 100,000 deaths annually and contributes to 15% of all strokes, the leading cause of death from AF, in the US. Caring for patients with AF is also expensive, costing approximately \$26 billion annually. An effective management strategy to mitigate AF is critical.

Pulmonary vein isolation (PVI) has emerged as the gold standard for management of paroxysmal AF with excellent success rates. A number of randomized controlled trials (RCTs) demonstrated superior efficacy of PVI by comparing it to drugs alone. In addition, although there are currently no prospective data to support this, retrospective data suggested that successful ablation seems to reduce stroke risk in patients with AF.

For patients with persistent AF, however, procedural efficacy from PVI is not optimal. Therefore, improved ablation strategies for these patients are needed.

Safety and efficacy data reviewed from our clinical practice over the last 10 years of two PVI ablation strategies, PVI alone and PVI plus posterior wall isolation, did not favor either technique currently used by our physicians, not suggest harm, and so we feel there is equipoise presently between the techniques.

3.0 OBJECTIVES/STUDY AIMS

The objective of this RCT is to compare 2 ablation strategies, PVI alone and PVI plus posterior wall isolation, in patients with persistent AF. Both of these strategies are currently used to treat patients with persistent AF. However, no RCT has been

conducted to investigate which strategy is more efficacious. Primary outcome will be freedom from any documented atrial arrhythmia (including AF, atrial flutter, or tachycardia longer than 30 seconds) after one ablation procedure. Secondary endpoints will be freedom from atrial arrhythmia and after two ablation procedures, use of antiarrhythmic medication, procedure time, incidence of repeat procedures, and incidence of periprocedural complications.

4.0 ELIGIBILITY

Inclusion Criteria:

1. Patients 18 years of age or older.
2. Have symptomatic persistent AF (i.e., a sustained episode lasting more than 7 days).
3. Undergoing ablation for the first time.

Exclusion criteria:

1. Paroxysmal AF
2. Sustained atrial fibrillation lasting more than 3 years
3. Left atrial diameter of 60 mm or greater
4. Severe Pulmonary hypertension

5.0 SUBJECT ENROLLMENT

Consecutive eligible patients will be approached in the clinics of the investigators. Informed consent shall be obtained in writing and documented in accordance with the principles of Informed Consent, according to Good Clinical Practice.

6.0 STUDY DESIGN/PROCEDURES

Randomized study of 100 participants into groups of 50 to undergo a radiofrequency ablation procedure for AF (defined below).

Procedure

For both groups, a standard approach by our lab which has previously been described will be used. Briefly, general anesthesia will be provided by an anesthesiologist. A TEE will be done to confirm no left atrial appendage thrombus. The anesthesiologist will place a radial art line and place an esophageal temperature probe posterior to the left atrium to monitor esophageal temperatures during ablation on the posterior wall of the left atrium. The right groin catheter insertion site will be prepped and draped in sterile fashion. Local anesthesia will be used. An 8, 8, and long 9 French sheath will be placed percutaneously in to the right femoral vein utilizing ultrasound guidance and seldinger technique with visualization of vascular entry with the needle. A 20 pole deflectable catheter will be placed in the right atrium with the main body wrapped along the tricuspid valve annulus and tip in the proximal coronary sinus. An intracardiac ultrasound catheter will be used for transeptal access. The short 8 french sheath will then be exchanged over a long guidewire for a long 8.5 french transeptal sheath. A transeptal cardiac catheterization will be performed in standard fashion utilizing

intracardiac echo, fluoroscopic guidance, and hemodynamic monitoring. A Baylis RF needle will be used for transeptal puncture utilizing RF energy of 10 watts over 2 seconds. A heparin bolus will be administered immediately upon left atrial access followed by further boluses and a heparin drip through the transeptal sheath. ACT target will be 250. Serial ACT measurements will be made at least every 20 minutes. All sheaths will meticulously flushed and maintained with heparinized saline. An electroanatomic map of the left atrium will be created using a circular mapping catheter (CMC) and a three dimensional mapping system. Radiofrequency ablation (RF) will be performed using a 3.5 mm irrigated force sensing catheter in power control mode. Force will be targeted for 10-20 grams 85% of the time. RF settings will be between 30-50 watts depending on the location of RF application. It is anticipated that the majority of RF ablation in the left atrium will be performed with 50 watts. Mapping will be performed fluoroscopically and electro-anatomically. Esophageal temperature will be monitored, and ablation discontinued if the temperature rises by 1 degrees Celsius. Rapid pacing will be performed in the left atrium with isoproterenol to induce atrial fibrillation and any organized arrhythmias. Any clinically relevant organized arrhythmias will be mapped and ablated. No specific trigger mapping will be performed unless patient is unconvertible due to immediate return of AF.

For Group 1, a series of RF applications will be delivered around both sets of pulmonary veins with complete entry and exit block obtained around the antrums of all 4 pulmonary veins (Figure 1).

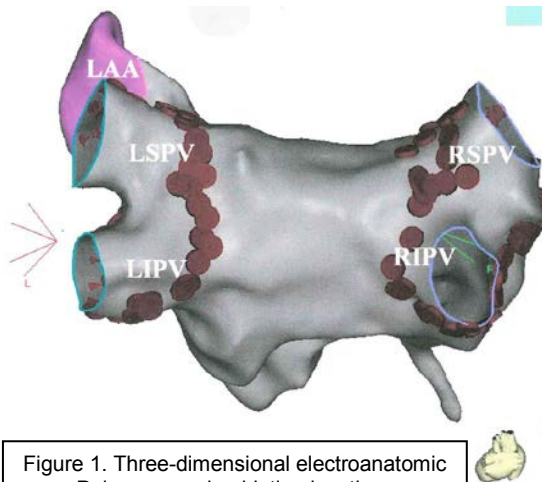


Figure 1. Three-dimensional electroanatomic map. Pulmonary vein ablation locations.

For Group 2, a series of RF applications will be delivered around both sets of pulmonary veins with complete entry and exit block obtained around the antrums of all 4 pulmonary veins. Then, a roof and low posterior line will be placed to achieve entrance and exit block on the posterior wall. Entry block on the posterior wall will be confirmed by placing the circular mapping catheter in multiple locations along the posterior wall

and confirming lack of presence of any local potentials. Exit block will be confirmed on the posterior wall with pacing at 10 amps from the ablation catheter at multiple locations within the box as well as all lines (Figure 2).

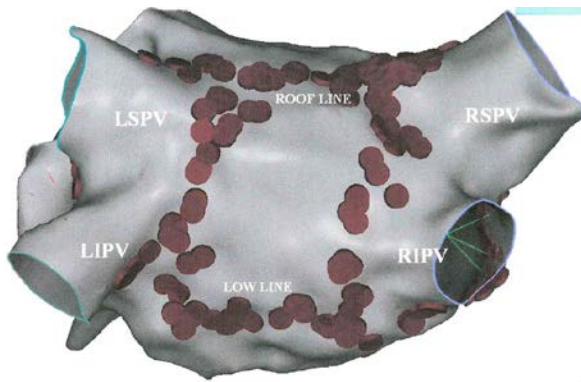


Figure 2. Three-dimensional electroanatomic map. Pulmonary vein and posterior wall ablation locations.

In both cases, a pace and ablate strategy will be completed around all lesions sets in a standard fashion. Isuprel will be employed to look for further AF, but will not be further ablated. If cavotricuspid dependent typical flutter is seen, this will be ablated in either group.

Follow-up

Follow-up visits will occur either in doctors office or by phone at 1 month, 3 months, 6 months, and 1 year post ablation. Antiarrhythmic drugs (AAD) may be discontinued at 1 month if indicated. All patients would receive a continuously recording electrocardiogram (ECG) heart card to monitor for AF for the first month, and then two week ambulatory monitors at 3 months and one year post ablation.

7.0 SPECIMEN/DATA COLLECTION/PROCEDURES

The investigators and study staff will obtain the necessary data during the ablation procedure, from electronic and paper medical records and monitoring devices. The information will be entered in a secure database with access limited only to study personnel. No specimens will be collected.

Data will be collected at baseline, during the ablation procedure and at each follow-up visit.

Baseline - Medical history, demographics, height, weight, BMI, cardiac medications, creatinine and 12-lead ECG.

Procedure - Ablation procedure details, medications administered, and adverse events.

Pre-discharge – Cardiac medications, arrhythmia events, adverse events.

Follow-up – In-Clinic/Telephone Visits -

The study requires total of 4 follow-up visits at (months 1, 3, 6 and 12) that can be completed either by telephone or in doctor's office. Telephone contact will last approximately 10 minutes each. Following assessments will be collected.

- Current concomitant medication documentation.
- ECG Recording – will be collected only if participant had ECG done at their own doctor's office or if the site has provided the ambulatory event monitor after the procedure to collect ECG recordings,
- Documentation of any adverse events/ serious adverse events occurring since the previous evaluation. All clinically significant adverse events should be carefully documented by the research staff using the adverse event data forms.

If a clinic visit occurs as part of the subject's regular medical care during the specified follow-up window, the follow-up assessment may be conducted during this visit, and no separate telephone contact is necessary.

8.0 LABORATORY/DATA ANALYSIS

Laboratory specimens will not be collected.

9.0 STATISTICAL CONSIDERATIONS

Demographics, baseline and treatment characteristics will be summarized for the study population. Descriptive statistics for baseline characteristics will be prepared for the two treatment groups for all randomized subjects. Continuous variables will be summarized using the number of subjects with data (n), mean, standard deviation, median, minimum and maximum. Chi-square statistics and Wilcoxon rank sum tests will be used to evaluate baseline differences between the arms for categorical and continuous variables respectively.

An interim data analysis will be performed after 40 subjects are enrolled.

10.0 CONFLICT OF INTEREST

There are no potential conflicts of interest.

References

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2. Dixit S, Marchlinski FE, Lin D, et al. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. *Circ Arrhythm Electrophysiol*. 2012;5(2):287-294.